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Cervical cancer is an important public health problem worldwide. It is the second most common cancer among women, ranking first in many developing countries (Parkin et al, 1993). In the United States and other countries with broad-coverage, cervical cytologic screening ("Pap smear") programs, there has been a marked decline in cervical cancer incidence and mortality over recent decades (Coleman et al, 1993; Beral et al, 1994). The reduction has apparently been due to detection and treatment of intraepithelial, preinvasive lesions. Nonetheless, rates of invasive cancer have recently started to increase again among young women in several countries, including white women in the United States, despite costly and laborious screening programs. At present in the United States, there are approximately 15,000 cases of invasive cervical cancer per year, and about 4600 deaths (Boring et al, 1994). Carcinoma in situ, the most severe intraepithelial precursor detected through cytologic screening, accounts for another 55,000 cases yearly.

The success of cervical cytologic screening in the past led to decreased epidemiological study of cervical cancer. Recently, however, there has been renewed research interest in cervical cancer, particularly after the discovery of an etiologic role for the human papillomaviruses (HPV). It now appears that the large majority of cases of cervical cancer worldwide can be attributed to HPV infection. However, cervical infection with HPV is extremely common compared to the relatively rare development of cervical cancer. Thus, additional critical etiologic factors must be involved, such as HPV type and intensity of infection, variability in the host immunologic response, co-infection with other viral or bacterial agents, parity, cigarette smoking, oral contraceptive use, and diet. Behavioral characteristics of male sexual partners also may play an etiologic role, adding a further level of complexity to epidemiological investigations.

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Although there are still major challenges in clarifying the multistage pathogenesis of cervical cancer, epidemiological understanding of this tumor now rivals our understanding of any other malignancy. As a result, it may soon be possible, using a variety of molecular epidemiological approaches, to define new prevention strategies that will be even more effective than cervical cytologic screening alone. For example, HPV DNA testing may prove to be a useful adjunct to Pap smears. In the long term, the most exciting possibility is the primary prevention of cervical neoplasia via HPV immunization of the general population.

## BACKGROUND

### *The Cervical Transformation Zone*

The cervix is the cylindrically shaped lower third of the uterus extending into the vagina from the anterior vaginal wall (Fig. 50-1). The cervical epithelium is derived from two embryologically distinct sources. The part of the cervix that projects into the vagina, called the *portio*, is covered by nonkeratinized stratified squamous epithelium similar to the neighboring lining of the vagina. The endocervical canal is covered by tall, mucus-secreting columnar cells of the same embryologic derivation as the uterine endometrium. At birth, the columnar epithelium extends out onto the portio, but with age the squamocolumnar junction recedes into the endocervical canal, as columnar epithelium is replaced by squamous epithelium in a process called *squamous metaplasia*. The metaplastic area adjacent to the receding squamocolumnar junction is called the transformation zone, and it is this area that appears to have a unique sensitivity for neoplastic events (Fenoglio and Ferenczy, 1982). Accordingly, women with an increased area of squamous metaplasia, such as diethylstilbestrol (DES)-exposed daughters, may have an increased incidence of

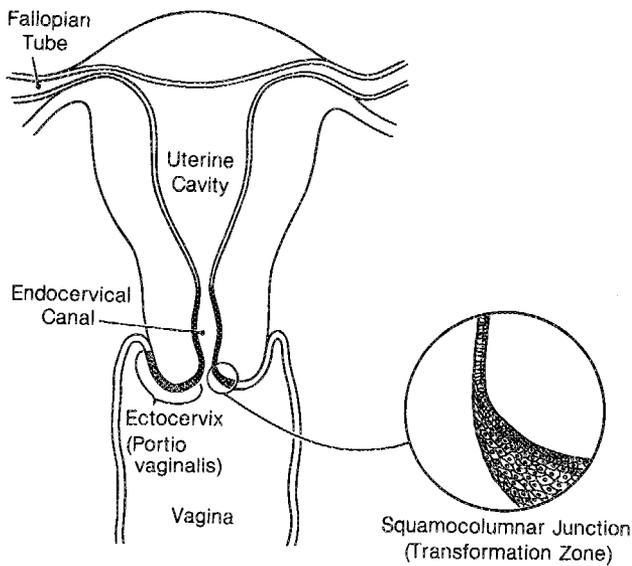


FIG. 50-1. Diagrammatic representation of cervical anatomy.

cervical neoplasia (Robboy et al, 1984). As the great majority of cervical cancers arise in the transformation zone, treatment of this ring of epithelium by cryotherapy, laser surgery or, most recently, loop electrical excision (LEEP) is the mainstay of clinical intervention when preinvasive lesions are found (Ferenczy and Wright, 1993).

### Classifying the Intraepithelial Precursors of Cervical Cancer

Squamous carcinomas of the cervix result from the progression of preinvasive precursor lesions called cervical intraepithelial neoplasia (CIN), dysplasia, dyskaryosis (British), or a variety of other names (see Table 50-1

for a comparison of common classification schemes in the United States).

To bring order to the diagnostic confusion, a new cytology classification called the Bethesda System was recently introduced in the United States (Kurman and Solomon, 1994; National Cancer Institute Workshop, 1989). The Bethesda System combines clinically similar intraepithelial diagnoses into broad categories, specifically, low-grade squamous intraepithelial lesions (SIL) and high-grade SIL. The new classification was designed for use in cytologic screening. It remains technically more correct to use the more detailed CIN scale when discussing histopathology (ie, biopsies). Nonetheless, the Bethesda System will be employed primarily for this discussion, because it has proven very useful for epidemiological studies of multistage cervical carcinogenesis.

Low-grade SIL combines CIN 1 (mild dysplasia) with the cytologic diagnosis of HPV infection (Meisels and Fortin, 1976), called koilocytotic (or condylomatous) atypia. The two older categories shared virtually the same epidemiological and HPV DNA profiles and were so overlapping morphologically as to be indivisible. Typically, koilocytotic atypia was about two to three times as common a diagnosis as CIN 1. Of the two diagnoses, CIN 1 was thought to be slightly more severe and more closely linked to "pre-cancer." Accordingly, the new category of low-grade SIL is much larger and, on average, slightly less severe than CIN 1.

The distinction between low-grade SIL and high-grade SIL (Table 50-1) is quite important for epidemiologists studying cervical carcinogenesis. Low-grade SIL is common and represents the usually benign cytopathologic signs of HPV infection. In contrast, high-grade SIL is rare and represents a truly premalignant lesion in the most severe cases (carcinoma in situ). Whereas low-grade SIL can be viewed as an epidemiological "exposure" or risk factor for cervical cancer, high-grade SIL

TABLE 50-1. Common Classifications of Cervical Squamous Neoplasia

Dysplasia Scale	Pap Smear Class <sup>a</sup>	CIN <sup>b</sup> Scale	Bethesda <sup>c</sup> System
Normal	1	Normal	Normal
Inflammatory or reactive atypia	2a	Inflammatory or reactive atypia	Normal or ASCUS <sup>d</sup>
Koilocytotic or condylomatous atypia	2b	Koilocytotic or condylomatous atypia	Low-grade SIL <sup>e</sup>
Mild dysplasia	3	CIN 1	Low-grade SIL
Moderate dysplasia	3	CIN 2	High-grade SIL
Severe dysplasia	3	CIN 3	High-grade SIL
Carcinoma in situ (CIS)	4	CIN 3	High-grade SIL
Invasive squamous carcinoma	5	Invasive squamous carcinoma	Invasive squamous carcinoma

<sup>a</sup>Numeric scale still in widespread use, but not recommended.

<sup>b</sup>CIN = cervical intraepithelial neoplasia.

<sup>c</sup>Recommendations of the 1988 Bethesda System (National Cancer Institute Workshop, 1989).

<sup>d</sup>ASCUS = atypical squamous cells of undetermined significance.

<sup>e</sup>SIL = squamous intraepithelial lesion.

can be viewed as more tightly linked to the cancer "outcome."

This useful conceptual distinction is not perfect, however, because there exists a continuum of changes encompassing low-grade and high-grade SIL, without a clear cut point. At the microscopic level, for example, the characteristic cells of low-grade SIL are abnormal but terminally differentiated (Fig. 50-2). The atypical cells progress to the surface, produce keratins, die, and slough, as would normal cells. The gradient from low-grade SIL to high-grade SIL (CIN 2-3) is characterized by increasing nuclear atypia and failure of cellular differentiation in progressively more superficial levels of epithelium, with carcinoma in situ representing full thickness replacement with undifferentiated, immortalized, atypical cells. Despite inevitable misclassification from such a continuum of changes, the Bethesda System remains the best available simplifying schema for epidemiological research.

**HPV Infection**

HPV infection is the primary risk factor for cervical cancer and for certain other anogenital cancers (Barrasso et al, 1987; Kurman et al, 1993; Reid et al, 1987; Stanbridge and Butler, 1983). Interested readers are referred elsewhere for a thorough review of papillomavirus biology (Shah and Howley, 1995) or the epidemiology of HPV infection itself apart from cervical neoplasia outcomes (Schiffman and Burk, in press).

Human papillomaviruses are non-enveloped, double-stranded DNA viruses of approximately 8000 base pairs, part of a large group of papillomaviruses that includes wart viruses of cattle, cotton-tailed rabbits, deer, and horses. There are over 70 types of human papillomaviruses characterized according to DNA sequence homology, with a few more identified every year. The

types are numbered sequentially as they are characterized. Each type has its own tissue predilection and disease spectrum. For example, HPV 1 is the major cause of deep plantar warts; HPV 2 and 4 cause mainly common skin warts; and types 6 and 11 are the most common agents of venereal warts (condyloma acuminatum) as well as laryngeal polyps. Based on current data, types 6, 11, 16, 18, 26, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 64, 66, and 68 are the types most commonly found to infect cervical epithelia.

The epidemiological study of HPV has been limited by HPV measurement techniques. Reliable serologic assays are not available to define cumulative lifetime incidence of HPV infection (Galloway, 1992), although serologic tests that detect the majority of recent infections have just been developed (Kirnbauer et al, 1994). At present, cervical HPV infection is still most accurately measured by current detection of HPV DNA sequences in infected tissues.

Epidemiologists studying cervical HPV infection have relied on DNA testing of cervical specimens obtained noninvasively using swabs, scrapes, brushings, and lavages. HPV prevalence estimates have varied accordingly, due to differences in cell sampling (Vermund et al, 1989), the poorly understood intermittency of viral DNA detectability (de Villiers et al, 1987) and, most importantly, the choice of DNA detection method (Schiffman, 1992a). Misclassification resulting from the first, poorly validated DNA tests severely limited early epidemiological studies of HPV infection (Franco, 1991).

Essentially there are two categories of HPV DNA detection methods used in population studies: those that identify the nucleic acids directly and those that amplify nucleic acids first and then detect the amplified product (Gravitt and Manos, 1992; Lorincz, 1992; Schiffman, 1992a). In the first category are Southern blot hybridization, dot blot hybridization (eg, ViraPap and Profile kits), and Hybrid Capture liquid hybridization kit. The only amplification methods currently used for HPV epidemiology are polymerase chain reaction (PCR)-based techniques. In general, PCR-based tests yield HPV population prevalence estimates about two to three times higher than those of nonamplified tests. However, if ample specimen is tested, the detection of HPV DNA in prevalent cases of SIL or cancer is similar regardless of whether nonamplified or amplified tests are used, because viral load is typically much higher in cases than in infected but cytologically normal controls.

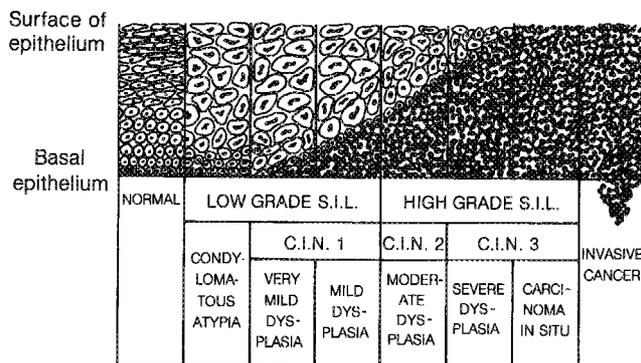


FIG. 50-2. Cervical cancer precursor lesions (adapted from Fenoglio and Ferenczy, 1982). Early cervical cancer precursors are characterized by superficial cellular abnormalities that represent the koilocytotic changes of human papillomavirus infection. More severe precursors demonstrate a progressive increase in undifferentiated, malignant-appearing cells.

**DEMOGRAPHIC PATTERNS**

**Histopathology**

Consistent with their origin in the transformation zone, most cervical cancers (80% or more) are squamous cell

carcinomas, with adenocarcinomas and mixed adenocarcinomas accounting for most of the remainder. Other histologic types, such as melanomas, sarcomas, and metastatic tumors, are very rare. The relative and absolute frequencies of adenocarcinomas are rising, particularly among younger women, for reasons that are only partly understood (Kjaer and Brinton, 1993). Almost all epidemiological studies of cervical cancer have focused on squamous carcinomas or have ignored histologic distinctions altogether.

**Incidence and Mortality of Invasive Cervical Cancer in the United States**

Figure 50-3 illustrates the historically downward trend for invasive cervical cancer in the United States through the early 1990s (updated from Devesa et al, 1987). In whites, incidence per 100,000 declined 76%, from 32.6 in the late 1940s to 7.9 in 1989-1991. Mortality rates in whites also declined, especially during the 1960s and 1970s. Average decreases in both incidence and mortality were about 4% per year until the 1980s, when rates started to level or, most recently, perhaps increase slightly. Although mortality and incidence declined also

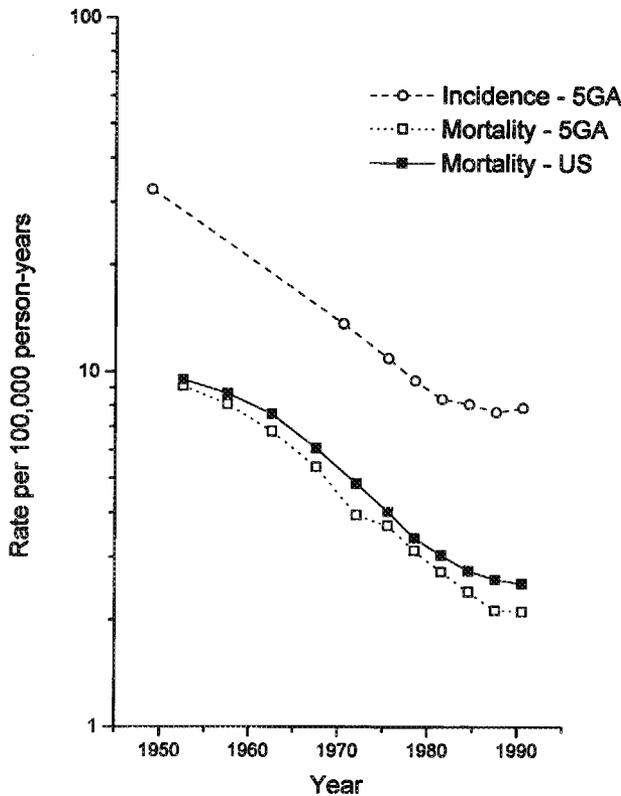
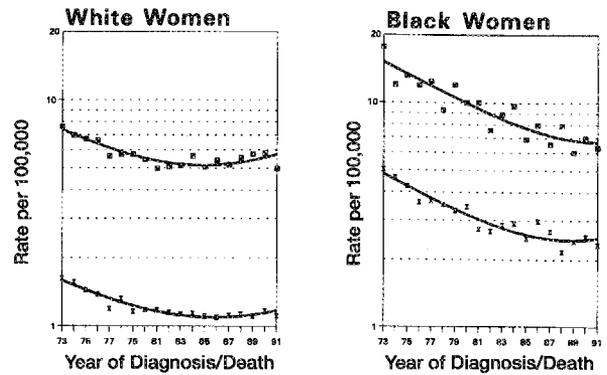


FIG. 50-3. Incidence and mortality trends for invasive cervical cancer in the United States (rates age-adjusted using the 1970 U.S. population; data from five geographic areas [5GA] of the National Cancer Surveys, the SEER program of National Cancer Institute, and the National Center for Health Statistics; updated from Devesa et al, 1987).



All Rates Age-Adjusted to 1970 U.S. Standard

FIG. 50-4. Recent annual incidence and mortality rates for invasive cervical cancer, U.S. whites and African Americans under age 50 (from Ries et al, 1994).

among African Americans in the past decades, the decrease in mortality started later than among whites.

As shown in Figure 50-4, since the mid-1980s, among white women under age 50 years, the long decline in cervical cancer incidence has stopped and even reversed (Ries et al, 1994). Similar but weaker trends are evident in older white women. In contrast, cervical cancer incidence has continued to fall among African American women. Although data for 1987-1991 from the Surveillance, Epidemiology, and End Results (SEER) Program indicate an 80% excess in age-adjusted incidence of invasive cervical cancer in African Americans compared to whites (Ries et al, 1994), this differential appears restricted now to older women. Specifically, the incidence of cervical cancer continues to rise with age among African Americans (Fig. 50-5). Among whites, there is a plateauing of rates after age 40, an unusual pattern of risk compared to that of other epithelial tumors.

Examined by race and histology (Table 50-2), invasive cervical carcinoma incidence declined from 9.8 to 7.6 among whites and from 23.4 to 14.3 among blacks from 1975-1979 to 1985-1989, respectively. The majority of cervical carcinomas were squamous cell carcinomas, for which the rates continued to decrease among both races. Adenocarcinomas of the cervix are relatively rare, and adenosquamous carcinomas are even less frequent. Some increases in adenocarcinoma were suggested, at least among whites. These were seen primarily among young and middle-aged women (Devesa et al, 1989; Beral et al, 1994).

In addition to black-white differences, the incidence of cervical cancer is also about twice as high among Hispanics and even higher among Native Americans, while most Asian-American groups experience rates similar to those of whites (National Cancer Institute, 1984). The racial-ethnic differences in cervical cancer incidence are paralleled by differences in the incidence

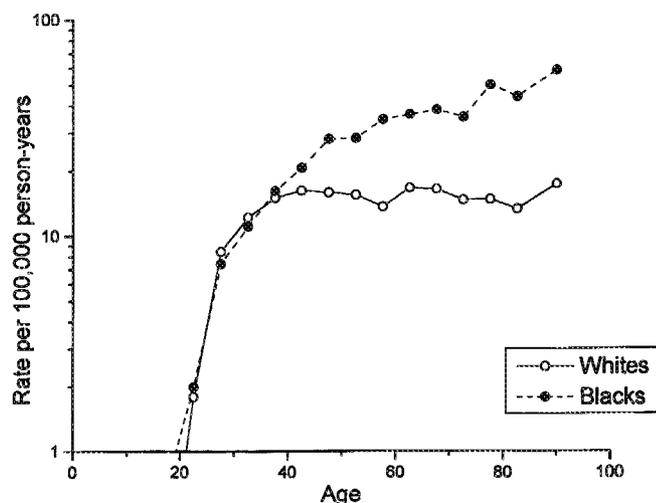


FIG. 50-5. Age-specific incidence of invasive cervical cancer, U.S. whites and African Americans, 1987-1991 (data from Ries et al, 1994).

and prevalence of SIL (Schiffman et al, unpublished data).

Moreover, racial differences also exist in survival experience (Ries et al, 1994). Women diagnosed with invasive cervical cancer in the United States experienced 5-year relative rates of 70% among whites and 56% among blacks, based on about 8000 cases diagnosed during 1983-1990 (Table 50-3). More than half of all cases among whites were diagnosed at a localized stage and about one third at a regional stage, in contrast to about 40% at each of these stages among blacks. The differences in stage distribution partly explained the difference in overall survival, but survival rates were more favorable for whites than blacks at each stage of diag-

nosis. Among both whites and blacks, stage at diagnosis strongly influenced subsequent survival experience, ranging from 86% to 91% among those diagnosed at a localized stage to 11% to 12% with distant disease. Age at diagnosis also strongly influenced survival, with rates declining from 70% to 80% among women under age 45 years to 30% to 40% among those age 75 and older.

At least some of the racial/ethnic differences in demographic patterns can be explained by the strong inverse associations observed between socioeconomic indicators and the risk of invasive cervical cancer. These inverse relationships with income and education prevail among both whites and African Americans. In one analysis, when adjustment was made for socioeconomic

TABLE 50-2. Trends in Microscopically Confirmed Invasive Cervical Carcinoma Incidence by Histologic Type, SEER Program

	1975-1979		1980-1984		1985-1989	
	No.	Rate <sup>a</sup>	No.	Rate <sup>a</sup>	No.	Rate <sup>a</sup>
<b>WHITES</b>						
squamous	3747	7.63	3307	6.24	3236	5.71
adenosquamous	107	0.23	122	0.24	145	0.25
adenocarcinoma	508	1.02	535	1.01	694	1.23
Total <sup>b</sup>	4827	9.80	4251	8.02	4331	7.64
<b>BLACKS</b>						
squamous	868	19.44	731	14.07	681	11.61
adenosquamous	22	0.49	24	0.48	38	0.63
adenocarcinoma	51	1.20	63	1.28	72	1.23
Total <sup>b</sup>	1046	23.35	877	16.91	842	14.34

<sup>a</sup>Per 100,000 woman-years, age-adjusted using the 1970 U.S. population.

<sup>b</sup>Includes carcinoma, not otherwise specified.

TABLE 50-3. Stage Distribution and Relative Survival Rates for White and Black Patients Diagnosed with Invasive Cervical Cancer, SEER Program, 1983-1990

Number of Cases	Whites (n=6599)	Blacks (n=1319)
<b>STAGE DISTRIBUTION (%)</b>		
localized	53	39
regional	32	40
distant	9	13
unstaged	7	9
<b>FIVE-YEAR RELATIVE SURVIVAL RATES (%) BY STAGE</b>		
all stages	69.9	56.4
localized	91.1	86.1
regional	52.7	42.7
distant	11.8	11.2
unstaged	59.4	58.9
<b>FIVE-YEAR RELATIVE SURVIVAL RATES (%) BY AGE</b>		
<45	81.1	68.6
45-54	68.7	55.6
55-64	64.0	52.4
65-74	55.1	47.8
75+	42.5	29.7

Source: Based on data from Ries et al, 1994; n = number of cases.

variables, the excess risk of cervical cancer among African Americans was substantially reduced, from more than 70% to less than 30% (Devesa and Diamond, 1980).

In addition to racial and socioeconomic differences, there are distinct geographic patterns in the United States (Fig. 50-6), with mortality rates ranging from 1.5

to 6.8 per 100,000 woman-years. High mortality rates are scattered throughout the South, and particularly in Appalachia and the Midwest (NCI, unpublished data). This reflects the tendency of the disease to affect rural women in lower socioeconomic classes and possible differences in screening practices and subsequent survival experience.

The upturn in cervical cancer incidence among younger white women in the United States occurred more recently than the trend in other countries, and this delay may reflect the effectiveness of aggressive U.S. screening and treatment programs that have counteracted anticipated increases from changes in the prevalence of risk factors (Devesa et al, 1989). In particular, it is possible that spread of genital HPV infections into the general population during the "sexual revolution" of the 1960s-1970s might account for the recent increases in cervical cancer reported among younger women, with the lag time reflecting the long latency period in the development of cervical cancer. As would be expected with this hypothesis, intermediate increases in the rates of low-grade SIL and HPV-induced venereal warts were reported in the 1970s and 1980s (Koutsky et al, 1988; Evans and Dowling, 1990).

**International Patterns**

Cervical cancer is the second most common cancer of women worldwide, and the fifth most common cancer in humans (Parkin et al, 1993). The worldwide incidence of cervical cancer is about 440,000 cases per year. The incidence rate per 100,000 woman-years for invasive cervical cancer in various geographic areas is shown

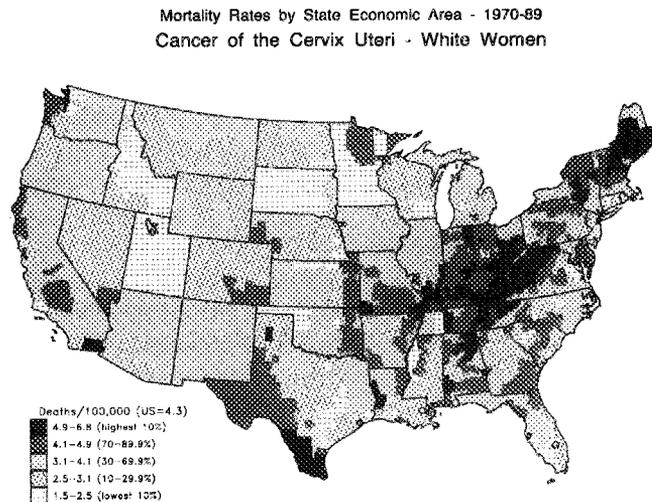


FIG. 50-6. Geographic patterns of cervical cancer mortality among white females according to state economic areas of the United States, 1970-1989 (rates age-adjusted using the 1970 U.S. population; based on data from the National Center for Health Statistics).

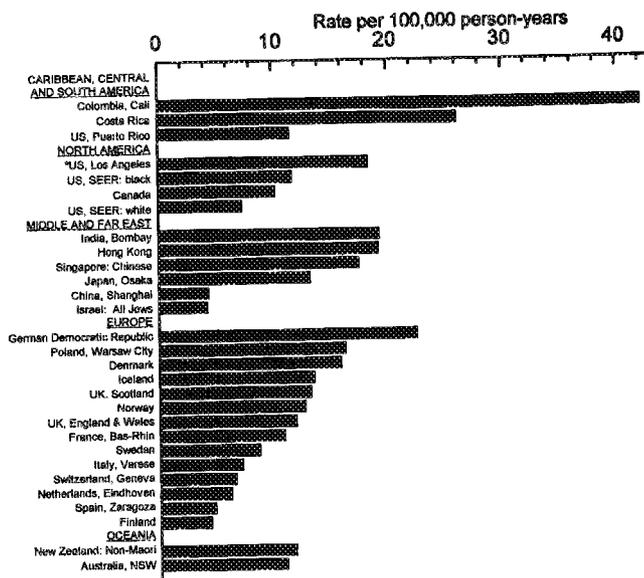


FIG. 50-7. Age-adjusted (world standard) incidence per 100,000 women for invasive cervical cancer by selected geographic areas (from Parkin et al, 1992).

in Figure 50-7 (Parkin et al, 1992). The highest rate was reported from Cali, Colombia, where the risk was almost six times that of U.S. whites, whose rate is among the lowest in the world. High rates were also reported in Costa Rica, among Spanish-surnamed whites in Los Angeles, in parts of Asia, and in eastern Europe. Notably low rates were reported for Jewish women in Israel, Chinese women in Shanghai, and women in Finland. However, the incidence and mortality rates of cervical cancer are profoundly influenced by the efficacy of available screening and treatment programs. Thus, the geographic variation in rates may not necessarily be useful in generating etiologic hypotheses.

Recent upturns in incidence and mortality rates among young women, preceding similar trends in the United States mentioned above, have been observed in a number of countries (Coleman et al, 1993; Beral et al, 1994), including Canada (Carmichael et al, 1986), Great Britain (Parkin et al, 1985), New Zealand (Green, 1979), and Australia (Holman and Armstrong, 1987).

The geographic distribution of HPV infection has been studied mainly in correlation with cervical cancer incidence rates, to determine whether variation in prevalences of HPV measured by DNA would be reflected in cancer rates. Recent geographic studies using sensitive PCR DNA testing methods to detect a wide spectrum of HPV types have generally observed HPV prevalences to correlate with the population risks of cervical cancer, although it has not been possible to take into account the relative efficacy of regional screening programs (Munoz et al, 1992).

## HPV INFECTION AS THE MAJOR CAUSE OF CERVICAL CANCER

The epidemiological association between HPV infection and cervical cancer fulfills all of the established epidemiological criteria for causality (Hill, 1965). These criteria include strength and consistency of the epidemiological association, time sequence, specificity of the association, and coherence with existing biological and epidemiological evidence.

The association between HPV infection and cervical cancer is remarkably strong and consistent, with virtually no negative studies. Selected case-control studies of invasive cervical cancer are summarized in Table 50-4, with relative risks ranging from about 4 to more than 40. Although not shown here, similar risks have been observed in studies of SIL that included expert cytopathology review to minimize misclassification of low-grade cases (Schiffman et al, 1993). Thus, the great majority of women with cervical cancer and/or SIL have detectable HPV DNA, compared to a consistently lower percentage of control women.

In case series worldwide, most squamous cervical cancers and adenocarcinomas, and their metastases, have been found to contain HPV of the same types (Lancaster et al, 1986). The most definitive study of invasive cervical cancer included 1050 cervical cancers from over 20 countries, tested for all known HPV types by PCR (Bosch et al, 1995). Over 85% of cervical cancers from each country contained HPV DNA, with the inclusion of "possible" infections raising the proportions even higher.

Accordingly, the cancer-associated group of genital HPV types is defined as those found with appreciable prevalence in invasive cervical cancers (Fuchs et al, 1988; Lorincz et al, 1992; Bosch et al, 1995). Based on this definition, the current list of cancer-associated HPV types includes at least types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 54, 55, 56, 58, 59, 64, and 68. Other, more restrictive definitions of "high-risk" types, based on relative risk or attributable proportion calculations, may be more useful for some purposes. By most definitions, HPV 16 is the most important cancer-associated type in almost all regions, along with HPVs 18, 31, and 45 (Bosch et al, 1995).

With regard to a logical time sequence, HPV infection (as measured by DNA) tends to precede and predict incident cervical neoplasia. Early results from large prospective studies of cytologically normal women show substantially elevated relative (>10) and absolute (>30%) risks of incident SIL, including high-grade SIL, within a few years of viral DNA detection (Koutsky et al, 1992; Schiffman et al, unpublished data). Cancer-associated HPV types are associated with a higher risk of developing cytologically evident lesions than are

TABLE 50-4. Selected Case-Control Studies Assessing the Relation between HPV DNA Detection and Invasive Cervical Cancer

Reference Year	Area	Adjustment Factors <sup>1</sup>	Testing Methods		Invasive Cancer		Controls		
			Cell Sampling	DNA Hybridization <sup>2</sup>	No.	Percent HPV Pos.	No.	Percent HPV Pos.	Relative Risk <sup>3</sup>
de Villiers, 1987	Germany	a	Swab	FISH	62	40	8755	9	10.3
Eluf-Neto, 1994	Brazil	a,b	Swab	PCR	199	84	225	17	37.1
Fuchs, 1988	Germany	None	Biopsy	Southern	44	72	31	10	23.1
Lorincz, 1987	North/South America	None	Biopsy	Southern	39	82	31	19	19.2
McCance, 1985	England	None	Biopsy	Southern	13	92	17	18	52.4
Meanwell, 1987	England	a	Biopsy	Southern	47	66	26	35	3.6 <sup>4</sup>
Munoz, 1992	Spain	a,b,c,d,e	Swab	PCR	142	69	130	5	46.2
	Colombia	a,b,c,d,e	Swab	PCR	87	72	98	13	15.6
Peng, 1991	China	a,b,f,i	Swab	PCR	101	35	146	1	32.9
Reeves, 1989	Latin America	a,b,c,e,g,h	Swab	FISH	759	62	1467	32	9.1 <sup>5</sup>

<sup>1</sup>a = age, b = socioeconomic status, c = number of sexual partners, d = age at first birth, e = Pap smear screening history, f = smoking, g = age at first intercourse, h = parity, i = age at first marriage.

<sup>2</sup>FISH = filter in situ hybridization; PCR = polymerase chain reaction, Southern = Southern blot hybridization.

<sup>3</sup>Relative risk calculated by DNA prevalence odds ratio  $P_{ca} (1-P_{co})/P_{co} (1-P_{ca})$  where  $P_{ca}$  is proportion of cases with DNA detected and  $P_{co}$  is proportion of controls. When adjustment factors were taken into account, adjusted RR is shown, although most varied little from the crude estimates.

<sup>4</sup>An interaction with age was observed, with RR = 10.5 under 40 years of age and RR = 1.2 for 40 or older.

<sup>5</sup>Relative risk associated with high levels of HPV types 16 or 18.

other HPV types (Stellato et al, 1994; Schiffman et al, unpublished data). Additionally, follow-up studies of women with low-grade SIL have observed that the finding of cancer-associated HPV types predicts an elevated risk of progression to high-grade SIL (Campion et al, 1986; Kataja et al, 1990). Finally, several small follow-up studies of women with invasive cancer have suggested that the presence or type of HPV might predict prognosis (Barnes et al, 1988; Walker et al, 1989; Riou et al, 1990; Higgins et al, 1991; Franco, 1992).

HPV infection causes a specific set of carcinomas of mucocutaneous epithelia (Daling et al, 1992), particularly anogenital tumors (cervical carcinoma, and some types of vulvar, vaginal, penile, and anal carcinomas). To a lesser extent, some subsets of head and neck carcinomas may also be associated with HPV. Numerous anecdotal reports of associations with a wide variety of tumor types, such as adenocarcinoma of the colon and Kaposi's sarcoma, have not been confirmed.

The animal data and experimental evidence for HPV carcinogenicity are strong, satisfying the causal criterion of "coherence." In fact, the potential for malignant transformation of papillomavirus-induced lesions has long been recognized. Cotton-tailed rabbit papillomavirus causes skin cancers in conjunction with exposure to coal tar (Rous and Kidd, 1938), and bovine papillomavirus causes alimentary tract cancers in cows ingesting the co-carcinogen bracken fern (Jarrett et al, 1978). In the rare genetic disorder epidermodysplasia verruciformis, patients develop multiple HPV-induced

cutaneous warts that are prone to squamous cell carcinomas, especially in sun-exposed areas (Orth et al, 1980).

Cellular and molecular biological evidence for the oncogenic potential of human papillomaviruses is especially compelling (zur Hausen, 1994). Certain types of HPV have been shown to transform human cell lines in culture (Yasumoto et al, 1986) and to cause growth abnormalities that stimulate low-grade SIL (Kreider et al, 1985; McCance et al, 1988). The types with the strongest known transforming abilities in vitro (16 and 18) are also the most important cancer-associated types defined epidemiologically. In addition, the cancer-associated types are observed to be genetically related when "phylogenetic trees" are constructed that categorize HPV types by DNA sequence homology (Van Ranst et al, 1992). In mechanistic studies, HPV DNA, though found in an episomal (nonintegrated) form in early cervical lesions, is often integrated into the cellular genome in cervical cancers and derived cancer cell lines; integration may therefore play a role in progression and maintenance of neoplasia (Cullen et al, 1991). Protein products of HPV early genes (E6, E7) have been identified that interact with growth-regulatory proteins of the human cell (p53, pRb), providing a possible mechanism for an HPV oncogenic effect (Dyson et al, 1989; Werness et al, 1990). Finally, as shown below, HPV infection explains much of the established epidemiology of cervical cancer, meeting the criterion of "coherence with existing epidemiologic knowledge," and it is now gen-

erally accepted to be the major causal factor for most cases of cervical cancer in the world (IARC Working Group, 1995; Munoz et al, 1992; zur Hausen, 1994).

### OTHER RISK FACTORS FOR CERVICAL CANCER

The recognition of the key etiologic role of HPV infection has profoundly altered the epidemiological study of cervical cancer. Yet this shift in theoretical paradigms to include HPV infection is still new and incomplete. Specifically, it is not yet clear which "established" risk factors for cervical cancer are mere correlates of HPV infection, which are HPV cofactors operating only in the presence of infection, and which are independent risk factors. As a result of the uncertainty, it is important to start by summarizing the established epidemiological risk factors for cervical cancer without consideration of HPV infection, analogous to a "crude" statistical analysis that precedes consideration of confounding and causal intermediacy. In each section, there will be an attempt to reconsider each of the established risk factors in light of the central role for HPV.

#### Sociodemographic Factors

Both descriptive and analytic studies have demonstrated that cervical cancer predominantly affects women in lower social classes, as defined by levels of income and education (Brinton et al, 1987a; Fasal et al, 1981; Jones et al, 1958; West et al, 1984). As a partial explanation, cervical HPV infections appear to be more prevalent in women of lower educational and income levels (Hildesheim et al, 1993). Other correlates of low socioeco-

nomie level, including deficient nutrition, multiparity, and concurrent genital infections, could also be involved.

#### Religion

Low cervical cancer risks have been recorded among Catholic nuns (Fraumeni et al, 1969), the Amish (Cross et al, 1968), Mormons (Lyon et al, 1994), and Jews (Boyd and Doll, 1964; Graham and Schotz, 1979). It is probable that a reduced number of sexual partners and subsequently lowered risk of HPV infection among these groups accounts for their historically lower cancer risk. However, no study of religion and cervical cancer incorporating accurate HPV testing has been reported.

#### Marital and Sexual Factors

Early studies (Boyd and Doll, 1964; Jones et al, 1958) revealed that the risk of cervical cancer is especially high among women marrying at young ages. Subsequent investigations indicated the importance of sexual activity (Kessler et al, 1977; Martin, 1967; Pridan and Lilienfeld, 1971; Rotkin, 1967; Terris et al, 1967), with women who have sexual relationships at early ages being at higher risk than either virgins or women whose sexual experiences began later in life. Thus, it has been shown in a variety of case-control studies that women who become sexually active before age 16 have about a twofold or greater risk compared with women who start after the age of 20 years (Table 50-5).

The risk of cervical cancer is also influenced by the number of sexual partners, often indexed by multiple marriages, separations, and divorces. A number of stud-

TABLE 50-5. Selected Case-Control Studies Assessing the Relation between Age at First Sexual Intercourse and Invasive Cervical Cancer

Reference Year	No. of Cases	No. of Controls	Type of Controls	Adjustment Factors <sup>1</sup>	Relative Risk	Comparison Categories
Bosch, 1992	436	387	Population	a,c,d,g,h,p	4.3	<16 vs ≥24
Brinton, 1987a	418	704	Community	a,c,g,h,i,j,k,l	2.3	<16 vs ≥22
Clarke, 1982	178	855	Neighborhood	c,g <sup>2</sup> ,k	1.8	≤19 vs ≥20
Ebeling, 1987	129	275	Hospital	a,g,h,j,k	2.0	≤16 vs ≥20
Eluf-Neto, 1994	199	225	Hospital	a,c,g,h,j,l,p	1.3	≤14 vs ≥20
Herrero, 1990b	759	1430	Hosp/Comm	a,c,g,h,j,p	1.8	14-15 vs ≥20
Kjaer, 1992	59	614	Population	a,c,g,i,l	3.7	≤13 vs ≥20
La Vecchia, 1986b	327	327	Hospital	a,g	5.4	≤17 vs ≥23
Peters, 1986b	200	200	Neighborhood	a,b	16.1	<16 vs ≥23

<sup>1</sup>a = age, b = race, c = socioeconomic status or religion, d = country of origin or residence, e = marital status or age at marriage, f = age at first intercourse, g = number of sexual partners, h = Pap smear screening history, i = genital infection, j = menstrual and reproductive factors, k = smoking, l = contraceptive use, m = noncontraceptive hormone use, n = anthropometric or dietary factors, o = male partner characteristics, p = HPV.

<sup>2</sup>"Sexual stability" rather than number of sexual partners.

TABLE 50-6. Selected Case-Control Studies Assessing the Relation between Number of Sexual Partners and Invasive Cervical Cancer

Reference Year	No. of Cases	No. of Controls	Type of Controls	Adjustment Factors <sup>1</sup>	Relative Risk	Comparison Categories
Bosch, 1992	436	387	Population	a,c,d,g,h,j,p	5.6	≅6 vs 1
Brinton, 1987a	418	704	Community	a,c,f,h,i,j,k,l	2.8	≅10 vs 1
Ebeling, 1987	129	275	Hospital	f,h,i,j,k	3.9	≅5 vs 1
Eluf-Neto, 1994	199	225	Hospital	a,c,f,h,j,l,p	3.4	≅4 vs 1
Herrero, 1990b	759	1430	Hosp./Comm.	a,c,f,h,j,p	1.7	≅6 vs 1
Kjaer, 1992	59	614	Population	a,c,f,i,l	3.0	≅5 vs 0-1
La Vecchia, 1986b	327	327	Hospital	a,f	2.7	≅3 vs 0-1
Peters, 1986b	200	200	Neighborhood	a,b	2.6	≅10 vs 0-1

<sup>1</sup>a = age, b = race, c = socioeconomic status or religion, d = country of origin or residence, e = marital status or age at marriage, f = age at first intercourse, g = number of sexual partners, h = Pap smear screening history, i = genital infection, j = menstrual and reproductive factors, k = smoking, l = contraceptive use, m = non-contraceptive hormone use, n = anthropometric or dietary factors, o = male partner characteristics, p = HPV.

ies (Martin, 1967; Pridan and Lilienfeld, 1971; Rotkin, 1967; Terris et al, 1967) have shown that women with cervical cancer more frequently report multiple sexual partners than control subjects. Furthermore, within many data sets, risk appears to increase directly with the number of sexual partners reported. Selected recent studies are shown in Table 50-6.

When HPV infection is taken into account, the effect of lifetime number of partners is weakened but still apparent, especially in the HPV-negative group (Bosch et al, 1992; Eluf-Neto et al, 1994). This residual effect could reflect false-negative HPV testing of some cases or might indicate an independent role for other sexually transmitted agents. Age at first intercourse (or the correlated variable, age at first birth) also remains a weak risk factor even after HPV positivity is taken into account (Bosch et al, 1992; Eluf-Neto et al, 1994). Age at first intercourse might be viewed logically as a proxy for time of HPV infection; that is, the start of "latency." However, it might also suggest a "vulnerable period" of the cervix when the transforming effect of HPV is greatest.

In view of suggestions that the cervix may be more vulnerable at early ages, when the transformation zone is more exposed, the number of different sexual partners at specific ages has been of interest. Brinton and colleagues (1987a) and Herrero and colleagues (1990b) failed to find that number of partners before age 20 was more of a risk discriminator than lifetime number of partners, but Peters and colleagues (1986b) observed that the effect of lifetime number of partners was totally attributable to effects associated with number of sexual relationships before the age of 20. Peters and colleagues (1986b) also found some evidence that subjects with short intervals between menarche and initiation of sexual intercourse were at elevated risk (with associations stronger than those observed with age at first inter-

course alone), but this effect was not subsequently confirmed (Brinton et al, 1989a).

Most investigations have failed to note any effect of frequency of intercourse on risk after accounting for the effects of number of partners (Boyd and Doll, 1964; Brinton et al, 1987a; Herrero et al, 1990b; Jones et al, 1958; Martin, 1967; Rotkin, 1967; Terris et al, 1967). This would be concordant with the assumption that HPV is relatively easily transmitted during vaginal intercourse. In one of the few age-specific studies of frequency of intercourse and cervical cancer (Herrero et al, 1990b), high frequency was a significant risk factor only before age 20, supporting the notion of a vulnerable period.

The number of steady sexual partners (relationships lasting more than 3 months) was more related to risk of cervical cancer than the number of non-steady partners in the studies of Brinton and colleagues (1987a) and Herrero and colleagues (1990b). However, there are HPV data suggesting that the total lifetime number of sexual partners might be a better predictor of HPV infection than number of steady partners (Schiffman et al, 1993).

### Gynecologic and Obstetrical Events

There is little evidence that the risk of cervical cancer is affected by age at menarche, age at menopause, or character of menses (Boyd and Doll, 1964; Brinton et al, 1987a; Fasal et al, 1981; Jones et al, 1958; Rotkin, 1967; Wynder et al, 1954), or by hygiene factors (Brinton et al, 1987a; Herrero et al, 1990b).

Early reports suggested that poorly managed parturition may increase risk (Smith, 1931), but subsequent studies dismissed a true effect because of the presumed correlation of pregnancy with sexual activity. However,

several recent studies controlling for the separate effects of reproductive and sexual factors, including HPV infection, have found a persistent influence of multiparity (Brinton et al, 1987a; Brinton et al, 1989b; Kjaer et al, 1992; Parazzini et al, 1989).

In a Latin American study in which multiparity was commonly observed, the adjusted relative risk rose steadily to over 5 for those with 14 or more pregnancies, with effects relating primarily to live births rather than to short-term pregnancies (Brinton et al, 1989a). Two other recent studies in Latin America showed a relation of risk with multiparity independent of HPV infection (Bosch et al, 1992; Eluf-Neto et al, 1994).

It has been suggested that pregnancy could influence cell growth either directly or indirectly through immunologic or hormone-dependent influences on HPV (Pater et al, 1990). Although HPV detection rates may increase slightly during current pregnancies (Schneider et al, 1987; Hildesheim et al, 1993), the prevalence of HPV infection is not increased in multiparous women. Thus, whether there is any interaction between HPV and multiparity is unclear. Alternatively, the effect of pregnancy could reflect cervical trauma during parturition; this is supported by findings from two studies of reduced cervical cancer risk associated with a caesarean section (Brinton et al, 1989b; Bosch et al, 1992). Finally, nutritional effects of reproduction deserve attention.

### ***Characteristics of the Male Sexual Partner***

Despite extensive evidence implicating sexual factors in the etiology of cervical cancer, until recently there has been little attention given to a role of the male partner. Geographic clusters of cervical and penile cancers (Cartwright and Sinson, 1980; Li et al, 1982; MacGregor and Innes, 1980), as well as elevated rates of cervical cancer among the wives of men with penile cancer (Graham et al, 1979; Martinez, 1969; Smith et al, 1980), provided the first suspicion that a "male factor" might be important. This notion was supported by a follow-up study in which the wives of men previously married to cervical cancer patients were found to have elevated rates of cervical neoplasia compared to control wives (Kessler, 1977). Further interest in the role of a male factor derives from findings that some female populations exhibit high incidence rates of cervical cancer, despite traditions of having few sexual contacts—for example, many Latin American populations (Skegg et al, 1982).

Most recently, the role of the male in the etiology of cervical cancer has been examined by comparing the sexual and other behavioral characteristics of husbands of cervical cancer patients with husbands of control patients (Brinton et al, 1989c; Buckley et al, 1981; Kjaer et al, 1991; Niruthisard and Trisukosol, 1991; Pridan

and Lilienfeld, 1971; Zunzunegui et al, 1986). In all of these studies, the husbands of case patients were found to report significantly more sexual partners than husbands of control patients. In several of the studies, husbands of patients with cervical cancer were also more likely to report histories of various genital conditions, including venereal warts (caused by HPV types 6 and 11), gonorrhea, and herpes. Consistent with these associations was a low relative risk of cervical cancer when husbands reported frequent usage of condoms (Kjaer et al, 1991).

Of specific interest in these studies has been the relation of cervical cancer risk to the type of sexual activity engaged in by the husbands. Some studies (Buckley et al, 1981; Kjaer et al, 1991; Niruthisard and Trisukosol, 1991) have found visits by the male partners to prostitutes to relate to cervical cancer risk, but other studies have failed to confirm this association (Brinton et al, 1989c; Agarwal et al, 1993). This may relate to differences in types of prostitutes visited (eg, streetwalkers, house prostitutes, "cabaret entertainers"), since these groups have been found to differ in the prevalence of sexually transmitted diseases (Reeves and Quiroz, 1987).

Reliable prevalence estimates for genital HPV infections in males are more difficult to obtain than those for females. It appears from the available data that genital HPV infections are about equally common in both sexes, although the HPV-containing penile lesions are usually very subtle and difficult to detect (Barrasso et al, 1987; Barrasso, 1992; Bergman and Nalick, 1992).

Apart from HPV infection, poor hygiene of the male partner has been postulated to play a role in the etiology of cervical cancer, with special attention given to the effects of circumcision. Lilienfeld and Graham (1958) discussed the difficulties of defining circumcision status by interview, a problem confirmed in a recent study where there was limited agreement between interview and clinical reports (Brinton et al, 1989c). Despite several reports of a protective effect associated with circumcision of the partner (Agarwal et al, 1993; Kjaer et al, 1991; Terris and Oalman, 1960; Wynder et al, 1954), many other studies have shown no substantial differences between case and control husbands (Boyd and Doll, 1964; Brinton et al, 1989c; Jones et al, 1958; Rotkin, 1967). Studies with good clinical documentation of circumcision status and penile HPV infections are needed to address this issue further.

### ***Infectious Agents Other Than HPV***

Despite the evidence linking HPV to cervical cancer, it would be premature to conclude that HPV is the only agent involved. Of the other agents examined, most at-

tention has been focused on herpes simplex virus 2 (HSV-2) and chlamydia.

Laboratory studies have demonstrated that HSV-2 infection can transform cells in culture and that HSV-2 proteins and integrated DNA can be found in some cervical cancers (McDougall et al, 1986). Multiple serologic studies have observed higher prevalence of antibody to HSV-2, unadjusted for HPV, among cases of cervical neoplasia than controls (Adam et al, 1973; Jha et al, 1993). This association has been documented in many geographic areas, using various assay methods.

Research interest in the oncogenic potential of HSV-2 declined when HSV-2 DNA and protein were not detected consistently in tumors and when a large follow-up study of Czechoslovakian women failed to demonstrate a significantly increased risk of cervical neoplasia related to HSV-2 serology at enrollment (Vonka et al, 1984). It is possible that the serologic evidence of elevated exposure to HSV-2 among cases could represent an immunosuppressive effect of cancer or a noncausal association resulting from the correlation of HSV-2 with sexual activity and HPV infection. The association of HSV-2 with risk of cervical cancer has been weak and inconsistent when HPV infection has been taken into account (Hildesheim et al, 1991; de Sanjose et al, 1994).

Chlamydial cervicitis has been suspected to be a risk factor for cervical cancer, based on case-control comparisons of serology (Schachter et al, 1982) and of chlamydia-associated changes seen on stored cervical smears (Allerding et al, 1985). Again, however, the risk of cervical cancer associated with chlamydia seropositivity

has been inconsistent after adjusting for HPV infection (de Sanjose et al, 1994).

Additional infections that have been studied include syphilis, gonorrhea, cytomegalovirus, Epstein-Barr virus, and bacterial vaginosis. No consistent association with cervical cancer risk has been observed for any one of these agents. One investigation (Schmauz et al, 1989) but not another (de Sanjose et al, 1994) noted a rise in risk of cervical cancer with multiple, concurrent infections, consistent with the hypothesis that chronic cervicovaginal inflammation might increase the oncogenicity of HPV infection.

### Smoking

A correlation between the distribution of cervical cancer and other smoking-related cancers prompted Winkelstein (1977) to suggest that cigarette smoking may affect the risk of cervical cancer. A number of case-control studies (Table 50-7) and one cohort investigation (Greenberg et al, 1985) subsequently demonstrated excess risks of cervical cancer (and SIL) among smokers. A number of the investigations that were able to control for age at first intercourse, number of sexual partners, and/or social class found the associations with smoking to persist (Brinton et al, 1986b; Clarke et al, 1982; Harris et al, 1980; Hellberg et al, 1983; La Vecchia et al, 1986a; Lyon et al, 1983; Peters et al, 1986b; Slattery et al, 1989b; Trevathan et al, 1983).

In most studies not adjusted for HPV, the relative risks for smokers have been around twofold, with the

TABLE 50-7. Selected Case-Control Studies Assessing the Relation between Smoking and Invasive Cervical Cancer

Reference Year	No. of Cases	No. of Controls	Type of Controls	Adjustment Factors <sup>1</sup>	Relative Risk	Measure of Exposure
Baron, 1986	1174	2128	Hospital	a,e,j,n	1.8	≥15 pack-years
Bosch, 1992	436	387	Population	a,c,d,g,h,j,p	1.5	Ever smoked
Brinton, 1986b	480	797	Community	a,b,c,f,g,	2.4	≥40 cigs/day
Clarke, 1982	178	855	Neighborhood	a,c,f,g <sup>2</sup>	2.2	Current smokers
Daling, 1992	207	426	Random-digit dialing	a,d,g	3.1	Current ≥40 cigs/day
Eluf-Neto, 1994	157 <sup>3</sup>	32 <sup>3</sup>	Hospital	a,c,f,g,h,j,l,p	<1.0	Ever smoked
Herrero, 1989	667	1430	Hosp/Comm	a,g,n	1.5	≥40 years
LaVecchia, 1986a	230	230	Hospital	j,l	1.8	Current ≥15 cigs/day
Marshall, 1983	513	490	Hospital		1.6	Current smokers
Peng, 1991	101	146	Hospital	a,c,e,p	1.2	Ever smoked
Peters, 1986b	200	200	Neighborhood	a,b	3.7	≥20 cigs/day

<sup>1</sup>a = age, b = race, c = socioeconomic status or religion, d = country of origin or residence, e = marital status or age at marriage, f = age at first intercourse, g = number of sexual partners, h = Pap smear screening history, i = genital infection, j = menstrual and reproductive factors, k = smoking, l = contraceptive use, m = noncontraceptive hormone use, n = anthropometric or dietary factors, o = male partner characteristics, p = HPV.

<sup>2</sup>"Sexual stability" rather than number of sexual partners.

<sup>3</sup>HPV-positive subjects only; exact RR cannot be calculated from data presented.

highest risks generally observed for long-term or high-intensity smokers. In several studies, the smoking relation was restricted to current smokers; in one investigation, the effect was further limited to continuous smokers and those who started smoking later in life (Herrero et al, 1989). It is noteworthy that the smoking effect is restricted to squamous cell carcinoma, with no relation observed for the rarer occurrences of adenocarcinoma or adenosquamous carcinoma (Brinton et al, 1986b).

In the most definitive case-control studies of cervical cancer to date, taking HPV infection into account, the role of smoking has been practically null (Bosch et al, 1992; Eluf-Neto et al, 1994). These studies were conducted mainly in Latin America, where even crude smoking effects on cervical cancer are often weak. Perhaps the full influence of smoking on risk of cervical cancer could only be observed in regions where prolonged, heavy smoking among women is prevalent, such as in the United States.

Recently, several investigations have attempted to define possible mechanisms by which smoking might alter cervical epithelium. Smoking is not strongly associated with risk of cervical HPV infection once correlations with sexual behavior are taken into account (Hildesheim et al, 1993). However, several studies have demonstrated high rates of smoke-derived nicotine and cotinine in the cervical mucus of smokers (McCann et al, 1992; Sasson et al, 1985; Schiffman et al, 1987). The immunosuppressive effects of smoking (Barton et al, 1988; Phillips et al, 1985) could theoretically enhance the persistence of HPV infection (Burger et al, 1993; zur Hausen, 1982).

### **Oral Contraceptives**

Studies examining the relation between oral contraceptive use and cervical cancer risk are especially complex, with questions arising about the potential for confounding, particularly by sexual and screening behavior (Brinton et al, 1986a; Brinton et al, 1990; Brinton, 1991; Piper, 1985).

Because of limited information on potential confounding factors, prospective studies (Andolsek et al, 1983; Beral et al, 1988; Peritz et al, 1977; Vessey et al, 1983a) are difficult to interpret. In the study of Vessey and colleagues (1983a), the incidence of cervical neoplasia (preinvasive and invasive) rose from 0.9 per 1000 woman-years among those with up to 2 years of oral contraceptive use to 2.2 among those with more than 8 years' use. Of note in this prospective study, as well as another (Andolsek et al, 1983), was that all cases of invasive cancer occurred among oral contraceptive users. In the study of Beral and colleagues (1988), the incidence of cervical cancer after 10 years of use was

more than four times that of nonusers. It did not appear from a sub-study conducted by Vessey and colleagues (1983b) that oral contraceptive users were different in their sexual histories from the comparison group (IUD users). Swan and Brown (1981), however, concluded that the excess risk associated with long-term oral contraceptive use in their prospective study (Peritz et al, 1977) was likely to be highly confounded by sexual activity.

Results from recent case-control studies, mainly without consideration of HPV, are summarized in Table 50-8. Although several studies have noted no relation between oral contraceptives and cervical cancer risk, the majority of studies indicate that long-term users are at excess risk, even after adjustment for sexual and social factors. Studies showing no relation of risk to oral contraceptive use are generally those that have used neighborhood controls (Celentano et al, 1987; Peters et al, 1986b), which may reflect overmatching, or those that have included noninvasive abnormalities, presenting difficulties for interpretation because of possible detection biases (Coker et al, 1992; Irwin et al, 1988; Molina et al, 1988). In addition, the absence of an effect in several studies may merely reflect the limited number of long-term oral contraceptive users. In a recent, large study by the World Health Organization (1993), a risk of 2.2 was associated with contraceptive use of 8 or more years.

The effects of oral contraceptive use may be somewhat stronger for adenocarcinomas than for squamous cell neoplasms (Brinton et al, 1986a; Ursin et al, 1994), in line with descriptive surveys showing increasing rates of cervical adenocarcinoma among young women (Chilvers et al, 1987; Peters et al, 1986a; Schwartz and Weiss, 1986; Beral et al, 1994). In view of clinical studies suggesting that cervical adenocarcinoma may result from exogenous hormones (Chumas et al, 1985; Dallenbach-Hellweg, 1984), further investigation appears warranted.

Recent interest has focused on possible interactive effects of oral contraceptives and HPV, especially in view of studies showing that the transcriptional regulatory regions of HPV DNA contain hormone-recognition elements and that transformation of cells in vitro with viral DNA is enhanced by hormones (Auborn et al, 1991; Monsonogo et al, 1991; Pater et al, 1990). Oral contraceptive use has been only inconsistently associated with increased rates of HPV infection (Hildesheim et al, 1993; Lorincz et al, 1990; Ley et al, 1991; Moscicki et al, 1993). However, two recent studies found an especially elevated risk of invasive cervical cancer among HPV-positive women who used oral contraceptives (Bosch et al, 1992; Eluf-Neto et al, 1994). Perhaps oral contraceptive use promotes the activity of HPV once infection has occurred.

TABLE 50-8. Selected Case-Control Studies Assessing the Relation between Oral Contraceptives and Invasive Cervical Cancer

Reference Year	No. of Cases	No. of Controls	Type of Controls	Adjustment Factors <sup>1</sup>	Relative Risk	Measure of Exposure
Bosch, 1992	436	387	Population	a,c,d,g,h,j,p	1.3	Ever use
Brinton, 1986a	479	789	Community	a,b,c,f,g,h,i	1.8	≥10 years' use
Brinton, 1990	759	1430	Hosp/Comm	a,b,d,f,g,h,i,j	1.2	≥10 years' use
Celentano, 1987	153	153	Assorted	a,b,f,h,j,k	0.7	Ever use
Ebeling, 1987	129	275	Hospital	f,g,h,i,j,k	1.8	≥7 years' use
Eluf-Neto, 1994	199	225	Hospital	a,c,f,g,h,j,p	2.5	≥5 years' use
Irwin, 1988	149	764	Community	a,f,g,h,i,j	0.9	≥5 years' use
Kjaer, 1993	59	614	Population	a,g,h,i,j,l	1.3	≥6 years' use
Parazzini, 1990	367	323	Hospital	a,c,e,f,g,h,j,k,l	2.5	≥2 years' use
Peters, 1986b	200	200	Neighborhood	a,b	1.1	≥10 years' use
WHO, 1993	2361	13644	Hospital	a,d,h,j	2.2	>8 years' use

<sup>1</sup>a = age, b = race, c = socioeconomic status or religion, d = country of origin or residence, e = marital status or age at marriage, f = age at first intercourse, g = number of sexual partners, h = Pap smear screening history, i = genital infection, j = menstrual and reproductive factors, k = smoking, l = contraceptive use, m = noncontraceptive hormone use, n = anthropometric or dietary factors, o = male partner characteristics, p = HPV.

### Other Hormonal Contraceptives

Evidence linking oral contraceptives to cervical abnormalities has raised concern about long-acting steroid preparations, notably depot-medroxyprogesterone acetate (DMPA). Although these agents are widely used in many countries, studies evaluating their effects are limited. Two studies conducted in the United States (Powell and Seymour, 1971; Litt, 1975) have reported the prevalence of SIL to be elevated in DMPA users, but information on other risk factors was not available. A study in Chile (Dabancens et al, 1974), which was able to account for other factors, failed to find any effect on cervical neoplasia of either DMPA or chlormadinone acetate. Data from the WHO Collaborative Study of Neoplasia and Steroid Contraceptives also failed to confirm any significant relation (Thomas et al, 1989). However, a study from Latin America showed an approximate doubling of risk of invasive cervical cancer associated with use of injectable contraceptives for 5 or more years, with the risk particularly enhanced among women with limited screening histories (Herrero et al, 1990a). These findings support the need for further monitoring of cervical cancer risks among users of injectable contraceptives, taking HPV infection into account. Additional studies of HPV infection in the context of hormone replacement therapy and menopause are also indicated.

### Other Contraceptive Methods

In a number of studies, users of barrier methods of contraception (diaphragm and condom) were found to have

a low risk of cervical cancer (Boyce et al, 1977; Boyd and Doll, 1964; Fasal et al, 1981; Martin, 1967; Melamed et al, 1969; Terris and Oalman, 1960; Worth and Boyes, 1972). The apparent protective effect, however, has usually been small with limited information on other risk factors. The most convincing evidence derives from the Oxford-Family Planning Association Contraceptive Study (Wright et al, 1978) in which the incidence of cervical neoplasia (per 1000 woman-years of observation) was 0.17 among diaphragm users compared to 0.95 and 0.87 among oral contraceptive and IUD users, respectively. Because this difference could not be explained by other risk factors, it is plausible that the diaphragm (like the condom) may protect the cervix from venereally transmitted agents like HPV. It has also been suggested that part of the protection associated with diaphragm use may reflect concurrent use of spermicides, which have anti-viral properties (Hildesheim et al, 1990). However, the most common spermicide has no appreciable anti-HPV activity in vitro (Hermonat et al, 1992).

Several studies (Brinton et al, 1987a; Graham and Schotz, 1979; Peters et al, 1986b) have found frequent vaginal douching, especially with other than vinegar or water, associated with increased cervical cancer risk. If real, the douching association could possibly relate to local irritation or to the destruction of normal vaginal flora.

### Occupational Factors

Findings regarding the role of occupational factors in the etiology of cervical cancer have been limited to high

rates among prostitutes (Moghissi et al, 1968; Rojel, 1952), cleaners and food preparation workers (Savitz et al, 1995), and waitresses (Kjaerheim and Andersen, 1994), most likely reflecting the effects of correlated sexual behavior linked to HPV infection. Of note, the point prevalences of HPV DNA found in surveys of immunocompetent (HIV-uninfected) prostitutes have not necessarily been elevated (Kreiss et al, 1992), possibly suggesting immunity in some women following intense exposure.

Other occupational studies have centered on the male partner. Beral (1974) found a high rate of cervical cancer among spouses of men whose work necessitated prolonged absences from home, and postulated that male extramarital affairs might be responsible. Robinson (1982) proposed a more direct effect of the male occupation, with certain dusts, metals, chemicals, tar, or machine oils as possible risk factors for cervical cancer in the wives. Zakelj and colleagues (1984), however, found no support for this hypothesis when British cervical cancer mortality data were examined in relation to occupational classification.

### **Dietary Factors**

The influence of nutrient status on risk of cervical neoplasia has received substantial research attention (reviewed in Potischman, 1993). Most studies have utilized case-control approaches, assessing dietary intake or blood levels at the time of diagnosis, but some prospective studies have been completed. No study to date has taken HPV infection properly into account, and firm associations between nutritional status and HPV infection have yet to be found.

The majority of case-control studies have shown no relation between preformed vitamin A intake and either SIL or invasive disease (Brock et al, 1988; de Vet et al, 1991; Harris et al, 1986; La Vecchia et al, 1988). However, direct (topical) application of a vitamin A analogue to high-grade SIL in a randomized trial was shown to influence favorably the natural history (Meyskens et al, 1994), analogous to the dermatologic use of similar compounds to suppress flat facial warts.

In some studies, but not others, low dietary intake of carotenoids (provitamin A) has been found to increase the risk of SIL (Brock et al, 1988; Liu et al, 1993; Van Eenwyk et al, 1991; de Vet et al, 1991; La Vecchia et al, 1988; Ziegler et al, 1991) and cervical cancer (Herrero et al, 1991; La Vecchia et al, 1988; Marshall et al, 1983; Verreault et al, 1989; Slattery et al, 1990; Ziegler et al, 1990). Studies that have focused on blood carotenoids provide additional support for a protective effect of carotenoids on both SIL (Batieha et al, 1993; Brock et al, 1988; Harris et al, 1986; Palan et al, 1991; Van Eenwyk et al, 1991) and invasive cancer (Potischman et

al, 1991), although the studies are not entirely consistent (Cuzick et al, 1990). In a study of SIL that measured a variety of serum carotenoids, the component most strongly related to reduced risk was serum lycopene, with ambiguous findings for alpha-carotene, beta-carotene and cryptoxanthin (Van Eenwyk et al, 1991).

Vitamin C has been of interest because of its role in the healing process and its antioxidant function. Several studies of SIL have shown reduced risks associated with high plasma levels of ascorbic acid (Basu et al, 1991; Romney et al, 1985), a relation for which there is support from dietary intake data for both SIL (Liu et al, 1993; Van Eenwyk et al, 1991; Wassertheil-Smoller et al, 1981) and invasive cancer (Herrero et al, 1991). Two studies that showed no overall effect did observe a reduced risk associated with vitamin C intake among smokers (Slattery et al, 1990; Ziegler et al, 1990), suggesting that an antioxidant function might underlie the association.

Because vitamin E is poorly measured through dietary intake data, most studies have focused on blood measures. Prospective studies have shown either a weak protective effect of serum alpha-tocopherol levels (Knekt, 1988) or no effect (Batieha et al, 1993). Case-control studies support an effect for SIL (Cuzick et al, 1990; Palan et al, 1991) but not for invasive cancer (Potischman et al, 1991).

Folate deficiency has also been suggested as a cervical cancer risk factor on the basis of megaloblastic features in cervical cells of oral contraceptive users (Whitehead et al, 1973) and findings that folate supplementation among oral contraceptive users with SIL leads to marked cellular improvement (Butterworth et al, 1982). One case-control study supported an etiologic role for folates as a cofactor of HPV 16 (Butterworth et al, 1992a). However, a subsequent intervention trial by these same investigators failed to show that folate supplementation altered the clinical course of SIL (Butterworth et al, 1992b). Further, most epidemiological studies employing dietary questionnaires have shown no relation between estimated folate intake or folate-rich foods and either high-grade SIL (Brock et al, 1988; Ziegler et al, 1991) or invasive cervical cancer (Herrero et al, 1991; Ziegler et al, 1990). One recent study, however, did find higher rates of SIL linked with low dietary and serologic folate (Van Eenwyk et al, 1992). The folate hypothesis deserves further attention, especially since folate depletion, which occurs during pregnancy, has been hypothesized as a possible explanation for high cervical cancer risks associated with multiparity.

### **Genetics**

Little attention has been given to familial occurrences of cervical cancer, although some reports suggest that a

familial tendency exists (Bender et al, 1976; Brinton et al, 1987b; Furgyik et al, 1986). Whether this tendency reflects environmental or genetic factors is yet to be resolved.

Several investigators have observed associations of human leukocyte antigen (HLA) alleles or haplotypes with invasive cervical cancer. Most current interest is focused on genotypes of the HLA-D loci (Apple et al, 1994). However, none of the reported associations have been consistently observed, raising concern of a multiple comparison problem.

### **Immunosuppression**

Much of what is known about HPV immunology derives from small investigations of HPV infections in immunodeficient individuals (Evans and Mueller, 1990). Cervical SIL rates are elevated among immunosuppressed women with renal transplants (Hoover, 1977; Matas et al, 1975; Porreco et al, 1975), who are prone to a variety of genital infections, including HPV and HSV-2 (Matas et al, 1975; Schneider et al, 1983; Sillman et al, 1984). However, the excess risks observed among patients with renal transplants are complicated by close medical surveillance and difficulties in obtaining reliable expected values (Hoover, 1977).

HIV infection provides perhaps the most important example of the effect of immunosuppression on HPV infection. Individuals infected with HIV through sexual contacts are likely also to be exposed to genital HPV. However, the increased diagnosis of HPV in HIV-infected individuals is so striking that the increase is apparently real and related to immunosuppression. Specifically, HIV infection is associated with a very high prevalence of HPV DNA detection, especially in immunosuppressed women with low CD4 counts (Ho et al, 1994; Maiman et al, 1991; Vermund et al, 1991). In such women, SIL is very commonly diagnosed. It is not known whether HIV immunosuppression permits reactivation of previously suppressed HPV infection, as opposed to allowing rapid infection or reinfection.

Although the association between HIV infection, HPV infection, and SIL is established, a causal role for immunosuppression in the risk of progression of SIL to invasive carcinoma is less clear. Anal carcinoma rates are increasing in the homosexual male population, probably related to HIV infection (Palefsky et al, 1991). In contrast, cervical cancer rates are not greatly elevated in HIV-infected female cohorts, possibly reflecting more limited follow-up time (Cote et al, unpublished data). It is unclear whether HIV immunosuppression could speed the normally long progression from SIL to invasive carcinoma, or whether it mainly increases the prevalence and persistence of SIL precursors. Of note, a

mildly immunosuppressive retrovirus, HTLV-1, has recently been linked to an increased risk of high-grade SIL and cancer among HPV-infected women (Strickler et al, 1995).

Based on animal experiments and the immunosuppression data, it is assumed that the key immune response involved in the clearance of HPV infections is cell-mediated (Lancaster and Olson, 1982; Sundberg, 1987). The two classes of cells thought to be involved in the cellular immune response to HPV are antigen-presenting cells (Langerhans cells) and cytotoxic T lymphocytes (Crawford, 1993; McArdle and Muller, 1986).

### **Risk Factors by Cell Type**

The vast majority of cervical cancers are HPV-containing, squamous cell tumors, but some important exceptions should be mentioned. Adenocarcinomas are increasing in absolute and relative frequency in the United States, especially among younger women (Kjaer and Brinton, 1993). As a result, adenocarcinomas are approaching 15%–20% of cervical cancer cases in the United States.

Although the comparison of risk factors by cell type has received little attention, there is some evidence that cervical adenocarcinoma may resemble endometrial adenocarcinoma, particularly with respect to associations with nulliparity and obesity (Brinton et al, 1987b; Parazzini et al, 1988; Kjaer and Brinton, 1993). Since adenocarcinomas are more likely to contain HPV 18 than squamous carcinomas, HPV type may be a determinant of histologic type (Shroyer, 1993).

### **CONCEPTS OF PATHOGENESIS**

The multistep pathogenesis of cervical cancer is understood more fully than for most cancers. Greater knowledge of pathogenesis implies increased complexity for the epidemiologist, in that the epidemiology of invasive cancer now includes the natural history of its precursor lesions, starting with the transmission of cervical HPV infection.

#### ***The Transmission of Cervical HPV Infection***

The epidemiology of cervical HPV infections can be studied either on the molecular level (DNA detection) or the microscopic level (low-grade SIL). Cytologic diagnoses of low-grade SIL represent only about 10%–30% of molecularly detectable HPV infections, depending on the DNA test method. (Schiffman, 1992b) However, 30% of the women in whom molecular evidence of HPV infection is found, using a non-amplified test method, develop incident low-grade SIL within 4

years of viral detection (Schiffman et al, unpublished data). Thus, there is great overlap between microscopic and molecular diagnoses. This is logical because, from the point of view of the HPV life cycle, the atypical cells recognized microscopically as low-grade SIL are the production and assembly sites of new virions.

HPV infections are usually transmitted by person-to-person contact. Specifically, it is clear that cervical HPV infection is usually sexually transmitted (Fisher et al, 1991; Ley et al, 1991; Hildesheim et al, 1993). HPV infection of the cervix is rare in virgins (Fairley et al, 1992). The prevalence of cervical HPV DNA increases with reported numbers of different sexual partners, particularly recent partners because infection is often transient (Hildesheim et al, 1994).

Although proper transmission studies have not been done, it appears that genital HPV infections are transmitted rather easily between sexual partners. For example, the scant HPV DNA acquisition data suggest that among HPV-negative women, having new male sexual partners is associated with a high prevalence of cervical HPV (DNA) within months. Also, the age curve of cervical HPV prevalence, with a peak at ages 16–25, suggests that the transmission of HPV infection to the cervix occurs soon after the initiation of sexual intercourse (Schiffman, 1992b).

Although sexual transmission is the most important route, fomite transmission of HPV to the cervix appears theoretically possible based on findings of HPV DNA on underclothes and gynecologic equipment (Ferenczy et al, 1989; Ferenczy et al, 1990). Vertical transmission of genital types of HPV is certainly possible, although the frequency is unknown (Roman and Fife, 1986; Shah et al, 1986).

### ***The Descriptive Epidemiology of Cervical HPV Infection***

The cumulative lifetime probability of cervical infection with at least one type of HPV is extremely high for sexually active individuals (Schiffman, 1992b; Schneider et al, 1992). Because the typical detectable duration of HPV infection is short (less than 2–3 years), estimates of HPV incidence are similar to prevalence, but both grossly underestimate the cumulative incidence.

The HPV prevalence of a given population depends most strongly on the age and sexual practices of the population. Young sexually active women have the highest HPV prevalences (Fisher et al, 1991; Ley et al, 1991; Melkert et al, 1993; Moscicki et al, 1990; Rosenfeld et al, 1989). Although cervical HPV prevalence is highly influenced by age and sexual behavior (as well as diagnostic definition), estimates generally range from 1% to 3% based on screening diagnoses of low-grade SIL, 5% to 10% using non-amplified DNA tests, and

15% to 30% using PCR-based surveys. Published HPV DNA prevalences can range from 1% to nearly 100%, however, depending on the analytic sensitivity of the assay and the risk profile of the study group (Guerrero et al, 1992).

Most HPV prevalence studies, apart from case series of SIL and cancer, have not distinguished between the different genital HPV types. The many types of cervical HPV can only be distinguished at the molecular level. Based on scant data, HPV 16 is probably the most common type among normal women (2.4% of cytologically normal women in one large series) (Schiffman, 1994). Most of the still uncharacterized types of HPV are found among normal women and probably have virtually no oncogenic potential. Among infected women, the proportion with multiple infections typically approaches 20%–30% using PCR (Bauer et al, 1993).

As mentioned, the prevalence of cervical HPV infection declines sharply with age, from a peak prevalence at 16–25 years of age (Schiffman, 1992b). This age trend is seen for both HPV DNA detection and low-grade SIL in parallel. The very high prevalence of HPV in young, sexually active women is consistent with an “epidemic curve,” a rapid rise in prevalence following first (sexual) exposure. The subsequent profound drop in cervical HPV prevalence in women over 30 might be due to immunologic clearance or suppression of existing infections, combined with less exposure to new HPV types because of fewer new sexual partners. The decrease in HPV prevalence with age might also be due partly to a “cohort effect,” with an increase over time in the amount of cervical HPV infection among young female populations. Both the immunologic and cohort explanations for the decrease in cervical infection rates with age have scientific support (Schiffman and Burk, in press).

### ***Progression to High-Grade SIL***

Most HPV infections disappear within months to a few years after diagnosis. This is true for infections detected only by HPV DNA tests (Hildesheim et al, 1994) and for low-grade SIL, which tends to regress to cytologic normalcy. Uncommonly, however, HPV infections progress to high-grade SIL. The absolute risk of progression from low-grade to high-grade SIL is about 15%–25% over 2–4 years.

The prospective data generating the estimates of progression rates from low-grade to high-grade SIL are somewhat conflicting because of different diagnostic terminology and study methods (eg, cytologic versus histologic definitions of low-grade disease at enrollment). For example, in a 1–3 year study, Richart and Baron (1969) found a progression rate of 20.3% from

what they termed "mild" to severe dysplasia. Using different pathologic criteria more akin to current terminology, Nasiell and colleagues (1986) observed that only 16% of 555 women with CIN 1 progressed to CIN 3 or invasive cancer ( $n = 2$ ), despite a longer median observation period of 4 years. A recent British study documented a 35% rate of progression to CIN 3 over 1–2 years among 538 women with mild "dyskaryosis," a slightly more severe start point than low-grade SIL (Flannelly et al, 1994). Whichever estimates of absolute risk are accepted, women with low-grade SIL are at a substantially (over 16-fold) increased risk of developing high-grade SIL and invasive cervical cancer, compared with women with normal cytologic diagnoses (Soutter and Fletcher, 1994).

Nonetheless, the overall incidence of high-grade SIL is much less than 1% in most cervical cytologic screening series, at least in the United States. When divided, CIN 2 and CIN 3 are typically about equally diagnosed. The low prevalence of high-grade SIL compared with low-grade SIL is not as pronounced in regions with deficient cervical cancer screening and treatment, where high-grade lesions can develop and accumulate.

The three kinds of risk factors postulated to influence the risk of progression to high-grade SIL are the same as the established risk factors for cervical cancer: viral factors, host factors, and environmental cofactors.

With regard to viral factors, the most obvious is HPV type. Among women with low-grade SIL, the cancer-associated types of HPV (about two thirds of infections) predict a higher risk of progression than either the non-cancer-associated types or HPV negativity (Kataja et al, 1990; Campion et al, 1986). Apart from viral type, it appears from cross-sectional analyses that high levels of HPV DNA are closely linked to high-grade SIL (Morrison et al, 1991; Cuzick et al, 1992). Time since first infection may also be important (Munoz et al, 1993), because the degree of nuclear atypia may increase with the duration of infection (zur Hausen, 1994).

The most important host factors related to progression from low-grade to high-grade SIL are probably immunologic. Another host factor could be parity, which might act by influencing immunity or by hormonal, nutritional, or traumatic mechanisms (Munoz et al, 1993). Age has not been shown to be a strong predictor of risk of progression to high-grade SIL, once the severity of the initial diagnosis is taken into account (Nasiell et al, 1986).

The most likely environmental cofactors for the development of high-grade SIL are the established risk factors for cervical cancer that do not appear to be mere proxies for HPV infection. A role for smoking has some epidemiological support (Schiffman et al, 1993), but smoking has not been found to be associated with the development of high-grade SIL in a few recent, well-

designed studies (Koutsky et al, 1992; Munoz et al, 1993). Other possible cofactors for the development of high-grade SIL include multiparity (Munoz et al, 1993), oral contraceptive use (Schiffman et al, 1993), deficiencies of folate, carotenoids, retinoids, or vitamin C (Butterworth et al, 1992a), and concurrent infection with other sexually transmitted agents such as chlamydia (Koutsky et al, 1992; de Sanjose et al, 1994).

It is unclear whether all cases of cervical cancer pass through each stage of the preinvasive continuum. For example, some cases of high-grade SIL arise in HPV-infected women within 1–2 years, without an appreciable intervening diagnosis of low-grade SIL (Koutsky et al, 1992), or adjacent to rather than arising directly from low-grade lesions (Kiviat et al, 1992). However, along with cohort studies, some "ecologic" support for a continuum of disease is provided by the observation that HPV infection and low-grade SIL are usually diagnosed among women in their late teens and early 20s, high-grade SIL in 25–35-year-olds, and invasive cancer after the age of 35–40 years.

### **High-Grade SIL to Invasive Cancer**

The invasive potential of high-grade SIL (particularly carcinoma in situ) is very high, and women with high-grade SIL are less likely to regress than those with low-grade SIL. Peterson (1956) noted a 33% progression rate after 9 years among 127 women with untreated carcinoma in situ. Longer follow-up would presumably have led to even higher progression rates, given that regression of carcinoma in situ is not typical (Kinlen and Spriggs, 1978).

No risk factors have been found in case-control studies to distinguish invasive cancer from high-grade SIL, with the sole exception of age. Women with invasive cancer are 10 or more years older on average than women with high-grade SIL (Devesa et al, 1984). It may be that invasion is related to molecular events (eg, integration of HPV DNA into the host genome) that occur with low, nearly random frequency in the setting of persistent high-grade SIL.

## **PREVENTIVE MEASURES**

### ***The Papanicolaou (Pap) Smear***

Because of the continuum of cervical neoplasia, there is little doubt that exfoliative cytology (the Pap smear), used to detect treatable cervical cancer precursors, can have profound effects on incidence and mortality. The eradication of precursor lesions has resulted in significant declines in cervical cancer rates in areas where screening has been widespread and prolonged, such as

Kentucky (Christopherson et al, 1970) and British Columbia (Boyes, 1981). In contrast, the rates for cervical cancer have not declined in regions or countries with limited screening programs (Hill, 1975).

A number of case-control studies have evaluated the role of Pap smear screening in preventing invasive cervical cancer. Clarke and Anderson (1979) found a relative risk of 0.37 associated with screening within the past 5 years; La Vecchia and colleagues (1984) found a risk of 0.18 if the patient had been screened within 3–5 years. In a Finnish study, even patients who had been screened more than 5 years previously had a relative risk of 0.67 compared to those who had never been screened (Olesen, 1988).

Although there is little doubt that cytology is an effective means of preventing cervical cancer, there is still extensive debate regarding the optimal interval of population-screening efforts. The American Cancer Society currently recommends that all women who are, or who have been, sexually active, or have reached 18 years of age, have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician (Fink, 1988).

### ***Ancillary Screening Methods***

Because Pap smear screening is imperfect and not feasible in many resource-poor countries, refinements of the Pap smear or ancillary screening methods are continually being proposed. Screening methods can be categorized as clinical (visual), microscopic, or molecular.

Clinical screening denotes the detection of cervical lesions by inspection, sometimes aided by a magnifying eyepiece and tissue stains. In some very poor regions, clinical inspection may be the only currently affordable strategy, although it is not accurate. A currently promising clinical screening test is cervicography, which relies on photography of the cervix after staining with acetic acid to highlight visible abnormalities. The resultant images are magnified by projection onto a screen and read by experts, a procedure analogous to radiology. Cervicography is especially useful in detecting high-grade SIL and cancer, but its detection of low-grade SIL tends to have low specificity.

The Pap smear continues to be the major microscopic technique. Promising refinements now under evaluation are (1) new cell collection instruments designed to improve sampling of the cervical transformation zone, (2) transport of cell specimens in liquid media permitting automation of slide preparation, and (3) computer-assisted screening or rescreening of smears.

On the molecular level, HPV testing can be used to

clarify and triage inconclusive Pap smear diagnoses (Cox et al, 1992; Schiffman and Sherman, 1994; Sherman et al, 1994). The borderline between normal and abnormal (SIL) cervical cytologic diagnoses has never been clear, as indicated by the plethora of uninformative terms such as "Class 2 Pap" or "atypia," which can account for up to 10% or more of diagnoses in some centers. HPV testing can be used as an independent reference standard for improving the diagnosis of equivocal smears in cytopathology laboratories.

More data are needed to establish whether HPV testing can be useful in two other important and theoretically appealing applications: general screening of older women and triage of low-grade SIL. HPV screening at older ages could be used to supplement Pap smears as a means of defining women at high risk (Melkert et al, 1993; Morrison et al, 1991). Because HPV DNA prevalence in cytologically normal women declines sharply with age, while HPV prevalence in women with cervical neoplasia remains very high regardless of age, the positive predictive value of finding HPV DNA rises with age (Morrison et al, 1991). Moreover, the use and accuracy of the Pap smear decline with age, due to inadequate sampling of receding transformation zones (false negatives) and overdiagnosis of atrophy-related changes (false positives). Thus, HPV detection and typing in older women might define a small subset of patients who remain at appreciable risk and could benefit from closer surveillance. Older women who are cytologically normal and have a negative HPV DNA test might be at very low risk for the development of cervical cancer and could be screened infrequently.

The diagnosis of low-grade SIL, by cytology or histology, is a poor marker of risk for the development of cervical cancer, because progression to invasive carcinoma is rare, even in untreated women. Many lesions regress spontaneously within months of detection. Colposcopically directed biopsy and ablation of all low-grade SIL represents possible overtreatment, with high costs and some associated morbidity. Natural history studies indicate that lesions associated with cancer-associated types of HPV are the most likely to progress (Campion et al, 1986; Kataja et al, 1990). A prospective clinical trial is needed to determine whether testing patients with low-grade SIL for both HPV type and a measure of viral load could result in safe and cost-effective clinical management, reducing the morbidity that can result from treatment. Cervicography might also be useful for this purpose.

### ***Prevention of HPV Transmission***

Prevention of transmission of HPV infections appears to be nearly unachievable, given current patterns of sex-

ual activity. The exception may be that genital HPV transmission might be reduced by condom use, although this has not been proven. Condom use cannot entirely prevent the spread of genital HPV infections, because genital HPV infections in the male are not limited to the penile skin. Viral spread from scrotal and perineal lesions cannot be prevented by condom use, although it appears that these sites of infection are uncommon compared to lesions on the glans, foreskin, urethral meatus, or shaft (Rosemberg, 1991).

## FUTURE RESEARCH

Multidisciplinary teams of investigators are attempting to piece together a coherent picture of HPV natural history and cervical carcinogenesis. Through large investigations that focus on increasing grades of neoplasia and time-related exposures, the multistage processes involved in tumor development and progression can be examined and factors that promote or inhibit transition to higher grades can be clarified.

Active areas of research include (1) validating reliable and inexpensive HPV test methods, to permit larger studies than are possible using intensive research techniques; (2) defining the epidemiology of HPV infection as a sexually transmitted disease, particularly the distribution of the different cancer-associated HPV types and the risk factors for transmission; (3) clarifying prospectively the natural history of HPV infections, focusing on viral persistence, disappearance, and latency; and (4) defining cofactors that may interact with HPV in the development of high-grade SIL and cancer.

The search for important HPV cofactors for high-grade SIL and cancer is likely to dominate future epidemiological research on cervical cancer. Although HPV infection explains much of what is known about classic risk factors for cervical neoplasia, particularly its venereal transmission, we still know little about potential cofactors. Therefore, even if HPV infection is the unifying, central risk factor for cervical neoplasia throughout the world, it is worth considering that necessary cofactors could vary considerably across different geographic regions. Smoking, for example, might be a cofactor in the United States, but as studies in Latin America have already demonstrated, it is unlikely to explain the occurrence of cervical cancer where heavy smoking among women is rare.

The importance of HPV persistence in the pathogenesis of high-grade SIL and cancer must be verified, and the determinants of persistence identified. If carcinomas arise only from persistent infections, not from molecularly inapparent ("latent") infections that suddenly reactivate, then prevention of carcinomas should be

achievable by screening for virus at ages preceding the usual onset of carcinoma. The study of HPV persistence requires repeated measurements and extremely reliable HPV testing. It will be necessary to distinguish variants of HPV types (Chan et al, 1992) to permit, for example, the distinction of new HPV 16 infections from recurrent ones.

Through continued descriptive analyses and cohort studies, the decrease in cervical HPV infection rates with increasing age should be better understood. The separate contributions to the age trend of cohort effects and immunologic suppression must be distinguished because any cohort effect of increasing HPV infection in currently younger women might predict further increases in invasive cervical cancer in the future.

Although the study of cervical neoplasia is now inextricably linked to HPV infection, it will be important to define separately the epidemiology of the minority (15% or less) of cervical cancers that do not contain HPV-related DNA. It is possible that unknown HPV types may account for some of these tumors, but recent molecular studies have suggested that HPV-negative cancers may be an etiologically distinct group, perhaps associated with somatic mutations in tumor suppressor genes (Scheffner et al, 1991). Moreover, HPV-negative cervical cancer might have a worse prognosis (Riou et al, 1990; Higgins et al, 1991; de Britton et al, 1993). If cervical cancer can arise, albeit rarely, from precursor lesions not associated with HPV infection, the morphologic appearance and natural history of those precursor lesions must be defined. Also needed are studies to define hormonal and other risk factors for the rarely occurring adenocarcinomas and adenosquamous carcinomas of the cervix, whose epidemiology is poorly understood.

It will be important to verify or exclude the role of HPV in carcinomas of other sites. The natural history of HPV infection in the cervix should be compared to its natural history in the vagina, vulva, and anus. In particular, why the transformation zone of the cervix is so prone to HPV carcinogenesis should be addressed.

As the highest priority, HPV immunology is likely to occupy epidemiologists studying cervical cancer etiology and prevention over the next decade. In the immediate future, the interactions of multiple HPV types in mixed cervical infections should be clarified, as one pathway to understanding HPV immunity. Assays of cell-mediated immunity must be developed and applied. The ultimate goal will be to define the successful immune response to HPV infection, in the hope that cancer-preventive immunity can be stimulated by vaccination (Crawford, 1993).

Because HPV is a central cause of most cervical neoplasia, it is reasonable to consider HPV immunization as the ultimate primary preventive strategy for elimi-

nating most cervical cancer. The protection of cattle herds from bovine papillomavirus infection by vaccination serves as a successful animal model (Campo et al, 1993). Use of the hepatitis B vaccine in Asia to reduce the incidence of hepatocellular carcinoma may serve as a public health model.

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