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Perspective on Cervical Cancer: Why Prevent?

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Abstract Cervical carcinoma (CC) remains a significant health problem in the United States (U.S.) despite the progressive fall in the mortality rate during the past 60 years. However, CC is still the most common cancer among women worldwide and the leading cancer cause of death in many countries. In the U.S., the current age-adjusted incidence of CC is about 8 per 100,000 population, which compares to 54.6 in Peru and 4.2 in Israel. The lifetime risk for acquiring CC in the U.S. is about 1%, while the lifetime risk in Peru is more than 5 times greater. Recently some industrialized countries have reported a 2–3-fold increase in the death rate from CC among women less than 35 years of age. The primary strategy to reduce the incidence and death rate from CC is screening by cervical cytology.

Because of the high incidence of CC precursor lesions, as well as the lack of specificity and sensitivity, CC screening has proven very costly. Nevertheless, in countries or regions where such screening has been repetitive and comprehensive, the mortality rate from CC has been reduced up to 80%, with most cases of CC occurring in non-compliant patients. The decrease in mortality results from detection of invasive cancer at an earlier, and therefore more curable stage, as well as detection and treatment of precursors which prevent the development of invasive carcinoma. Because the strategy involves detection of cancer precursors, the rate of abnormal Pap smears and the number of women requiring medical intervention is many times higher than the CC rate. The age-adjusted incidence of carcinoma *in situ* is reported to be 3–5-fold that of invasive cervical cancers. The age-adjusted incidence of all dysplasias is unknown, but it is reported that more than half (perhaps up to 90%) of mild and moderate dysplasias regress spontaneously. Considering that there are 15,000 cases of invasive cervical cancer diagnosed in the U.S. annually, cytologic screening involves the diagnosis and treatment of 750,000 or more women each year for precursor lesions. The impact of CC on the patient and society, as well as the role of other strategies for early diagnosis and prevention, will be briefly reviewed.

Key Words: Cervical cancer, prevention, screening

OVERVIEW OF THE CERVICAL CANCER PROBLEM

Cervical carcinoma (CC) is the most common malignancy (excluding non-melanotic skin cancers) among women in developing countries [1] and the third most common malignancy of the female genital tract in the U.S. [2,3]. During the last decade an estimated 465,000 new cases of invasive CC were diagnosed each year and more than 200,000 deaths occurred annually worldwide [4]. In the U.S. there are approximately 13,500 new cases of invasive CC and 4,400 deaths annually [2,3]. Within the U.S., incidence varies from group to group. There has been a consistent two-fold difference between Black and White women, (7.9 versus 14.3 per 100,000 person-years, respectively, during the years 1986–

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1990), although both incidence and mortality from cancer of the cervix have decreased in both groups since 1973 [2]. International incidence rates of invasive CC vary tremendously from 4.2 per 100,000 among Israeli Jewish women to 54.6 per 100,000 among women in Trujillo, Peru [1] (Fig. 1). This translates into a cumulative incidence of 0.43, 0.73, 1.23, and 5.84% for Israeli, U.S. White, U.S. Black, and Peruvian women, respectively, for invasive CC over a lifetime of 75 years [1]. There is geographic variation in mortality rates as well, ranging from 1.0 per 100,000 in Israel to 12.8 per 100,000 in Jamaica [5].

Observed geographic variation in incidence and mortality is due in part to differences in access to screening, since detection and treatment of precursors by the Papanicolaou (Pap) smear greatly reduces the risk of invasive CC. In fact, the age-adjusted incidence of carcinoma *in situ* (CIS), detected by the Pap smear and thought to be the immediate precursor of invasive cervical cancer, is reported to be 3–7-fold that of invasive cervical cancer [6,7]. In addition, detection at an *early stage* greatly reduces the risk of mortality; five-year survival rates for locally invasive CC are in excess of 80% compared to 30–35% for Stage III cancer [8]. The age-adjusted incidence of all dysplasias is unknown, but it is reported that more than half, perhaps up to 90%, of mild and moderate dysplasias regress spontaneously [9, 10].

TABLE I. Estimated New Cancer Cases and Deaths in the United States [3]

	New Cases	Deaths
Breast	182,000	46,000
GI	110,200	56,900
Respiratory	76,200	60,300
Genital	75,300	25,200
Corpus	(31,000)	(5,900)
Ovary	(24,000)	(13,600)
Cervix	(15,000)	(4,600)
Other	(5,300)	(1,100)
GU	23,800	8,100

TABLE II. Five-Year Survival Trends for Cancer of the Cervix in the United States [3]

Year	White	Black
1960–1963	73%	31%
1970–1973	81%	44%
1974–1976	89%	60%
1977–1979	86%	58%
1983–1989	85%	56%*

*$p < 0.05$ versus 1974–1976

CURRENT STATUS OF CERVICAL CANCER TREATMENT

The overall curability of cervical carcinoma is approximately 65% in developed countries, ranging from 85% for Stage I cases to 35% or less for Stage III cases. Treatment in early stages involves either radical hysterectomy or radiation therapy; more advanced stages are typically treated by irradiation, with or without radiation sensitizers. Treatment and recovery time averages six months, although many patients suffer chronically from mild to moderate urinary and bowel dysfunction. Treatment for cervical cancer almost invariably results in sterilization and, especially in the more advanced cases, vaginal stenosis which commonly produces a reduced or total incapacity for sexual intercourse. An occasional patient ends up with a permanent colostomy or urinary diversion. The clinical course of patients whose disease is not cured is often characterized by palliative surgery, irradiation or chemotherapy, and ultimately progressive pain, anorexia, wasting, and narcotic dependency.

Except for a small minority of patients, progress in the curability of cervical cancer has been at a standstill since the introduction of megavoltage radiation therapy in the early 1950s (Table II). All of the subsequent technological advances, including high dose rate therapy, treatment planning, new isotopes, new imaging techniques, and new machines, have had no clinically measurable effect on the curability of cervical cancer. Furthermore, there is no reason to believe that any breakthrough in the treatment of

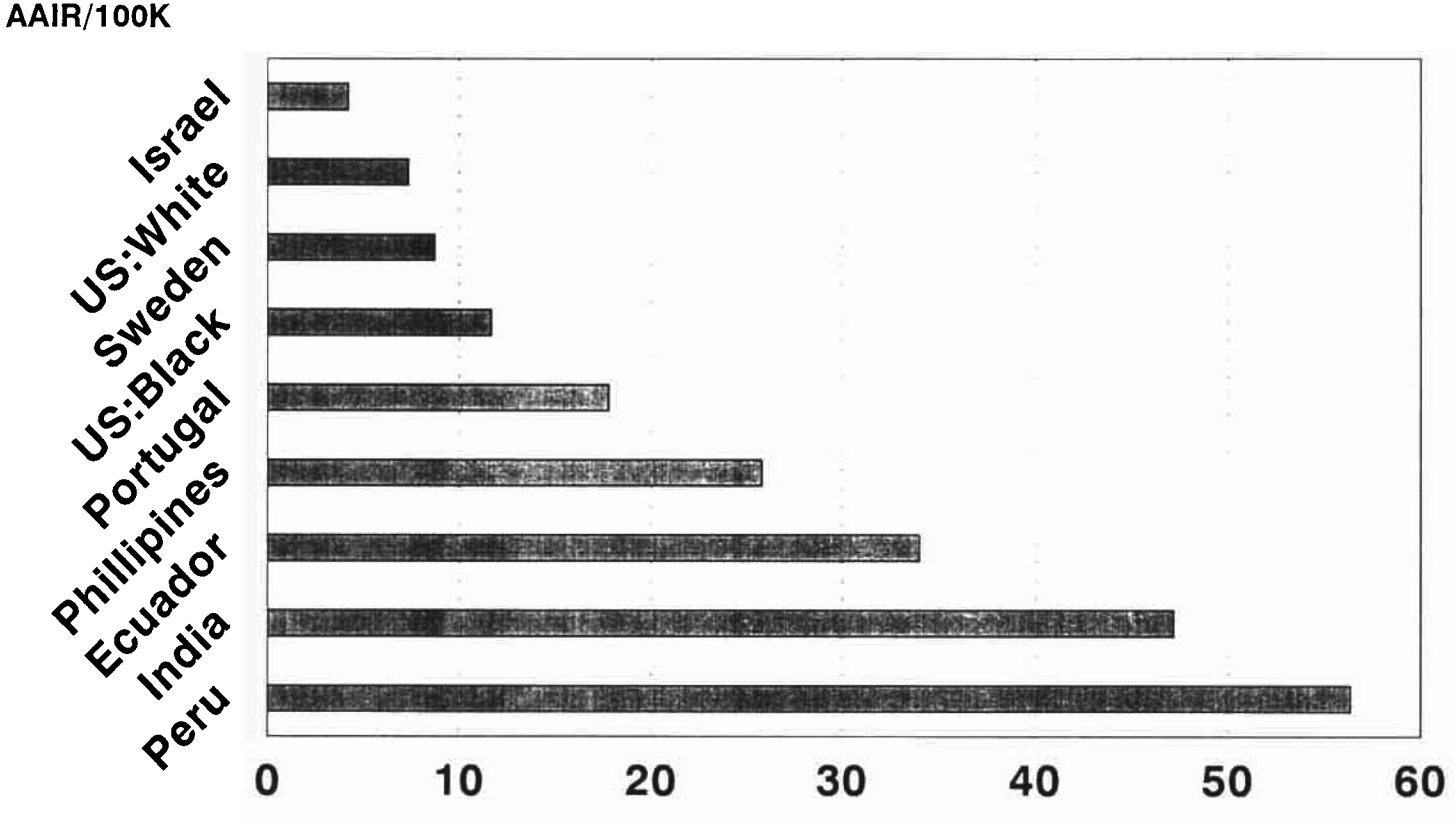

Fig. 1. Age-adjusted incidence of invasive cervical carcinoma by country, 1983–1987 [1].

cervical cancer will occur in our lifetime. In fact, with the emphasis in medicine turning toward cost containment, diagnostic and treatment advances of marginal clinical value will fall into disuse. Thus, only in communities and countries where women with cervical cancer do not currently have access to conventional medical care does cervical cancer therapy have any prospect for substantially reducing cervical cancer mortality.

CURRENT STATUS OF CERVICAL CANCER SCREENING AND DETECTION

Results

Cervical cancer is the only malignancy for which a suitable population-based screening technique is available that effectively detects not only the malignancy but also its precursors. This screening technique, cervical cytology, is the primary strategy employed world-wide to reduce the incidence of and death rate from CC. In the U.S. and many European countries, cervical cytology has been widely used since the 1960s. Countries and regions where such screening has been repetitive and comprehensive uniformly report a CC mortality rate decrease of up to 80%, with most cases occurring in non-compliant or underscreened patients [11]. In the five Nordic countries, cervical cancer screening has been highest in Iceland and lowest in Norway (Table III). Compliance of the targeted populations has been 70–80% in all five countries. The fall in the CC mortality rate ranges from 80% in Iceland to 10% in Norway and closely correlates with the fraction of the total population targeted for screening [12]. As expected, not only the mortality rate but also the incidence of cervical cancer declines in populations subjected to screening by cervical cytology. In Sweden [7] the age-adjusted incidence of invasive cervical cancer dropped progressively from 25 per 100,000 women in 1965 to 12 per 100,000 women in 1980 (Fig. 2). In the 40–44 year age group, which had the highest incidence of cervical cancer, the case rate dropped from over 70 to 12.3 (Fig. 3). In comparison, the age-adjusted incidence or detection rate of CIS rose rapidly from 20 to 100 cases per 100,000 women during 1964–1968, undoubtedly reflecting increased screening, and then stabilized at about 90 until 1980, the end of the study period (Fig. 4). Thus, the ratio of *in situ* to invasive cases in this study population is about 7.5.

The drop in mortality rates associated with cervical cancer screening is not entirely from detection and treatment of precursor lesions, but also from detection of invasive cancer at an earlier, more curable stage (Table IV). This is shown by Olesen [13] who reported that in Denmark, 56% of patients with invasive cervical cancer had never been screened. Among these, 42% were diagnosed at Stage I. Of the study patients with invasive cervical cancer who had only been screened once (19%), 61% were diagnosed at Stage I; 81% of study patients with cervical cancer who had been screened two or more times (25%) were diagnosed at Stage I.

TABLE III. Cervical Cancer Mortality and Screening [12]

	Denmark	Finland	Iceland	Norway	Sweden
Population age	30–50	30–55	25–69	25–60	30–49
Screened (%)	40	100	100	5	100
Compliance (%)	80	75	80	70	70
Interval (yr)	3	5	2–3	2–3	4
Year begun	1980	1970	1969	1960	1973
Reduction in mortality (%) (1965–1982)	40	50	80	25	50

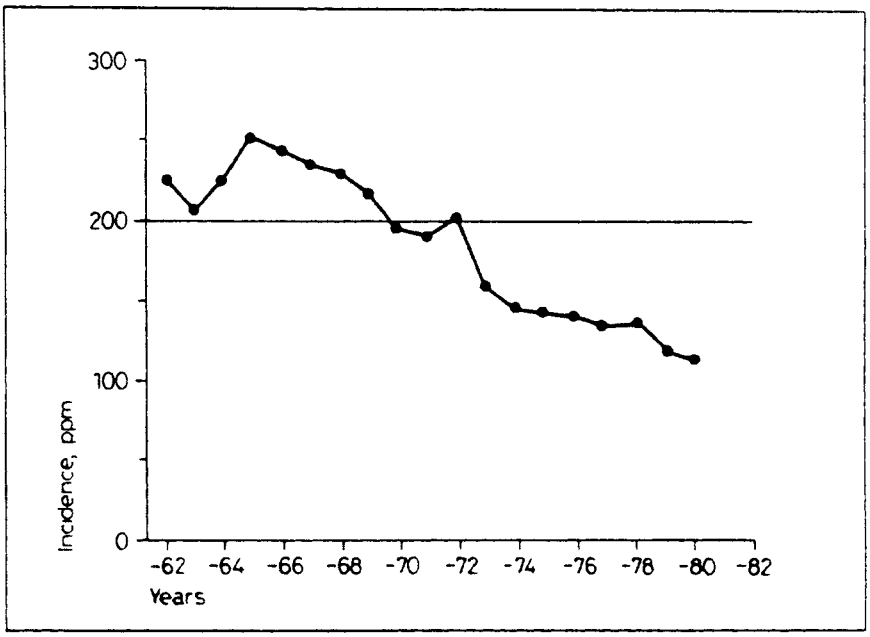

Fig. 2. Age-adjusted incidence of cancer of the cervix in Sweden, 1962–1980 [7].

Fig. 3. Incidence of cancer of the cervix in Sweden in the 40–44 year age group, 1962–1980 [7].

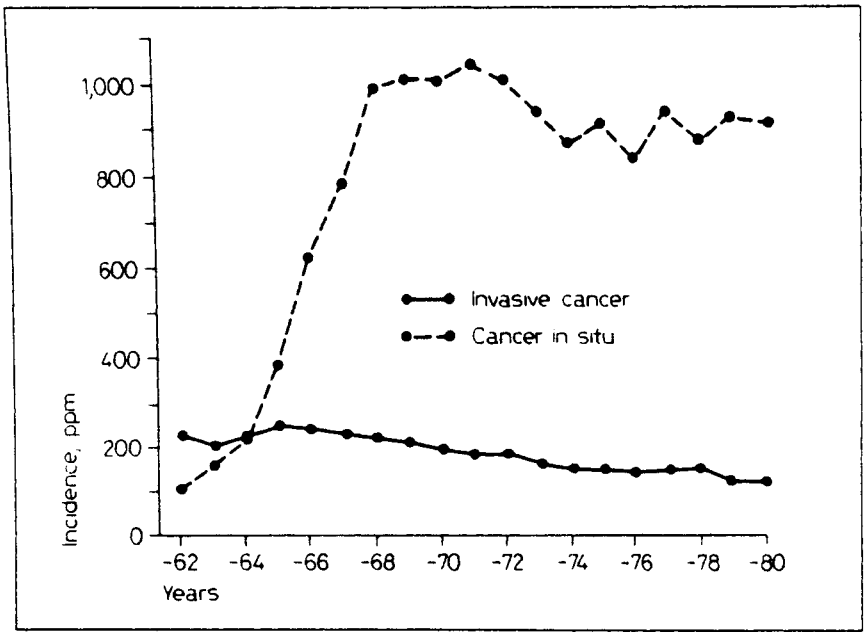

Fig. 4. Incidence of invasive cervical cancer and CIS in Sweden, 1962–1980 [7].

TABLE IV. Relationship of Cytologic Screening to Cervical Cancer Stage [13]

Prior Pap Smears	Cases in Stage I (%)	% of All Invasive Cervical Cancers
None	42	56
1	61	19
≥ 2	81	25

Problems With Cytologic Screening

The initial high expectations that cytologic screening would all but eliminate cervical cancer have long since abated. The major reasons screening has fallen short of its potential are the high incidence of cervical cancer precursors, the logistics of repetitive screening a large at-risk population, the financial burden of screening-based prevention, and its failure to be comprehensively applied to the populations at risk, either because of cost, patient ignorance, or noncompliance. Furthermore, cytologic screening suffers from suboptimal specificity and sensitivity, reported to range from 60–90% [14,15].

The major problems with the Pap screening system are the logistics and expense of getting a large at-risk population screened at the recommended minimum interval of three years. Currently in the U.S., it is estimated that 50 million Pap smears are performed annually, of which up to 5% have a cytologic abnormality designated atypical squamous cell of uncertain significance, but frequently associated with dysplasia [16]. A detailed look at Pap screening problems uses calculations of national rates based on the results of a Kaiser Hospital screening study. From a study sample of 11,061 women, the rate of abnormal smears, including high-grade and low-grade squamous lesions, was 28.4 per 1,000 patients, or 2.84%. Extrapolating the Kaiser data to the U.S. population based on the estimated 50 million Pap smears per year, the number of abnormal Pap smears, *i.e.* mild, moderate, severe dysplasia and HPV, equals 1.42 million (Table V). Under the dictates of contemporary clinical practice, most patients with these abnormal smears will undergo repeat Pap smear and colposcopy. This is not unreasonable considering

TABLE V. Annualized Frequency of Abnormal Pap Smears and Cervical Pathology in the U.S.

	Rates	Annual Total
Abnormal Pap Smear Rate	28 per 1000	1,420,000
Abnormal Pathology	55%	785,000
Low-grade squamous intraepithelial lesion	41%	585,000
High-grade squamous intraepithelial lesion	14%	200,000

* [Based on Kaiser Hospital and NCI data, 16, 23]

TABLE VI. Estimated Annual Cost of Pap Screening in U.S.

Item	No.	Unit Cost ($)	Total Cost ($)
Pap Smears	50 million	50	2.5 billion
Repeat Pap	1.5 million	100	0.150
Colpo, Biopsy	750,000	300	0.225
Cone/Leep	375,000	1,000	0.375
Total			**3.25 billion**

that abnormal pathology was found in 55% of the Kaiser patients, 14% high-grade squamous intraepithelial lesions (SIL) and 41% low-grade SIL. Thus, the cervical conization rate and the overall cost of evaluating patients with an abnormal Pap smear is expected to be quite high (Table VI). The optimal method of managing these patients has not been determined, and it is possible that more conservative means than currently employed will be sufficiently effective. However, a more conservative approach is not likely under the present medical-legal system, since reducing the intensity of screening and thoroughness of evaluation will inevitably lead to failed diagnosis and litigation, however small the rate may be.

Improving Cytologic Screening

Some improvement in the effectiveness of cytologic screening for cervical cancer can be gained by educating women with respect to the importance of screening, and of early symptoms. While some women may be ignorant of their risk for cervical cancer and the benefits of screening, and some women cannot afford it, others do not get screened at all or not at recommended intervals because they do not feel personally threatened by cervical cancer, or because obtaining a Pap smear is inconvenient, or because the expense entailed includes more than the cost of the office visit, *i.e.*, transportation, baby sitter, taking off work, *etc.* Screening, and therefore cervical cancer, has become associated with the use of oral contraceptives, pregnancy, and youth as risk factors, while the real risk factors are sexual intercourse and smoking. Thus, women beyond the reproductive age often fail to return for Pap screening, as do women who have been sterilized. Women need to realize that what makes them at risk for cervical cancer is not youth or oral contraceptives or pregnancies, but sexual intercourse and cigarette smoking. They also need to know that, unlike cervical dysplasia, invasive cervical cancer risk does not diminish with age (Fig. 5). Because the precursors are so

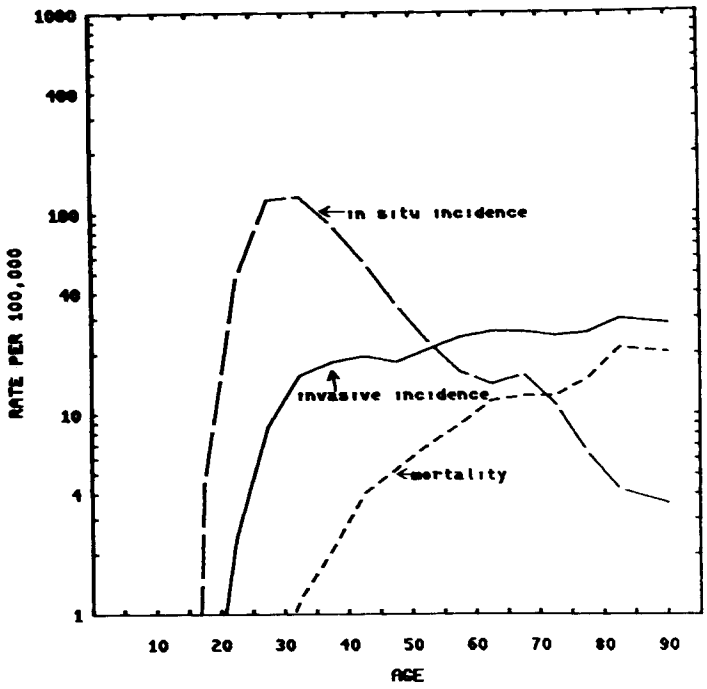

Fig. 5. Comparison of age-specific curves for cervical cancer among white women, 1973–1977: *in situ* incidence, invasive incidence, mortality [6].

common in young women, the impression is given that only young women get cervical cancer. Unfortunately the women most likely to be non-compliant with respect to screening and follow-up for an abnormal Pap smear are those women at greatest risk for developing cervical cancer: the indigent, and those with a history of drug abuse, sexually transmitted disease, abnormal Pap smears, cervical dysplasia, HPV, and anogenital condylomas.

Postmenopausal women are less likely to get Pap smears than women of reproductive age even though they continue to see a physician regularly. This is in part because they feel less need to get the test, but it is also because more of them are under the care of an internist, not a gynecologist. Hayward *et al.* [17] reported on the basis of a national survey that Pap screening was strongly age-related; 90% of women aged 20–39 had a Pap smear in the preceding five years compared to only 59% of women over age 65. Uninsured women were also less likely to have had a Pap smear (59% versus 78% in the 35–64 age group).

OTHER STRATEGIES FOR REDUCING CERVICAL CANCER INCIDENCE AND MORTALITY

Any method of preventing invasive cervical cancer which relies upon intervention at the precursor stage will not solve the current problem of high cost because ultimately the method is captive of the cytologic screening strategy. To by-pass the expensive screening process, a method of preventing cervical cancer precursors, *i.e.* HPV infection and/or cervical dysplasia, is required. The method must be so effective that cytologic screening becomes unnecessary. Several approaches to this problem are available or under study.

Cervical cancer is considered to be a sexually transmitted disease, and there is very strong scientific evidence that the causative agent is the human papillomavirus. The major epidemiological risk factors correspond with this scenario: multiple sexual partners, early coitarche, and a promiscuous sexual partner, *i.e.* the high-risk male, among others (Table VII). Cigarette smok-

TABLE VII. Epidemiologic Risk Factors for Cervical Cancer [24]

Feature	RR*	p Value
Menarche to coitarche < 1 yr	26.4	<.001
Coitarche < 16 yrs	16.1	< .001
Partners before age 20 (> 3)	10.2	< .001
Never had Pap smear	8.0	< .001
Cigarette smoking > 20 yrs	4.0	< .01
History of genital warts	2.5	< .01

* Relative risk

ing is also a risk factor; its products apparently act as a co-carcinogen to the virus. This suggests that cervical neoplasia risk can be reduced by a change in behavior, a strategy which is unlikely to be accepted in our society.

A promising strategy is the development of a vaccine against HPV. Vaccines are available which prevent HPV infection in cows and dogs, but the problem in humans is more complicated. There are 23 known subtypes of HPV infecting the human genital tract, versus only one or two types causing the animal diseases. It is believed that a vaccine to prevent HPV infection is feasible in humans. However, the prospects for commercial gain are such that almost no information regarding the progress in vaccines has been published.

Another potential preventive measure is cervical diathermy. Cashman and Pittsburgh [18] reported in 1941 that deep cauterization of the cervix prevented the development of CC and its precursors. The topic has emerged periodically since then, but has never achieved serious recognition by the medical profession. Peyton *et al.* in 1978 [19] estimated that the protection afforded by this procedure was 85%, and a Finnish study indicated a 6-fold reduced risk for invasive carcinoma if the cervix was cauterized [20]. Two recent case-control studies from Italy, however, failed to show a benefit of cervical diathermy in terms of reducing the risk for invasive or *in situ* cancer [21,22]. While it seems that electrocautery has potential to reduce the risk for cervical neoplasia, there does not appear to be great interest in it.

Finally, it may be possible to prevent cervical neoplasia by means of chemicals, including vitamins. The current status of this field of investigation is reviewed elsewhere in this publication.

SUMMARY

Invasive cervical cancer remains an important health problem in the U.S. and in the world. The reduction of cervical cancer mortality can be improved in many countries by instituting modern methods of therapy, but in countries where those treatments already exist there is no reason to expect any substantial reduction in cervical cancer mortality by progress in therapy. The stage-for-stage treatment results have not changed appreciably in the past 40 years. The current strategy of cytologic screening has the potential to reduce the occurrence of invasive cervical cancer by 80% or more. Despite the fact that cervical cytology is generally considered to be a model system for cancer detection and prevention, we dream of improvements because of the high expense incurred by the evaluation and treatment of precursor lesions, because of the suboptimal specificity of cervical cytology, and because of the need for repetitive testing, and the associated patient inconvenience, an important cause of non-compliance. Epidemiological data indicate that a change in human behavior could produce a major reduction in the incidence of invasive cervical cancer, but realistically this approach could only serve as an adjunctive measure. Our attention should be directed toward a one-stop or self-administered means of preventing HPV

infection and/or its carcinogenic potential. Nevertheless, new methods of detecting and treating cervical cancer precursors which reduce cost, morbidity, and patient inconvenience are welcome.

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