INTRODUCTION

Despite widespread acceptance of the Pap smear, death from cervical cancer has not been eliminated. Among the elderly, 1,867 women in the United States died from cervical cancer in 1986(96). Over 43 percent of deaths from cervical cancer occur in women age 65 and older (165).

Cervical cancer, and screening for the disease, has some unique features in the elderly age group. First, the profile of the disease is different in elderly than in non-elderly women; in particular, the disease in elderly women is more likely to be at an advanced stage at the time it is diagnosed (63). Second, elderly women have much lower screening rates than younger women (61), and they have a different perspective on the place of the test in gynecological care. Whereas most younger women have lived in an era in which Pap smear screening is part of the standard medical regimen, many of today's elderly women were already past childbearing, and no longer seeing a gynecologist, by the time the test came into widespread use.

This paper deals with the usefulness of the Pap smear in preventing morbidity and mortality from invasive cervical cancer in elderly women. This chapter reviews the known natural history of cervical cancer, the accuracy of the Pap smear in screening for cancer, the effectiveness of Pap smear screening programs in preventing the disease, and the utilization of screening by elderly women. Chapter 3 presents a cost-effectiveness model simulating a Pap smear screening program for the elderly and discusses the implications of the model results for Medicare if such a benefit were offered as part of that program.

CERVICAL NEOPLASIA

Terminology

The term "cervical neoplasia"l encompasses the spectrum of abnormalities of the uterine cervix (the neck of the uterus) that relate to cancer and its precursors. Cervical neoplasia can be divided into two categories depending on the extent that abnormal, undifferentiated cells have replaced normal tissue.[2]

In the first category, abnormal cells are confined to the surface (epithelial) tissue layer. Traditionally, *dysplasia* has been used to refer to the partial replacement of normal epithelial cells with abnormal cells (dysplasia is subcategorized as mild, moderate, or severe, depending on the extent of replacement). *Carcinoma in situ* (CIS) is the traditional term describing the condition in which abnormal cells extend throughout the entire depth of the epitheliums.

Under newer terminology, both terms are often subsumed under the single category of *cervical intraepithelial neoplasia (CIN).*

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1 "Neoplasia" is a generic term (meaning "new growth'1) that applies to the abnormal proliferation of cells and tissues.

2 Normal cells show normal maturation and growth and are "differentiated" with certain characteristics that accompany their function (e. g., as epithelial cells). In cancer, the mature cells are replaced by abnormal cells that are undifferentiated, immature in appearance, and have certain chromosomal changes indicative of the abnormal proliferation that is associated with cancer.

Three grades of CIN are distinguished by the extent to which abnormal cells occupy the epithelial layer:

- CIN grade 1 --abnormal cells are confined to the bottom one-third of the epitheliums (corresponds roughly to mild dysplasia).
- CIN grade 2--abnormal cells occupy the bottom two-thirds of the epitheliums (corresponds to moderate dysplasia).
- CIN grade 3--all, or all but the surface cell layer, of the epitheliums is composed of abnormal, undifferentiated cells (includes both severe dysplasia and CIS) (102).

The terms used in related literature vary depending on whether they predate the introduction of CIN terminology. Most early reports discuss the states of neoplasia in terms of dysplasia and CIS. In practice, however, severe dysplasia and CIS are difficult to distinguish. This difficulty was one of the reasons for implementing the CIN terminology, where the two are encompassed by the single state of CIN grade 3. To simplify the terms used and to represent literature results as accurately as possible, this paper uses "CIN" to represent mild and moderate dyplasia (i.e., CIN grades 1 and 2) and "CIS" as shorthand for severe dysplasia/CIS (i.e., CIN grade 3).

The second category of cervical neoplasia comprises all stages of *invasive cervical cancer,* in which abnormal cells "invade" the body by extending into inner cervical tissue and eventually spreading to other parts of the body. Cervical cancer has traditionally been subcategorized according to whether it was symptomatic and the extent to which it has spread to the uterus and the rest of the body. The four stages of invasive cancer are:

- Stage I--cancer is confined to cervix,
- Stage II--cancer extends beyond cervix but has not reached pelvic wall,
- Stage III--cancer extends to pelvic wall, and
- Stage IV--cancer extends beyond pelvis.[3]

Each of the four stages is further subcategorized according to spread and symptoms. For example, stage IA includes preclinical cancer--cancer that is visible only through a microscope and that has no overt signs. In this paper, "cervical cancer" and "invasive cancer" refer to stages I-IV; "early invasive cancer" refers to stage I only, and "late invasive cancer" to stages II through IV.

Incidence, Prevalence, and Risk

Incidence and Prevalence Rates

Data on the incidence and prevalence of cervical neoplasia in elderly women are scarce. Many programs do not target older women and consequently do not report age-specific rates for women in this age group. Existing incidence and prevalence rates for the various states of cervical neoplasia in elderly women are presented in tables I and 2.

These rates are derived from a variety of sources and require some caution in interpretation and comparison. Some important caveats are:

- Rates in each source are dependent on the protocol for that particular study or program (e.g., interval between screening tests, number of prior tests) and accuracy of diagnosis.
- Reported rates combine women who are asymptomatic (but test positive) with those who have symptoms of cancer.
- Rates may be underestimated in the elderly due to under-screening.

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3 Stage O is often used with this terminology to indicate CIS.

Table 1--Annual Incidence of CIN, CIS, and Invasive Cervica Cancer n Elderly Women

Source	Study setting	Number of elderly in study population	Rates per year (per 1,000 women in age group)[a] 60-64	65-69	70-74	75-79	≥80
CIN							
Stern, 1969[b]	Los Angeles, CA clinic; white population	Approximately 3,800 wome age 60 and over	----- 3.3 -----		---------- 3.2 ----------		
CIS							
Fidler, 1968[c]	British Columbia, Canada; screening program	8% age 65 and over	0.21	0.11	0.18	0.18	
National Cancer Institute, 1988[d]	United States; 9 population registries	All elderly women in 9 metropolitan areas	0.14	0.12	0.10	0.09	0.07 (80-84) 0.03 (85+)
Dunn, 1966[e]	Memphis, TN; population screening	Not stated	0.40	0.36	---------- 0.22 ----------		
Invasive Cervical Cancer							
National Cancer Institute, 1985[f]	United States; 9 population registries	All elderly women in 9 metropolitan areas	0.23	0.25	0.25	0.25	0.24 (80-84) 0.27 (85+)
Dunn and Schweitzer, 1981[g]	Alameda County, CA; lower/middle-class population	All elderly ome in county	--	----- 0.35 ------		0.35 (75-84)	

ABBREVIATIONS: CIN = cervical intraepithelia neoplasia; and CIS = carcinoma in situ.

[a]Continuous dashed lines indicate the age range over which the indicated rate applies.
[b]E. Stern, "Epidemiology of Dysplasia," Obstet. Gynecol. Surg. 24:711-723, 1969.
[c]H.K. Fidler, D.A. Boyes, and A.J. Worth, "Cervical Cancer Detection in British Columbia," J. Obstet. Gynaecol. Brit. Cwlth. 75:392-404, 1968.
[d]U.S. Department of Health and Human Services, National Institute of Health, National Cancer Institute, Division of Demographic Analysis, John Horm, CIS Incidence, 1978-1981, unpublished data, Washington, DC, 1988.
[e]J.E. Dunn, "The Presymptomatic Diagnosis of Cancer With Special Reference to Cervical Cancer," Proc. R. Soc. Med. 59:1198-1204, 1966.
[f]U.S. Department of Health and Human Services, National Institute of Health, National Cancer Institute, Surveillance, Epidemiology and End Results Program, Cancer Incidence: All Sites, 1973-1977 and 1978-1981 (Bethesda, MD: National Cancer Institute, 1985).
[g]J.E. Dunn and V. Schweitzer, "The Relationship of Cervical Cytology to the Incidence of Invasive Cervical Cancer and Mortality n Alameda County, California, 1960 to 1974," Am. J. Obstet. Gynecol. 139:868-875, 1981.

SOURCE: Office of Technology Assessment, 1990.

Table 2--Prevalence of CIN, CIS, and Invasive Cervical Cancer in Elderly Women

Source	Study setting	Number of elderly in study population	Rates (per 1,000 women in age group)[a]				
			60-64	65-69	70-74	75-79	≥80
CIN							
Mandelblatt et al., 1986[b]	New York, NY; public hospital clinic	816 women age 65 and over			3.7		
Dunn, 1966[c]	San Diego, CA; private practice	5% age 60 and over	0.8				
Stern, 1959[d]	Los Angeles, CA clinic; white population	Approximately 5,200 women age 60 and over	3.8		3.0		
Stern, 1969[e]	Los Angeles, CA clinic; white population	Approximately 3,800 women age 60 and over	4.8		3.0		
CIS							
Mandelblatt et al., 1986	New York, NY; public hospital clinic	816 women age 65 and over			2.5		
Fidler, 1968[f]	British Columbia, Canada; screening program	8% age 65 and over	3.9	2.4	3.0	1.8	1.3
Dunn, 1966	Memphis, TN; population screening	Not stated	3.8	4.2	3.3		
Dunn, 1959[g]	Charlotte, NC; private practice	Not stated	5.0		2.7		
Dunn, 1959	Memphis, TN; population screening	Not stated	5.6		3.6		
Dunn, 1959	Floyd, TN; population screening	Not stated			4.2		
Dunn, 1966	San Diego, CA; private practice	5% age 60 and over	5.5		7.5		

(continued)

Table 2--Prevalence of CIN, CIS, and Invasive Cervical Cancer (continued)

Source	Study setting	Number of elderly in study population	Rates (per 1,000 women in age group)[a] 60-64	65-69	70-74	75-79	≥80
Invasive Cervical Cancer[h]							
Mandelblatt et al., 1986	New York, NY public hospital clinic	816 omen age 65 and over		----------2.5----------			
Dunn, 1959	San Diego, CA; private practice	5% age 60 and over	-------8.6-------		----------2.5----------		
Dunn, 1959	Charlotte, NC; private practice	Not stated	-------5.0-------		-----6		
Dunn, 1959	Memphis, TN; population screening	Not stated	-------5.6-------		------7.3------		
Dunn, 1959	Floyd, TN; population screening	Not stated	----------7.4----------				

BBR IATIONS: CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ.

[a]Continuous dashed lines indicate the age range over which the indicated rate applies. For example, Mandelblatt et al. found that the average prevalence rate of CIN in women age 65 and over was 3.7 per 1,000 women.
[b]J.S. Mandelblatt, I. Gopaul, and M. Wistreich, "Gynecological Care of Elderly Women: Another Look at Papanicolaou Smear Testing," J.A.M.A. 256:367-371, 1986.
[c]J.E. Dunn, "The Presymptomatic Diagnosis of Cancer With Special Reference to Cervical Cancer," Proc. R. Soc. Med. 59:1198-1204, 1966.
[d]E. Stern, "Rate, Stage, and Patient Age in Cervical Cancer," Cancer 12:933-937, 1959.
[e]E. Stern, "Epidemiology of Dysplasia," Obstet. Gynecol. Surg. 24:711-723, 1969.
[f]H.K. Fidler, D.A. Boyes, and A.J. Worth, "Cervical Cancer Detection in British Columbia," J. Obstet. Gynaecol. Brit. Cwlth. 75:392-404, 1968.
[g]J.E. Dunn, T.A. Slate, J.W. Merritt et al., "Finding for Uterine Cancer From One or More Cytological Examinations of 33,750 Women," J. Nat. Cancer Inst. 23:505-527, 1959.
[h]The lifetime prevalence of invasive cervical cancer--the number of women who have the disease now or who have had it in the past--in women age and over has been estimated to be approximately 5 per 1,000 elderly women in Connecticut (A.R. Feldman, L. Kessler, M.H. Meyers et al., "The Prevalence of Cancer," N. Engl. J. Med. 315:1394-1397, 1986.

SOURCE: ffice o Technology Assessment, 990.

- Rates may be underestimated in the elderly due to under-ascertainment when death from other causes occurs before diagnosis.
- Incidence rates may be falsely elevated when women with prior false-negative smears and women who have not been screened previously are included in the rates. These factors are particularly likely to occur among elderly women.
- Many rates are from studies over two decades old and may not be applicable to current and future cohorts of elderly women.

Compared to younger women, elderly women have lower incidence rates of CIS but higher incidence rates of invasive cancer (3,27,30,39,46,69,157). This observation has prompted the suggestion that the course of cervical neoplasia may be faster in elderly women, with a high proportion of CIS progressing to invasive cancer. Some researchers have found a slower progression of CIN in older women, however (100). It remains unclear whether the lower apparent incidence of CIS in elderly women is due to less new disease, or whether it is due to lower screening rates (with elderly women more likely to have undiagnosed CIS or CIS detected just before it progresses to invasive cancer).

As shown in table 3, mortality from cervical cancer is higher in older women than in younger women and higher in black women than in white women (160). Rates have decreased substantially over time in both older and younger age groups; between 1973-1974 and 1985-1986, mortality rates declined by 17 percent for women age 50 and over and by a striking 43 percent for younger women. Nevertheless, mortality rates in black women age 50 and ever are still nearly triple the rates of white women in this age group (160).

Risk Factors

General Factors-- As discussed later in this chapter, prior screening reduces a woman's risk of developing invasive cervical cancer, presumably because precancerous abnormalities are discovered and treated. Based on the little information available, the protective effect of screening appears to be particularly strong for elderly women (29).

Table 3--Cervical Cancer Mortality Rates,[a] 1973-85

	1973	1975	1977	1979	1981	1983	1985	Percent change 1973-1985
Under age 50								
White women	1.6	1.4	1.2	1.2	1.2	1.1	1.1	-31 .3%
Black women	5.0	4.2	3.6	3.3	2.7	2.8	2.4	-52.0
Age 50 and over								
White women	12.9	11.6	10.6	9.8	9.0	8.1	7.5	-41.9
Black women	37.5	31.9	29.8	25.7	24.5	23.5	21.1	-43.7
All ages and races	5.2	4.6	4.1	3.8	3.6	3.3	3.1	-37.5

[a]Rates per 100,000 women. Rates are age-adjusted to the 1970 U.S. standard population.

SOURCE: Office of Technology Assessment, 1990; from data in U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1987 Annual Cancer Statistics Review, NIH Pub. No. 88-2789 (Bethesda, MD: National Cancer Institute, February 1988).

Most other information regarding the risk of developing invasive cervical cancer among different populations is derived from studies of nonelderly populations. In general, risk of cervical cancer is strongly related to sexual activity; women with a history of several sexual partners and women who were young at the age of first intercourse are at much higher risk than women who have never had sex (119). The observed association between cervical cancer and sexual activity may be due in part to the human papilloma virus (HPV), a sexually transmitted virus that has been implicated in cervical neoplasia (box A). Women who have used foam or jelly as contraceptive methods are at relatively low risk of cervical cancer, and women with genital infections are at higher risk, supporting the hypothesis that cervical cancer derives from a sexually transmitted disease (137).

Other personal and socioeconomic characteristics are also associated with risk of cervical cancer. Smoking has been associated with an increased risk of the disease (138,174). In addition, black women, women from the southwestern United States, and poor women have higher incidence and prevalence rates of cervical neoplasia than other groups (1 19,160). In 1986, for example, the incidence of invasive cervical cancer in black women age 50 and over was more than double that for white women in this age group (38 v. 15 per 100,000) (160).

Age-Specific Factors--Some indirect evidence suggests that elderly women may be more vulnerable to cervical cancer than younger women as a result of diminished immune function. First, viral agents, against which the immune system acts, are probably involved in the initiation or promotion of cervical neoplasia. Second, women whose immune systems are deliberately suppressed (e.g., as an adjunct to organ transplants) have higher than expected risks for developing cervical neoplasia (109,134). Elderly women with either latent viral infection or other promoting factors may therefore be predisposed to rapid progression of cervical neoplasia due to their reduced immune function. It is not clear, however, whether the decline in immune function seen as a part of normal aging is comparable to that seen in younger, iatrogenically immunosuppressed individuals.

The proportion of women who have had hysterectomies increases with age. This factor should generally decrease the risk of cervical cancer, since the number of women who have cervices, and therefore can get the disease, is reduced. However, prior to the early 1960s, many women had partial hysterectomies, leaving the cervix intact. In one study, one-third of the elderly women with a history of a hysterectomy had an intact cervix on clinical exam (92). Between 4 and 8 percent of cervical cancers arise in these cervical stumps (123,175). Also, women who have had a hysterectomy because of cancer have a high risk of subsequent development of vaginal cancer (1 3). Today, the majority of women with hysterectomies have their cervices removed. In the future, the reason for the prior surgery will be the best indicator of whether screening should be continued (screening would likely be advised only if the surgery was for malignant disease).

Cohort Factors--The incidence rate for cervical cancer at any point in time for a particular age group reflects not only changes in risk with age but the background risk of that cohort of women. Sexual practices, smoking habits, hysterectomy rates, and prevalence of HPV are different for each cohort. The changes in these risk factors make it difficult to predict accurately the risk of future 65-year-olds based on rates among the current cohort of 65-year-olds.

Researchers have noted higher rates of cervical neoplasia in two cohorts of women, those born between 1906 and 1921 (women age 68 to 83 in 1989), and those born after 1931 (women under age 58) (62,105). Recently, rates of cervical neoplasia seem to be increasing among young women as well

Box A--Human Papilloma Virus and Cervical Cancer

Human papilloma virus (HPV) was first proposed as a possible precursor of cancer in 1935 (121), but it did not receive widespread attention as a possible causative agent for cervical cancer until 1976 (95). Recently, with the use of technology permitting identification of subtypes of HPV, data have emerged implicating two specific subtypes (HPV-16 and HPV-18) as etiologic agents in cervical cancer. These viruses cause a distinctive concave lesion in cervical cells, known as "koilocytosis" (77).

Koilocytocis indicative of HPV is found in 1 to 3 percent of routine Pap smears (57), and HPV-associated venereal warts (condylomas) have been noted to coexist in approximately 25 to 50 percent of neoplastic cervical lesions (l10,151). Recent studies have reported that more than 75 percent of cervical cancers contain evidence of HPV types 16 and 18, and a further 20 percent contain evidence of other types (94). Only 5 percent of squamous carcinomas of the cervix have no detectable evidence of HPV. It is hypothesized that these cancers contain a type of HPV that has not yet been identified or contain too low a concentration of the virus to be detected by current technology.

Overall, preliminary reports suggest that women with HPV infections are up to 10 times more likely to develop CIN than women without HPV infection (57). In addition, some researchers have suggested that some types of HPV infection may be causing a new type of cervical cancer that has a shorter progression time than cancers that occurred in the past (38,106,126). If this is the case, shorter screening intervals and/or a test to screen for HPV might need to be implemented. One HPV test for this purpose was recently approved by the Food and Drug Administration (82).

There are few prospective studies of the natural history of HPV infection. Syrjaren et al., followed a cohort of 343 women with HPV infection for an average of 1 1/2 years (152). In a subsample of these infections, the behavior of the cervical lesion was correlated with HPV type. Progression was more likely with types 16 and 18 than with types 6 and 11 (153). Recently, two studies have followed women with abnormal smears and HPV infection without treatment. Virtually all of the lesions that progressed contained HPV type 16 0r 18(21,124).

Complicating this picture of HPV infection and cervical cancer is the detection of evidence of HPV in as many as 11 percent of healthy women. Although HPV is believed to be a transforming virus, infection with the virus is not a sufficient condition for the development of cervical neoplasia. Possible co-factors include age, immune status, and repeated infection (74).

There are no studies of the prevalence or behavior of HPV in cervical lesions in the elderly in the United States. A particularly important question is whether HPV behaves in a biologically similar manner in younger and older women. Factors such as the aging immune system, for example, might make elderly women more susceptible than younger women to the effects of the virus. Immunosuppression creates conditions favorable to maturation of HPV (131), and patients whose immune systems have been deliberately suppressed (e.g., renal transplant patients) are up to 14 times more likely than nonsuppressed patients to develop CIS (109,125). With the increasing prevalence of HPV in the population, understanding the interaction between this possible neoplastic promoter and various host factors, including aging and immune status, will assume greater importance.

(157), presaging future cohorts of elderly women at elevated risk. To the extent that screening history influences risk, however, future cohorts of elderly women (with high rates of past screening) should be at lower risk of developing cervical cancer than the present cohort of women in this age group.

Natural History

Cervical cancer screening is predicated on the assumption that the disease progresses through several preclinical and early clinical phases, and that treatment during these phases reduces morbidity and mortality. The effectiveness of screening, thus, crucially depends on the natural history of the disease and the extent to which assumptions about the systematic progression of the disease are true.

Cervical neoplasia most commonly arises in an area of the cervix known as the *transformation zone.* In the standard model of cervical cancer, the abnormal cells that arise in this area are first confined to the surface (epithelial) tissue (CIN and CIS) but eventually invade the body of the cervix. The cancer then spreads to surrounding pelvic tissues and, finally, to more distant parts of the body.

Indirect evidence supports the link between CIN, CIS, and invasive cancer. Cells from *in situ* and invasive tumors have similar biological properties (58), and biopsy studies have found CIS to both predate and coexist with invasive lesions (49,53,56). Furthermore, the epidemiologic evidence strongly supports the postulated disease progression; the peak incidence of each of the disease stages occurs at progressively older ages (22). Thus, it is generally agreed that cervical neoplasia passes through the states of CIN and CIS before becoming invasive. There is less agreement regarding:

1. what proportion of CIN and CIS develops into invasive cancer, and
2. how quickly the progression from CIN to CIS to invasive cancer occurs, particularly in elderly women.

Four methods have been used to estimate the probability and speed of progress of cervical neoplasia through its various states. The first has been through direct observation of patients with untreated nonmalignant disease (a method now considered unethical unless the subjects have been offered and have refused treatment) (see app. D). In two studies of small numbers of women with nonmalignant disease, most women eventually developed invasive cancer. In up to 30 percent of women, however, the disease apparently regressed (e.g., Pap smears no longer revealed abnormal cells) (71,107). Disease regression was more likely in young women and in women with lower grades of CIN. It is unclear whether this apparent regression represented false-positive cases or true regress ion of disease. Additional uncertainties are introduced because observation itself can alter the natural history of the disease. Diagnostic biopsy, which is necessary to accurately evaluate the extent of a lesion, may act as a curative procedure by excising the tumor (1 12). Women with CIN who have biopsies have higher regression and lower progression rates than those who do not have biopsies (100), and women who refuse biopsy as well as treatment have a high rate of invasive disease (142).

A second method uses modal age-specific incidence rates to estimate the duration of different states of neoplasia. For each state (e.g., CIS), the researchers determine the age at which the most cases of that state occur (the mode[4]). The assumption underlying this method is that the duration of a state is the difference between the modal age for that state and the modal age for the next state. For example, if the modal age of CIS were 35 and the modal age for invasive cancer were 50, the average duration of CIS would be estimated to be 15 years. This method may overestimate the duration of CIS if symptomatic as well as asymptomatic cases of in-

4 The mode is the point in a frequency distribution at which the most events occur.

vasive cancer are represented. This occurs because cases discovered as a result of symptoms, on average, are discovered at a later state than asymptomatic cases discovered through screening, resulting in a higher modal age for the apparent onset of invasive cancer.

A third method uses differences between incidence and prevalence rates to infer the duration of a state, which is estimated by dividing prevalence by incidence. In general, the average duration of a disease (or disease state) is a function of the prevalence of that disease (or state) at the end of a time period (e.g., the end of a year) and the incidence of new cases during that time period (e.g., the preceding year) (88). In a simplistic example, if there are 10 new cases each year and a total of 100 cases always exists at the end of each year, the average duration of the disease is 10 years. (This result is derived from the fact that if there are 10 new cases each year, it will take 10 years to reach the equilibrium of 100 cases, and at equilibrium, one case must be lost (e.g., cured) for every new case.) Somewhat more complicated formulas can be used to infer the duration of a disease (or disease state)at different ages.

The fourth method, used to estimate both the duration of different states and the proportion of each state that progresses to the next state, is modelling. Various researchers have used techniques such as statistical regression and simulation models to estimate duration times and progression probabilities (app. D). Coppleson and Brown, for example, used a Markov model and applied various estimates of progression probabilities until they succeeded in obtaining results that mimicked actual prevalence and incidence data. Based on the probability estimates and other assumptions that yielded these results, they concluded that the progression from CIN to CIS to invasive cancer was probably age dependent--i.e, that the probability of progression and the duration of each state depended on the age of the woman with the disease.

Table 4 summarizes estimates from the literature of the likelihood that someone diagnosed with CIN will progress to CIS and to invasive cancer. Tables 5 and 6 summarize estimates of the average duration of each state of neoplasia. The studies and methods on which these estimates are based are described in detail in appendix D. As a group, the existing estimates from the literature support the following conclusions:

- Most CIN (about two-thirds of grades 1 and 2) eventually progresses to CIN grade 3/CIS.
- The majority--probably the great majority--of CIS cases eventually progress to invasive cancer.
- Some CIN regresses to normal. The proportion may be a substantial minority, although it is likely that some "regressions" are actually the result of an initial false-positive test result (i.e., CIN never actually existed).
- Some CIS lesions probably also regress. However, CIS is less likely to regress than CIN. Also, Disappears to be less likely to regress in older than in younger women.
- There is little information on the average duration of CIN. More estimates exist for CIS. This state is estimated in various studies to last from 1 to 17 years, with about 10 years being rough middle estimate. However, CIS appears to be much shorter in elderly women, probably lasting an average of 1 to 5 years. It is possible that the apparent shorter duration is an artifact of lower screening and detection rates of CIS in elderly than in younger women (i.e., in the elderly, CIS may, on average, be detected at a later stage of disease).

Diagnosis and Treatment

Diagnosis

Three tools exist for detecting cervical cancer. The first is the Pap smear, a sample of cells from the cervix that is examined with

Table 4--Selected Prospective Studies of Progression/Regression of Cervical Neoplasia

Source	Basis for initial diagnosis of CIN	Population studied	Progression probability	Regression probability
Barron and Richart, 1968[a]	3 smears	557 women aged 20 to 39 with CIN in Virginia and New York	66% of CIN progressed to CIS in 10 years; progression more likely in higher-grade lesion	6% regressed in 10 years
Fox, 1967[b]	1 smear	278 women attending hospital-based clinics in Virginia (all under age 65)	60% of CIN progressed to CIS	31% (13% developed CIN again)
Stern and Neely, 1964[c]	Biopsy	130 women attending a clinic in Los Angeles, CA; about half over age 45	--	38%/year for CIS in women <45; 29%/year in women>45
Nasiell et al., 1983[d]	Abnormal smears (CIN grade 2) for one year	894 Stockholm women; 197 age 45-72	30% of CIN grade 2 progressed to CIS in average of 4.3 years; progression time longer in women over age 50 (6.5 years)	54% of CIN grade 2 regressed in average 6.5 years

ABBREVIATIONS: CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ.

[a]B.A. Barron and R.M. Richart, "A statistical Model of the Natural History of Cervical Carcinoma Based On a Prospective Study of 557 Cases," J. Nat. Cancer Inst. 41:1343-1353, 1968.
[b]C.H. Fox, "Biologic Behavior of Dysplasia and Carcinoma In Situ," Am. J. Obstet. Gynecol. 99:960-974, 1967.
[c]E. Stern and P.M. Neely, "Dysplasia of the Uterine Cervix: Incidence of Regression, Recurrence and Cancer," Cancer 17:508-512, 1964.
[d]K. Nasiell, M. Nasiell. and V. Vaclavinkova, "Behavior of Moderate Cervical Dysplasia During Long-Term Follow-Up," Obstet. Gynecol. 61(5):609-614, 1983.

SOURCE: Office of Technology Assessment, 1990.

Table 5--Duration of Cervical Neoplasia: Selected Study Characteristics

study	study type	Characteristics of study population
Canadian Task Force, 1976[a]	Cross-sectional	Women screened in British Columbia, Canada
Barren and Richart, 1968[b]	Longitudinal	Women at Medical College of Virginia, Columbia Presbyterian Hospital (New York), and Barbados, West Indies; no elderly women
Coppleson and Brown, 1975[c]	Cross-sectional	Used data from: 1) study of women attending Chicago clinics (University of Chicago Planned Parenthood), and 2) national data on U.S. women from the Third National Cancer Survey
Kashgarian and Dunn, 1970[d]	Cross-sectional	Over 110,000 women in Memphis, TN; over 2% age 65 and over
Dunn, 1966[e]	Cross-sectional	White women in Memphis, TN; a few age 65 and over
Fidler et al., 1968[f]	Cross-sectional	Uomen screened in British Columbia, Canada including over 12% of elderly women
Petersen, 1956[g]	Longitudinal	212 Danish women referred to the Copenhagen Radium Center for gynecologic care from 1930 to 1950; a few over age 40
Barron, Cahill, and Richart, 1978[h]	Cross-sectional	Data from studies of women in Barbados and British Columbia, Canada (see Fidler et al. 1968, and Barron and Richart, 1968)

[a] Canadian Medical Association Journal, "Cervical Cancer screening programs," Can. Med. Assoc. J. 114:1033. 1976.
[b] B.A. Barren and R.M. Richart, "A Statistical Model of the Natural History of Cervical Carcinoma Based on a Prospective Study of 557 Cases," Nat. Cancer Inst. 41:1343-1353, 1968.
[c] L.U. Coppleson and B.W. Brown, "Observation on a Model of the Biology of Carcinoma of the Cervix: A Fit Between Observation and Theory," Am. J. Obstet. Gynecol. 122:127-136, 1975.
[d] M. Kashgarian and J.E. Dunn, "The Duration of Intraepithelial and Preclinical Squamous Cell Carcinoma of the Uterine Cervix," Am. J. Epidemiol. 92:211-222, 1970.
[e] J.E. Dunn, "The Presymptomatic Diagnosis of Cancer With Special Reference to Cervical Cancer," Proc. Soc. Med. 59:1198-1204, 1966.
[f] H.K. Fidler, D.A. Boyes, and A.J. , "Cervical Cancer Detection in British Columbia," J. Obstet. Gynaecol. Brit. Cwlth. 75:392-404, 1968.
[g] O. Petersen, "Spontaneous Course of Cervical Precancerous Conditions," Am. J. Obstet. Gynecol. 72:1071, 1956.
[h] B.A. Barron, M.C. Cahill, and R.M. Richart, "A Statistical Model of the Natural History Of Cervical Neoplastic Disease: The Duration of Carcinoma In Situ," Gynecol. Oncol. 6:196-205, 1978.

SOURCE: Office of Technology Assessment, 1990.

Table 6--Duration of Cervical Neoplasia: Findings

Age group/study	Duration (Years) CIN	CIS	EiCC	Basis for estimate
hAll ages:				
Petersen, 1956[a]		average 3.7 (range: 0.4-8.8)		Direct observation
Dunn, 1966[b]		10.4	4.1	Prevalence/incidence=duration[c]
Canadian Task Force, 1968[d]		<-------25-35, all states-------->		Modal age
		9.7-13.4	3.4	Mean age
Fidler et al., 1968[e]		6-9.5		Prevalence/incidence=duration[c]
		12		Mean age
Kashgarian and Dunn, 1970[f]				
white women		10.7	5	Prevalence/incidence=duration[c]
black women		8.5		Prevalence/incidence=duration[c]
Barron et al., 1978[g]		10 (upper bound)		Prevalence/incidence=duration[c]
		3 (lower bound)		
Young women:				
Kashgarian and Dunn, 1970[f]				
age under 25		10		Prevalence/incidence=duration[c]
age 25-35		16		Prevalence/incidence=duration[c]
age 40-50		5		Prevalence/incidence=duration[c]
Barron and Richart, 1969[h]				
age 20-39	3.7			Markov model (median age)
	5.7			Markov model (mean age)
Coppleson and Brown, 1975[i]				
under age 50		17		Markov model
Older women:				
Coppleson and Brown, 1975[i]				
age 50 and over		4		Markov model
Kashgarian and Dunn, 1970[f]				
over age 65		1		Prevalence/incidence=duration[c]

ABBREVIATIONS: CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ; and EICC = early invasive cervical cancer.

[a]O. Petersen, "Spontaneous Course of cervical precancerous conditions," Am. J. Obstet. Gynecol. 72:1063-1071, 1956.

[b]J.E.Dunn, "The Presymptomatic Diagnosis of Cancer With Special Reference to Cervical Cancer," proc. R. Soc. ~ 59:1198-1204, 1966.

[c]Dunn (1966) estimated the duration of a given state of neoplasia by dividing the sun of all age-specific prevalence for that state by the sum of all age-specific incidence of the state. Kashgarian and Dunn (1970) estimated duration by first graphing the incidence of each state (CIS, preclinical invasive, clinical invasive), with age along the bottom axis of the graph. They then estimated the area under the graph between given ages for CIS. Next, they calculated the age at which the graph of the incidence of preclinical invasive cancer had an area under it equivalent to the area under the defined CIN age interval. The duration of CIS was then presumed to be the difference between this age and the upper limit of the specified CIS age range. This latter method yields results that are equivalent to those derived from the first method.

[d]Canadian Medical Association Journal, "Cervical Cancer Screening programs: Summary of the 1982 Canadian Task Force Report," Can. Med. ASSOC. J. 127:581-589, 1982.

[e]H.K.Fidler, D.A. Boyes, and A.J.Worth, "Cervical Cancer Detection in British Columbia," J.Obstet. Gynaecol. Brit. Cwlth. 75:392-404, 1968.

[f]M. Kashgarian, and J.E. Dunn, "The Duration of Intraepithelial and Preclinical Squamous Cell Carcinoma of the Uterine Cervix," Am. J. Epidemiol. 92:211-222, 1970.

[g]B.A. Barron, M.C. Cahill, and R.M.Richart, "A Statistical Model of the Natural History Of Cervical Neoplastic Disease: The Duration of Carcinoma In Situ," Gynecol. Oncol. 6:196-205, 1978.

[h]R.M.Richart, and B.A. Barron, "A Follow-Up Study of Patients With Cervical Dysplasia," Am. J. Obstet. Gynecol. 105:386-393, 1969.

[i]L.W. Coppleson, and B.W. Brown, "Observation on a Model of the Biology of Carcinoma of the Cervix: A Poor Fit Between Observation and Theory," Am. J. Obstet. Gynecol. 122:127-136, 1975.

SOURCE: Office of Technology Assessment, 1990.

a microscope for abnormalities. The Pap smear is most commonly used for screening and as supportive information for a diagnosis. A second tool is direct examination of the cervix through a colposcope, a magnifying instrument that allows the examiner to see the surface of the cervix in detail. Colposcopy is most often used after a Pap smear has been judged positive for abnormal cells. In addition to verifying the results of a positive Pap smear, COlPOSCOPY can identify the appropriate site from which a biopsy should be taken. The third tool, generally used (together with COlPOSCOPY) for confirmatory diagnosis after one of the other methods has disclosed a possible abnormality, is biopsy --a tissue sample removed from the cervix and examined for evidence of cancer.

It can be difficult for the examiner to gain access to and sample the transformation zone (where neoplasia most commonly arises) in elderly women, for three reasons:

- the vagina narrows with age;
- the cervix undergoes atrophic changes (wasting and diminution of tissue); and
- the transformation zone moves into the inner cervix after menopause (60).

Thus, Pap smears are often more difficult to take and to assess in elderly than in younger women, probably leading to a higher rate of false-negative results and lower test sensitivity. Unfortunately, there are no studies that shed light on the magnitude of this potential problem.

In addition to a probable higher rate of false negatives, smears from elderly women may also have a higher rate of false-positive results (and lower test specificity) than smears from younger women. An initial abnormal smear in an elderly woman may simply reflect a lack of adequate estrogen or an infection. Thus, some physicians suggest that elderly women with an initial smear whose results indicate a mild abnormality undergo treatment with estrogen or anti-inflammatory agents, to eliminate certain potential causes of noncancerous abnormalities, before further diagnostic testing is employed (68,143,168).

Before being treated, a woman with a smear indicating cervical neoplasia undergoes a thorough evaluation to determine the extent of the lesion (i. e., the area of physical manifestation of disease) and to assess the possibility of invasive cancer. For most early lesions, this may be accomplished by removing a small tissue sample (biopsy) from the suspect area identified by colposcopy. This procedure can usually be done on outpatients without general anesthesia (130). However, in up to one-third of elderly women, the transformation zone is inaccessible and the appropriate area is consequently very difficult to visualize (18,72,120,135). In these cases a cone biopsy--removal of a conical segment from the cervix --must be taken (120,143, 177). Women with diagnosed invasive disease subsequently undergo in-depth evaluation to determine the extent to which the cancer has spread. This "staging workup" can also disclose coexisting diseases or problems that may influence treatment decisions (102).

Treatment and Followup

The course of treatment and followup medical care provided to women with cervical neoplasia varies depending on the physician providing the care and considerable controversy exists regarding which protocol is most appropriate. Nonetheless, there is little disagreement regarding the goal of treatment: to remove all abnormal tissue as early as possible in order to prevent the development (or spread) of invasive cancer. Differences in treatment practices are often due to differences in judgment regarding the trade-off between sufficiently aggressive treatment to "cure" the patient-- i.e., eradicate the entire lesion- -and the desire not to inflict unnecessarily invasive treatments on the patient.

Depending on the extent of the lesion, treatment for noninvasive cervical neoplasia may include local therapy (e. g., freezing, cautery, or laser treatment), cone biopsy, or hysterectomy. In general, lesions that cannot be fully visualized require more aggressive

treatment to ensure that the entire lesion is removed. Most CIN is fully removed after a single treatment with local therapy or cone biopsy, with a small proportion requiring further treatment (45, 102). For CIS, however, a hysterectomy may be performed if visualization of the full extent of the lesion is difficult. After re-treatment of patients in whom the initial treatment did not fully remove the lesion, the overall treatment failure rate (i. e., the proportion of patients in whom some CIN remains after treatment) is about 3 percent (12). Fewer than 1 percent of treated patients develop invasive cancer within the subsequent 5 years (33).

Treatment of invasive cervical cancer is guided by the stage of disease. Generally, stage I disease, with lesions confined to the cervix, is treated with a radical hysterectomy (removal of the uterus and surrounding tissue). For elderly women whose other medical conditions make them poor surgical candidates, radiation therapy would be the likely treatment of choice. Although surgery is often considered preferable to radiation therapy, the two treatments yield similar outcomes, with 5-year survival rates of 85 to 88 percent (33,45,160).

Women with more advanced disease (stages II, III, or IV) are generally treated with radiotherapy. If the patient's condition permits, pelvic exenteration--the removal of the pelvic organs--can be considered, but this drastic procedure is rarely performed on elderly women (45,130). Five-year survival rates are 51 percent for women with regional cancer and 14 percent for women with cancer that has spread to distant sites (157).

Cervical neoplasia recurs in less than 5 percent of all women with CIN (grades 1 and 2), approximately 2 to 10 percent of women with CIS, 10 to 20 percent of women with early invasive cancer, and 30 to 100 percent of women with late invasive cancer. Among women with late cancer, those at the most advanced stage (stage IV) have the greatest likelihood of recurrence (130). Most recurrences are within 3 years (130).

Medical textbooks recommend that all women with cervical neoplasia be followed for life (102). The type of followup depends on the state of neoplasia (and, of course, the practice style and preferences of the physician). Women with former low-grade CIN should receive regular Pap tests. Women with CIS should have frequent Pap tests and/or Colposcopy. Women with invasive disease are recommended to have regular checkups, which may include x-ray and other diagnostic procedures as well as physical exams (130).

SCREENING: THE PAP SMEAR

Pap Smear Accuracy

The Pap smear is the universal screening test for cervical cancer in asymptomatic women. Although other tests have been proposed for this purpose, none has so far proven to be as simple and as useful as the Pap test (box B).

A Pap smear consists of a sample of cells, scraped or aspirated from the cervix, affixed to a glass slide.[5] The sample is derived from the thin layer of cells on the surface of the cervix that is continually being exfoliated, or shed, in the normal day-to-day process of cellular growth and aging. The sample includes cells from the outer surface of the cervix, the inner cervix, and the transformation zone between. The slides are sent to a laboratory, where they are examined and the results communicated back to the physician. The physician then decides what course of followup is necessary, based on the abnormalities reported.

Components of Accuracy

Accuracy of the Pap smear has two basic components: the sampling component when the smear is taken, and the evaluation com-

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S See the recent review by Koss (76) for a detailed discussion of ideal methods of sampling and issues in the evaluation of Pap smears.

Box B--Other Potential Screening Technologies

Both colposcopy and cervicography (a method combining colposcopy with a permanent photographic record) have been suggested as methods of screening for cervical neoplasia. In general, screening by these technologies has not been considered practical due to the cost of performing the procedure and the additional skill required of the examiner. No published data exist on the use of these technologies in screening elderly women.

A recent study of colposcopy in younger age groups found that this technology, when used in conjunction with a smear, has greater accuracy in identifying small CIN lesions than the Pap smear alone (54), but whether the smaller lesions are clinically important is not known. The cervigram has been noted to be more sensitive than the Pap smear (17,141,154), but much less specific (154). The cervigram's high rate of false positive results and associated costs have led to some skepticism regarding its usefulness as a screening procedure (139).

A test to screen for HPV has recently been approved by the Food and Drug Administration for marketing (82). It is possible that simultaneous Pap smear and HPV typing will detect cervical neoplasia more accurately than the Pap smear alone (box A) (103,1 13), but this has not yet been shown. No studies of the accuracy and use of the HPV test in elderly women have been published.

ponent when the smear is read. Each component includes both avoidable errors (e.g., due to an error in reading the slide) and unavoidable errors (e.g., due to the biological characteristics of a lesion) that prevent Pap smear accuracy from being 100 percent even under the best circumstances.

Sampling errors, which generally lead to false-negative results, occur when no neoplastic cells are included on the smear even though a woman actually has cervical cancer. Some of these errors are introduced by the examiner and can be minimized by careful sampling. However, if a lesion is small or inaccessible, or if too few abnormal cells exfoliate, it is entirely possible that an adequately taken smear will still not detect potentially cancerous lesions.

Sampling errors that are due to biological characteristics of the lesion and its accessibility are particularly likely in elderly women. A failure of exfoliation of abnormal cells is more likely in post-menopausal than in younger women (64), as a result of anatomic changes associated with aging (e.g., the movement of the transformation zone up into the cervix). Also, narrowing of the vagina and entry to the cervix may make adequate sampling more difficult. All of these biological factors suggest higher false-negative rates in older than in younger women.[6]

Evaluation errors lead to false-negative results (generally avoidable ones) when cancerous cells on a smear are missed by the cytotechnologists. Evaluation errors lead to false-positive results when normal cells are identified as abnormal or when abnormalities that are unrelated to cervical cancer are identified as possible neoplasia. Some false-positive evaluation errors are also avoidable (e.g., mislabeling or inadequate reporting of a slide), but many are not; they arise because infections, estrogen deficiencies, and many other causes can result in abnormal smears that require comprehensive followup to rule out cervical neoplasia.

6 Despite these problems, the International Agency for Research on Cancer has noted that the sensitivity of the Pap test is not appreciably lower in older women (age 50 to 64) than in younger women (66) . This group did not draw any conclusion regarding test sensitivity in women age 65 and over.

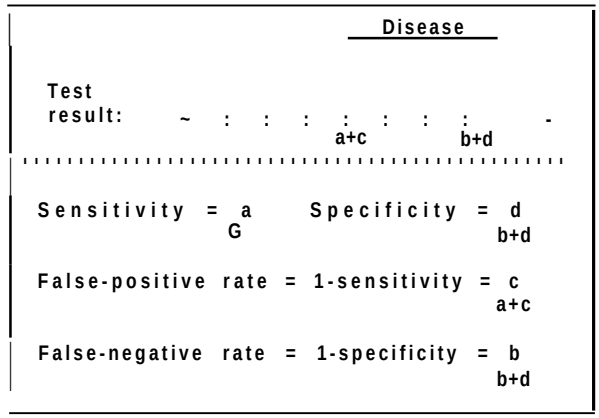
In some cases, efforts to minimize evaluation errors may increase sampling errors. For example, lubricating jelly is generally not recommended for use when a Pap smear is taken because it is believed to diminish cellular detail, making accurate evaluation of the smear difficult. In elderly women, however, the use of lubrication can increase patient comfort and thus enable the examiner to obtain a more complete smear. One recent study found that small amounts of lubrication could be used without sacrificing the adequacy of smears (92).

Overall Pap Smear Accuracy

A Pap smear is not simply reported by the laboratory as "positive" or "negative"; rather, there are a number of categories with different implications for followup (e.g., "atypia," "suspicious for malignancy"). In general, for the purposes of cervical cancer and this paper, a "positive" slide is any slide diagnosed as atypia or worse, except that atypical smears that are judged to be attributable to a cause other than neoplasia (e.g., infection) would be considered negative. The term "positive" is not consistently defined, and most studies give little detail regarding the exact definition that is used.

The overall accuracy of the Pap smear is the sum of both the sampling and evaluation components. It is quantified by estimating the sensitivity and specificity rates for smears. (Figure 1 displays the calculation of sensitivity and specificity and the relationship of these measures to false-positive and false-negative rates). Calculating these rates is not always simple. For example, determining the true sensitivity requires retesting all women who originally tested negative, while determining the true specificity requires knowing the number of women who are truly free of the disease.

Figure l--Calculation of Sensitivity and Specificity



SOURCE: Office of Technology Assessment, 1990.

A substantial number of published studies exist that attempt to measure the accuracy of the Pap smear (table 7). A review of these studies requires three comments. First, the majority of the studies were designed to ensure very careful smear evaluation. Consequently, the rates they report represent accuracy under ideal circumstances, rather than under normal conditions of varying laboratory quality. Second, few elderly women are represented in the studies; because sampling is more difficult in elderly than in younger women, and because estrogen deficiencies and other abnormalities may confound the interpretation of the smear, rates for older women are probably lower than those reported here. Third, study designs and environments vary considerably. Some of the studies were conducted outside the United States, and it is quite possible that the differences in the other nations' health care systems (e.g., in how services are delivered, how laboratories are run, who evaluates smears and how the evaluators are trained) would make the results of those studies inapplicable to the United States.

Table 7--Studies Assessing the Accuracy of the Pap Smear

study	Country (region)	Population	Study design	Sensitivity	Specificity[a]	Elderly population	Comments
Richart and Barron, 1969[b]	United States	Patients receiving screening from two hospitals	After initial screening 120 slides were relabeled and examined again	95%	NA	None	Since results were never verified by colposcopy or biopsy false-negative rate only reflects evaluation error
Coppleson and Brown, 1974[c]	United States	Women in two screening programs in the United States	Mathematical model using empirical incidence and prevalence data to estimate a false-negative rate	MDYS = 60.1% CIS = 55.1-80% ICC = 76%	NA	NA	Rates not derived directly from successive smears on. individual women
Davis, Hindman, PapLanus et al., 1981d	United States (Arizona)	87 women referred to hospital dysplasia clinic	Comparison of smears and biopsies	79%	NA	NA	Group is not representative since all participants were referred because of cytologic abnormalities; false negative errors were categorized by type of error; of 19, 13 were either purely sampling (10) or combined sampling and evaluation (3); 6 were evaluation errors
Dunn and Schweitzer, 1981[e]	United States (California)	Women who deveL-oped cervical cancer	Retrospective review of 53 negative slides (for 27 women who Later developed cervical cancer); also reviewed 50 control slides (both negative and positives); original and review interpretations were compared	81.5%	NA	NA	False-negative rate only an estimate of evaluation errors
Gay, Donaldson, and Goellner, 1985[f]	United States	339 tissue proven cases of cervical malignancies between January 1980 and December 1983	Retrospective review of negative slides of women who developed malignancy within a year of smear	Overall = 80% CIS=83% ICC = 77%	NA	NA	False-negative rate includes both evaluation and sampling components; rate also includes detection of lymphoid and adenocarcinoma

Table 7--Studies Assessing the Accuracy of the Pap Smear (continued)

Study	Country (region)	Population	Study design	Sensitivity[a]	Specificity[a]	Elderly population	Comments
Boyes, Morrison, Knox et al, 1982[g]	Canada	Women participating in British Columbia Screening Program from 1949-1969	Retrospective examination of smears of women with abnormalities to assess the effectiveness of screening in British Columbia	Cohort 1: DYS = 80.7% CIS or worse = 81.9% Cohort 2: DYS = 73.5% CIS or worse = 74.7%	99.64-99.72%	None	False-negative rate includes both the evaluation and sampling components; sampling component estimated by comparing difference between incidence rates derived from short versus long screening intervals
[illegible]sain Butler, Evans et [illegible]74[h]	Great Britain	14,437 women with negative smears recalled for new smear within 3 months	Comparison of initial versus second smear	85.1%	NA	NA	False-negative rate includes both evaluation and sampling errors
Rylander, 1977[i]	Sweden	Women receiving mass cytologic screening in Stockholm	56 negative slides from women who developed cervical cancer combined with 7 control slides and reexamined	37.5%	NA	None	Study calculates false-negative rate based only on evaluation errors, but suggests that the specimen collection might not have been optimal in many of the false negatives
Berget, Olsen and Poll, 1977[j]	Denmark	13,224 women between ages 30 and 50	Comparison of smears taken in 1967-1969 with ones taken in 1971-1975; any changes in diagnosis from first to second smear were investigated further	93.4%	99.3%	None	False-negative rate includes both evaluation and sampling components; sampling component is estimated based on known sampling errors for diagnostic categories
Beilby, Bourne, Guillebaud et al., 1982[k]	Great Britain	21,332 women [illegible] England	Comparison of two smears taken during one visit	81.4%	NA	NA	Errors divided into those that were evaluation and those that were sampling; no confirmation of diagnosis by biopsy or colposcopy

Table 7--Studies Assessing the Accuracy of the Pap Smear (continued)

study	Country (region)	Population	Study design	sensitivity[a]	Specificity[a]	Elderly population	comments
MacCormac, Lew, Kim et al., 1988[l]	Australia	Women screened between 1959 and 1982	Comparison of biopsies with n-ret recent smear result	Overall = 84.6% DYS = 77.9% CIS = 88.2% ICC = 82.6%	94.6%	NA	Smears were not reexamined, original diagnosis presumed correct; no indication of time intervals between smear and biopsy; sensitivity was higher if calculated on the basis of the mast abnormal smear instead of the most recent
Giles, Hudson, Crow et al., 1988[m]	Great Britain	200 asymptomatic women in a general practice	Comparison of colposcopy and cytology done during the same visit	Overall = 68.2% CIN1 = 100% CIN2 = 40% CIN3/CIS = 69%	99%	2.5% of study population >65 years old	None of the elderly women had abnormal Pap smears

ABBREVIATIONS: CIN = cervical intraepithelial neoplasia (includes grades 1,2,3); CIS = carcinoma in situ; DYS = dysplasia (corresponds roughly to CIN); ICC = invasive cervical cancer; MDYS = mild dysplasia (corresponds roughly to CIN grade 1); NA = not available.

[a]Sensitivity is related to the false-negative rate; specificity is related to the false positive rate. See figure 1 for definitions. The false-negative rate has two components: errors resulting from the probability that the sample did not collect dysplastic cells present on the cervix (sampling error) and errors resulting from the cytologists evacuation of the slide (evacuation error). Not all studies estimated both components (see text).

[b]R.M. Richart and B.A. Barron, "A Follow-Up Study of patients With cervical Dysplasia," Am. J. Obstet. Gynecol. 105:386-393, 1969.
[c]L.W. Coppleson and B. Brown, "Estimation of th. Screening Error Rate From the Observed Detection Rates in Repeated CervicalCytology," Am. J. Obstet. Gynecol. 119(7):953-958, 1974.
[d]F.R. Davis, W.M. Hindman, S.If. Pap[anus et al., "Value of Duplicate Smears i. Cervical Cytology," Acta. Ctyol. 25(5):533-538, 1981.
[e]J.E.Dunn and V. Schweitzer, "The Relationship of Cervical Cancer andMortalityinAlamedaCounty, California, 1960-1974," Am. J. Obstet. Gynecol. 139(8):868-876, 1981.
[f]J.D. Gay, L.D. Donaldson, and J.R. Goellner, "False-Negative Results i. CervicalCytologic Studies,"Acta.Cytol. 29:1043-1046, 1985.
[g]D.A. Boyes, B. Morrison, E.G. Knox et al., "A Cohort of Cervical Cancer Screening in British Columbia," Clin. Invest. Med. 5:1-29, 1982.
[h]O.A. Husain, E.B. Butler, D.M. Evans et al., "QualityControl in Cervical Cytology," J. Clin. Pathol. 27(12):935-944, 1974.
[i]E. Rylander, "Negative Smears in Women Developing Invasive Cervical Cancer," Acta. Obstet. Gynecol. Scand. 56(2):115-118, 1977.
[j]A. Berget, J. Olsen, and P. Poll, "Sensitivity and Specificity of screening by Cervico-Vaginal Cytology," Dan. Med. Bull. 24(1f):26-29, 1977.
[k]J.O. Beilby, R. Bourne, J. Guillebaud et al., "Paired Cervical Smears: A Method of Reducing the False-Negative Rate in Population Screening," Obstet. Gynecol. 60(1):46-48, 1982.
[l]L. MacCormac, U. Lew, G. King et al., "Gynecological Cytology screening in South Australia: A 23-Year Experience," Med. J. Aust. 149(10):530-536, 1988.
[m]J.A.Giles,E. Hudson, J. Crow et al., "ColposcopicAssessment of the Accuracy of Cervical Cytology Screening," Br. Med. J. 296:1099-1102, 1988.

SOURCE: Office of Technology Assessment, 1990.

Sensitivity --Most sensitivity rates reported in the literature are between 56 and 95 percent (i.e., false-negative rates of 5 to 44 percent), with a few studies reporting lower rates (table 7). In some cases, the rates reflect only the evaluation component of accuracy. For instance, Barren and Richart calculated the false-negative rate based on the accuracy of one smear reading compared to the result when the same slide is read by different individuals (114). The calculated sensitivity rate in this case (95 percent) is a maximum one, since it does not take into account the probability that the slide sample might not contain precancerous cells that actually are present on the cervix.

Other studies attempt to account for both evaluation and sampling components. These studies compare the diagnosis based on a Pap smear with the diagnosis based on another procedure (a second Pap smear, colposcopy, or biopsy). The studies comparing two smears assume that if a woman actually has cervical cancer, one of the two smears will be positive. For studies comparing a single smear with colposcopy or biopsy, it is assumed that "true positive" is defined by a positive result on the second procedure.

In general, the Pap smear sensitivity rates determined by these studies range from about 69 to 85 percent (false-negative rates of 15 to 31 percent) (11,36,54,64,85), although there are a few studies where Pap smear sensitivity has been substantially lower. Rylander, for example, found sensitivity to be 37.5 percent (122). In this study, the incorrectly diagnosed smears could be subcategorized into those obtained at a mass screening (with a sensitivity rate of 30 percent) or those done by private practitioners (with a 50 percent sensitivity rate). In a study of 50 postmenopausal women referred for hormone therapy, Roberts and colleagues (116) found a sensitivity rate of zero. Eleven of the 50 women in this study had abnormal colposcopic exams, including 4 cases diagnosed as CIN; all of them had had normal Pap smears. It is unknown what effect the need for hormone therapy might have on the accuracy of the test, so this study's results are not easily generalizable. However, they do suggest that the Pap test may have a low sensitivity in this subpopulation of elderly women.

Finally, some studies attempt to estimate sensitivity rates by reviewing the negative slides of women who were later diagnosed with cervical cancer. Dunn and Schweitzer, following this procedure, found a sensitivity rate of 91.5 percent (41). These researchers reviewed slides only to see if they were improperly diagnosed, so this rate does not reflect sampling errors. One study from Denmark took this method a step further by combining the observed evaluation errors with an estimated sampling error, to come up with an overall sensitivity of 93.4 percent (14). This rate is quite high and probably represents the minimum error that can be obtained under optimal conditions.

Specificity --The few studies that calculate the specificity of the Pap smear place the rate within a range of 95 to 99 percent for nonelderly women (20). The specificity of the test in elderly women is potentially lower, since the normal atrophic changes occurring in post-menopausal women can result in vulnerability to inflammation and injury, responses that can mimic the cellular changes characteristic of CIN (50,78,92).

A study by Weintraub and colleagues demonstrated the variety of abnormalities that may complicate the interpretation of a Pap smear in elderly women (172). In this study, 127 elderly women were given cytologic and physical examinations. Nineteen of the Pap smears (15 percent) were positive for an abnormality requiring some sort of followup, and 16 of the patients remained in the study for followup. Of these, 7 were followed up for possible cervical neoplasia; 1 of the 7 was subsequently diagnosed as having invasive cervical cancer, and a second had persisting atypia at the time the study was concluded. The remaining 9 patients were followed up because the Pap smear suggested other abnormalities; followup resulted in a significant diagnosis in one of these patients.

Communication and Followup Errors

Although not strictly a component of the accuracy of the Pap smear itself, communication and followup errors can complicate appropriate patient followup after an abnormal (or normal) smear. They also result in lower real-world rates of sensitivity and specificity than the rates reported from research studies.

Communication errors are compounded by variations in reporting of results. One study of Pap smear evaluation at eight Baltimore, Maryland laboratories found that they varied substantially in the nomenclature used to report results back to physicians (127). For example, one laboratory used "atypia" to mean "dysplasia," while at another, "atypia" implied that the smear specimen was neither normal nor dysplasia. Laboratories in this study also varied in the extent to which the laboratory pathologist included followup recommendations to the clinician (one laboratory always provided a recommendation for followup for all abnormal smears, while another never did).

Most communication and followup errors are theoretically avoidable. A recent workshop convened by the National Cancer Institute published its recommendations on how to minimize such errors (101). The recommendations proposed a new classification system for the reporting of Pap smear results, under which each report from the laboratory to the physician would include:

- a statement of the adequacy of the smear specimen (for unsatisfactory slides, the cytopathologist would recommend that the physician take a repeat smear);
- a general categorization of the smear to indicate whether any abnormalities exist (i.e., whether the smear appears to be within normal limits); and
- a descriptive diagnosis for slides with abnormalities, such as "infection- -cellular changes associated with herpesvirus simplex," or "high-grade squamous intraepithelial lesion" (i.e., CIN grade 2 or 3).

A major purpose of this classification system is to ensure that inadequate slides are described as such and returned to the sampler (reducing false-negative errors due to poor samples). In the case of adequate slides, the purpose is to ensure that the information conveyed to the physician leads to appropriate followup decisions. For example, a descriptive diagnosis of "infection--cellular changes associated with herpesvirus simplex" would indicate that the abnormality detected is not likely to be cervical neoplasia and that followup for herpes probably will be the appropriate course of action.

Effectiveness of Screening

The effectiveness of Pap smear screening in preventing cancer mortality and morbidity has never been tested directly in a prospective, controlled study. Instead, evidence for screening effectiveness is based on two types of studies:

1. Trend studies--analyses of cancer incidence and mortality in a population before and after the institution of Pap smear screening. Trend evidence is more convincing if it can be linked with a "dose-response" effect- -i.e., if the incidence of cancer drops more sharply as the intensity of screening increases.
2. Case-control studies--studies in which cases (women who developed cervical cancer) are compared with controls (a sample of women from the general population) with respect to their utilization of screening, to see if screening utilization is associated with a lower risk of developing cancer.

As with the studies of Pap smear accuracy, a discussion of these studies as they relate to elderly women requires some important caveats. Elderly women make up a relatively small proportion of the populations in most of the studies. Consequently, the conclusions that can be drawn from these studies regarding the effectiveness of Pap smear

screening are less clearly applicable to older than to younger women. (This issue is addressed at the end of the discussion.) Both types of studies are subject to important forms of bias that can artificially inflate or deflate the apparent effectiveness of the screening program, particularly when variables other than incidence and mortality rates are used as endpoints (box C). In addition, each study type has its own characteristics that confound simple evaluations. The relevant studies and their implications are discussed below.

Trend Studies

Pre- and Post-screening Trends--In Virtually every study reported, the incidence of invasive cervical cancer and the mortality from the disease declined after the introduction of Pap smear screening. Several U.S. studies have reported such trends. The studies have focused on nonelderly populations, so the results are not necessarily directly applicable to the elderly.

- In Toledo, Ohio, average annual incidence rates of invasive cancer declined

Box C--Types of Bias in the Evaluation of Screening Programs

Many screening services are sufficiently integrated into normal medical practice that it is not considered ethical to perform a prospective, randomized controlled trial to assess their effectiveness. Consequently, the assessment of effectiveness is based on less rigorous experimental designs and historical observations. The use of such techniques introduces the possibility of bias in interpreting the results. Three important types of bias that frequently confound the interpretation of Pap smear screening programs are lead-time bias, length bias, and selection bias. These types of bias are most severe when the outcome measure is survival rates or survival time after diagnosis; mortality rates are the least affected by these types of bias.

Lead-time bias makes a screening program appear effective because it increases the time between diagnosis of the disease and death from disease. Individuals whose disease is diagnosed as a result of screening are identified earlier in the course of the disease than those whose disease is diagnosed as a result of symptoms. Thus, the screened group will have a longer survival after diagnosis than the unscreened group regardless of the actual effectiveness of the screening program (and resultant treatment) in preventing disease, simply because their disease is identified earlier.

Length bias also tends to make a screening program appear more effective than it is. It occurs because slow-growing tumors are more likely to be "picked up" over time in a screening program than are fast-growing tumors, which may progress quickly between screening encounters. Consequently, those individuals with disease identified as a result of screening are more likely to have slow-growing tumors than individuals identified as a result of symptoms. Since those with slow-growing tumors will have better prognoses and longer survival times, the overall effect is to enhance the apparent effectiveness of the screening program.

Selection bias often causes the effectiveness of a screening program to be overstated, although it can potentially cause it to be understated as well. Selection bias results from the fact that people who choose to be screened often differ from those who avoid screening. The factors associated with this self-selection to be screened are themselves associated with the risk of disease and can confound interpretation of the program results. If middle-class, low-risk women are more likely to participate in a cervical cancer screening program than poor, high-risk women, for example, the incidence of cervical cancer in the screened group will be correspondingly lower, regardless of whether screening itself contributes to disease prevention.

by 66 percent over a 16-year period after screening was introduced, and this decline was accompanied by a 61 percent reduction in mortality rates (70).
- In Louisville, Kentucky, incidence rates 8 years after screening was introduced were 23 percent lower than in the pre-screening period.
- Dickinson et al., noted declines in incidence and mortality during the period of screening in Minnesota, compared to a pre-screening period. The decline in mortality paralleled an increase in screening rates (37).

Before-and-after trend studies present a major difficulty for interpretation, because a change in cancer incidence after the introduction of Pap smear screening may be due to other factors (such as a change in the epidemiology of the disease itself), rather than to the screening program. In fact, incidence of invasive cervical cancer was apparently beginning to decline in the United States even before the introduction of screening (108), and the decline did not accelerate with the onset of screening. However, other countries have experienced a reversal of rising incidence immediately after comprehensive Pap smear screening was introduced, implying that screening played a role in bringing about lower incidence rates (67). Also, since the introduction of screening in the United States, invasive cancer incidence and mortality rates have continued to fall steadily (160) despite indications that greater numbers of women are at risk of invasive disease, and despite a dramatic increase in the rate of CIS in some age groups (108).

Canadian researchers tested the possibility that the general decline in cervical cancer incidence rates in that country might be due to increased hysterectomy rates in the population. To address this potential bias, data from British Columbia were adjusted for age-specific hysterectomy rates. This adjustment did not change the rate of decline in incidence rates to any substantial degree (99).

Comparisons Between Intensely and Less Intensely Screened Populations--Studies from various parts of the world have concluded that regions with aggressive, intensive screening programs show a greater decrease in the incidence and mortality from cervical cancer than regions where screening is less intensive. In Canada, data on the intensity of screening within a province have been linked to cancer registry incidence and mortality rates, and provinces with the most comprehensive screening have the largest decline in incidence and mortality rates (98).

Comparisons among the Nordic countries show similar trends. Denmark, Sweden, Finland, and Iceland have introduced organized population screening, while Norway has not. The first four countries have seen considerable reductions in cervical cancer incidence rates, but rates in Norway have declined very little (59). The amount of decline in these countries is correlated with the proportion of women screened, with the greatest decline in the country with the most extensive screening program.

Studies from Canada and Iceland have found that while cancer incidence rates have declined over time for women who are screened, rates among unscreened women are equal to or higher than pre-screening rates for the entire population (46,67). While selection bias undoubtedly accounts for some of the differences in rates among screened and unscreened groups, the continued decline in incidence even while an increasing proportion of women are being reached by screening suggests that screening itself is contributing to the decline.

If screening is effective, the proportion of invasive cancer diagnosed early should increase, and later-stage diagnoses should decrease.' This expectation has been largely

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'7 Women with late stage disease (II-IV) are likely to have symptoms (e.g., vaginal bleeding) and therefore are likely to be diagnosed even in the absence of screening. Women with early disease are less likely to be diagnosed without screening. In a recent review of one New York City hospitals experience with cervical cancer, 75 percent of elderly women with stage IA disease, and 17 percent of women with stage IB disease, were asymptomatic at the time of diagnosis (51).

borne out. In Minnesota, the proportion of invasive disease diagnosed at stage I increased from 7 percent in the period 1935-1946 to 63 percent in the period 1957-1967 (37). In Kentucky, stage I disease increased from about one-third of all invasive disease in 1953-1955 to slightly less than half of diagnosed invasive disease in 1971-1973 (27). Differences among screened and unscreened women in stage at diagnosis are also consistent with the hypothesis that screening increases the proportion of invasive cancer detected at an early stage. Of unscreened women 14 to 40 percent (median 32 percent) are diagnosed at stage I (22,28,37,44,46, 104,146), compared to 22 to 65 percent (median 50 percent) of all women (22,28,37, 46,158).

Opposite trends were found in British Columbia, with a higher proportion of invasive cancer detected at later stages after screening became well-established (19). Total incidence and mortality continued to decline, however (3), and the author attributed the worsening state distribution to the most difficult and aggressive lesions being unaffected by screening (19).

Case-Control Studies

Another method of assessing the effectiveness of screening programs is the case-control method, in which women with invasive cancer (cases) are compared with other women (controls) regarding their use of screening. If women with cancer are less likely to have been screened, then screening presumably lowers the risk of developing invasive cancer. Selection bias often confounds interpretation of case-control studies, since some factors (e.g., lower socioeconomic status) are independently correlated with both a higher risk of cervical cancer and a lower probability of screening. The more closely matched the cases and controls are for such confounding risk factors, the more confidence one can have that screening, not other risk factors, accounts for the difference in cancer between the groups.

Case-control studies have been conducted in several areas of the world and have all yielded similar results. These studies are summarized in table 8. Overall, women who have never been screened have a risk of developing invasive cervical cancer that is 2 to 10 times greater than the risk in women who have been screened at least once (4,15).

Of particular interest is the Toronto case-control study, which included only symptomatic invasive cancer cases. In this study attempts were made to minimize selection bias by matching study subjects for age and location and type of housing (as a proxy for socioeconomic status). The study found that over half of the control subjects had been screened by Pap smear within the past 5 years, compared with only one-third of cases (29). The relative risk of invasive cancer was 2.7 times greater in women who had not been screened than in those who had been, and for unscreened elderly women (over age 60) the relative risk was even higher (3.4).

Effectiveness of Screening in the Elderly

Despite the problems in assessing studies of cervical cancer screening effectiveness, the evidence from a multitude of settings and geographic locations is fairly consistent and supports the contention that, in general, Pap smear screening is effective in reducing the incidence of invasive cervical cancer and the mortality from this disease. There is far less evidence regarding Pap smear effectiveness in reducing morbidity and mortality in elderly populations, since elderly women are poorly represented in screening programs and studies.

Most studies that have examined incidence rates by age group have found that younger women are both more likely to be screened and have a lower incidence of invasive cancer than older women (27,28,39,70). Mortality rates from cervical cancer have also declined less in older than in younger women (39,87) and, in some studies, the mortality rate for women in the oldest age group did not decline at all (27,1 15).

Table 8--Case-Control Studies of Pap Smear Effectiveness

Source	Country	Control population	Increased risk of ICC for never-screened women: All ages	Increased risk of ICC for never-screened women: Older women
Aristizabal et al., 1984[a]	Columbia	Women matched for age, neighborhood of residence	9.9	11.5[b]
Berrino et al., 1986[c]	Italy	Hospital patients	2.0	--
Celentano et al., 1989[d]	United States (Maryland)	Women matched for age, neighborhood of residence	5.0	--
		Randomly selected women matched for age, race, and geographic area	3.3	--
Clarke and Anderson, 1979[e]	Canada	Middle-class women matched for age, housing type	2.7	3.4[f]
LaVecchia et al., 1984g	Italy	Hospital patients	4	--
MacGregor et al., 1985[h]	Scotland	Other residents who had been screened at least once	3.3[i]	--
Raymond et al., 1984J	Switzerland	Swiss residents matched for age, marital status	5.3[k]	--
Stenkvist et al., 1984	Sweden	Cross-section of entire country	4	--
van *r Graaf et al., 1988[m]	Netherlands	Age-matched women from registrar's rolls	4.5	--

ABBREVIATION: ICC = invasive cervical cancer.

[a] N. Aristizabal, C. Cuello, P. Correa et al., "The Impact of Vaginal Cytology on Cervical Cancer Risks in Cali, Colombia," Int. J. Cancer 34:5-9, 1984.

[b] Age 45 and older.

[c] F. Berrino, G. Gatta, M. d'Alto et al., "Efficacy of Screening in preventing Invasive Cervical Cancer: A Case-Control Study in Milan, Italy," Screening for Cancer of the Uterine Cervix, M. Hakama, A.B. Miller, and N.E. Day (eds.), IARC Scientific Publications No. 76 (Lyon, France: International Agency for Research on Cancer, 1986).

[d] D.D. Celentano, A.C. Klassen, C.S. Weisman et al., "Duration of Relative Protection of Screening for Cervical Cancer," Prev. Med. 18:411-422, 1989.

[e] E.A. Clarke and T.W. Anderson, "Does Screening by 'Pap' Smears Help Prevent Cervical Cancer?" Lancet 2(8132):1-4, 1979.

[f] Age 60 and older.

[g] C. LaVecchia, S. Franceschi, A. Decarli et al., "'Pap' Smear and the Risk of Cervical Neoplasia: Quantitative Estimates From a Case-Control Study," Lancet 2(8406):779-782, 1984.

[h] J.E. MacGregor, S.M. Moss, M.D. Parkin et al., "A Case-Control Study of Cervical Cancer Screening in North East Scotland," Br. Med. J. 290:1543-1546, 1985.

[i] Relative risk for women with no previous negative smear compared with negative smear 10 or more years ago.

[J] L. Raymond, M. Obradovic, and G. Riotton, "Une Etude Cas-Temoins Pour l'Evaluation du Depistage Cytologique du Cancer du Col Uterin," Rev. Epidemiol. Sante Publ. 32:10-15, 1984, as summarized in IARC Working Group on Cervical Cancer Screening, "Screening for Squamous Cervical Cancer--The Duration of Low Risk Following Negative Results in Cervical Cytology Tests: Introduction," and "Summary Chapter," Screening for Cancer of the Uterine Cervix, M. Hakama, A.B. Miller, and N.E. Day (eds.), IARC Scientific Publications No. 76 (Lyon, France: International Agency for Research on Cancer, 1986).

[k] Relative risk for women with no previous negative smear compared with negative smear 5 or more years ago.

[l] B. Stenkvist, R. Bergstrom, G. Eklung et al., "Papanicolaou Smear Screening and Cervical Cancer: What Can You Expect?" J.A.M.A. 252:1423-1426, 1984.

[m] Y. van der Graaf, G.A. Zielhuis, and P.G. Peer, "The Effectiveness of Cervical Screening: A Population-Based Case-Control Study," J. Clin. Epidemiol. 41(1):21-26, 1988.

SOURCE: Office of Technology Assessment, 1990.

Elderly women with invasive cancer are more likely than younger women to have advanced disease at the time of diagnosis. In the Kentucky study, 76 percent of newly diagnosed invasive disease in women aged 20 to 29 was stage I, compared to only 38 percent for women aged 60 to 69, and only 29 percent for women aged 70 or more (83). The authors attribute the age-related differences to less Pap smear coverage in older women, although no age-specific rates of screening are presented in their published research. Even though the 29 percent figure for elderly women presumably includes a large proportion of unscreened women, it may be high. A study that included unscreened women aged 60 to 69 found that only 14 percent were diagnosed early (44).

In summary, it appears that Pap smear screening has had some effect in reducing the general incidence of and mortality from invasive cervical cancer, and it may also have had some effect on the stage at diagnosis. For elderly women, however, these trends are much weaker. In many studies there is no apparent improvement in cervical cancer statistics for the older age group at all. Population denominators and age-specific screening rates are unavailable in most studies, so firm conclusions about the reasons for the poorer outcomes in this age group cannot be drawn. It is possible that screening may be less effective in elderly women (e.g., due to faster progression of tumors and lower accuracy of Pap smears). But it seems likely that at least some of the age-related differences in incidence and mortality when screening is offered are related to lower screening rates among elderly women.

Screening Recommendations

Government, professional, and consumer groups, both in the United States and abroad, have published recommendations regarding Pap smear screening (table 9). Current recommendations for Pap smear screening of U.S. women vary depending on the recommending organization, but they generally suggest that screening every 1 to 3 years is appropriate, with the exact frequency to be determined by a woman's physician based on her risk status (47,140,170). Of existing recommendations by various U.S. groups, two specifically address screening in elderly women. Both advise that screening may cease at some upper age limit, but only if the woman has a well-documented history of negative smears (140,162). Several other countries that have developed Pap smear screening recommendations have concluded that screening elderly women is not productive (table 9).

U.S. Recommendations

From the 1950s through the 1970s, the American Cancer Society (ACS) recommended that Pap smears be one component of an annual pelvic examination. This policy was supported by the American College of Obstetricians and Gynecologists (ACOG). Then, in 1981, ACS amended its recommendations to suggest that asymptomatic women aged 20 and over, and those under 20 who were sexually active, have a Pap smear annually until there are two consecutive negative examinations and then at least once every 3 years until age 65 (43). Until 1988, however, ACOG continued to recommend annual screening for cervical neoplasia in most women beginning at age 18 (or when a woman became sexually active) (l).

In the fall of 1987, ACS developed new guidelines for cervical cancer screening, which recommended that:

- All women who are or have been sexually active, or are 18 years or older, should have an annual Pap test and pelvic examination.
- After 3 consecutive normal exams the Pap test may be performed less frequently at the discretion of the physician (47).

The recommendations place no upper age limit on screening.

Table 9--Recommendations for Cervical Cancer Screening

Country/organization (date of recommendation)	Recommended screening frequency	Distinctions for screening elderly women
United States=		
ACS, ACOG, NCI, et al. (1988)[a]	Three consecutive annual normal Pap tests starting at age 18 or onset of sexual activity, then screening frequency determined at physicians discretion	None; no upper age limit is given for screening
USPSTF (1989)[b]	Screening at 1 to 3 year intervals determined by physician	Screening may be discontinued at age 65 if previous smears have been consistently normal
NIH (1980)[c]	Screening at 1 to 3 year intervals determined by physician	For women over 60 with two negative smears screening is not productive
ASCP (1988)[d]	Annually	No distinctions made between elderly and younger women
Canada:		
Task Force on Cervical Cancer Screening (1982)[e]	Annually for sexually active women aged 18 to 35; every 5 years from age 35 onward	Discontinue screening at age 60 if repeated satisfactory smears were obtained previously
Canadian Task Force on the Periodic Health Examination (1979)	When first sexually active, and once within a year of first smear; every 3 years until age 35; every 5 years thereafter	Every 5 years or at interval based on Physician's clinical judgment
lhiited Kingdom:		
Working Party on Cervical Cytology Screening (1987)[g]	Every 3 years	Screening may end at age 64 if 3 consecutive negative smears have been obtained (the latest not more than 3 years previously)
Denmark:		
Department of Health (1988)[h]	Every 3 years	Women are not invited for smear after age 70
Australia:		
National Health and Medical Research Council (1987)[i]	Every 3 years	No distinctions made between elderly and younger women

ABBREVIATIONS: ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; ASCP = American Society of Clinical Pathologists; NCI = National Cancer Institute; NIH = National Institutes of Health; and USPSTF = U.S. Preventive Services Task Force.

[a] D.J. Fink, 'Change in American Cancer Society Checkup Guidelines for Detection of Cervical Cancer," ~ [b] Cancer Journal for Clinicians 38(2):127-128, 1988.
U.S. Department of Health and Human Services, Preventive Services Task Force, Guide to Clinical Preventive Services (Baltimore, MD: William & Wilkins, 1989).
[c] Southern Medical Journal, "NIH Consensus Develo~nt panel Smnary--Cervical Cancer Screening: The pap dSmear," Southern Medical Journal 74(1):87-89, 1981.
Washington Report, IIO_rgan i_zat i_on s Speak Out on Pap Smear Frequency,rl Washington Rem_rt 6(2):1, 1988.
[e] Canadian Medical Association Journal, "Cervical Cancer Screenin, Programs: Summary of the 1982 Canadian Task Force Report," Canadian Medical Association Journal 127:581-589, 1982.
[f] Canadian Task Force on the Periodic Health Examination, "The periodic Health Examination 1979," Canadian Medical Association Journal 121:1193-1254, 1979.
[g] Intercollegiate Working Party on Cervical Cancer Screening, Report of the Intercollegiate Working Party on Cervical Cytology Screening (London, England: Progress Press Ltd., 1987).
[h] E. Lynge, "Mass Screening for Cervical Cancer and Breast Cancer in Denmark," unpublished paper for the Danish Cancer Society, June 1988.
[i] P.W. Shield, B. Daunter, and R.G. Wright, "The Pap Smear Revisited," The Australian and New Zealand Journal of Obstetrics & Gynecology 27(4):269-282, 1987.

SOURCE: Office of Technology Assessment, 1990.

The National Cancer Institute (NCI), ACOG, and a number of other medical associations have approved similar or identical recommendations. Three other groups, however--the American Society of Clinical Pathologists (ASCP), the American Society of Cytology, and the College of American Pathologists-- do not entirely agree with these guidelines. ASCP recommends, for example, that all women who are (or have been) sexually active continue to have annual Pap smears even after a past series of normal smears. ASCP makes no distinctions between elderly and younger women (170).

The National Institutes of Health (NIH), of which NCI is a part, have been actively involved in the formulation of cervical cancer screening recommendations. In 1980, NIH convened a Consensus Development Panel to examine the scientific basis for screening and make recommendations for the use of the Pap smear in screening for cervical cancer. The panel recommended that all asymptomatic women who are or have been sexually active be screened at intervals between 1 and *3* years if the first and second smears are normal, with the exact frequency to be determined by the woman and her physician (140). Screening in women over age 60 who had had two previous negative smears was believed to be "unrewarding." These recommendations of the consensus pane 1 participants are slightly at variance with the 1988 ACS guidelines adopted by NCI itself.

In 1984, the Federal Government appointed a Task Force on Preventive Services to develop age- and sex-specific recommendations for a variety of clinical preventive services, including Pap smears. The recommendations, published in spring 1989, included regular Pap testing for all women starting at the beginning of sexual activity, with repeat smears every 1 to 3 years at the physician's discretion. The task force recommended that screening stop at age 65 if previous smears have been consistently normal. However, since many older women have not been screened regularly throughout their lives, the task force recommended that elderly women without a documented history of negative smears continue to receive screening (162).

Recommendations in Other Countries

Canada--Canada's first recommendations regarding Pap smear screening were issued in a 1976 report from the Canadian Task Force on Cervical Cancer Screening Programs. This report suggested that all sexually active women over age 18 receive an initial smear followed by a second smear done within 1 year. If the two initial smears and all subsequent smears are satisfactory, further smears should be taken at 3-year intervals until the age of 35, and at 5-year intervals from 35 to 60. Women over 60 who had repeated satisfactory smears may be dropped from the cervical cancer screening program (22). The task force amended its recommendations in 1982, advising annual screening for sexually active women between ages 18 and 35. Annual screening of women over 35 was concluded to be unnecessary if a woman had had normal smears until that time. The task force reaffirmed its recommendation that women over 60 who have had repeated satisfactory smears without significant atypia may be dropped from a screening program (23). The recommendations of the Canadian Task Force on the Periodic Health Examination, issued in 1979, echoed this advice (24).

Great Britain -- Until the government-appointed Working Party on Cervical Cytology Screening issued standard guidelines for cervical cancer screening, groups in Great Britain supported varied and contradictory screening protocols. The working party, composed of representatives of relevant medical organizations, recommended routine Pap smear screening every 3 years for all women beginning at age 20. The group also recommended opportunistic screening of younger women at high risk due to sexual activity. They suggested that screening should end at age 64 provided the woman has had 3

consecutive negative smears, the most recent one no more than 3 years previously (65). The policy of the National Health Services towards screening for cervical cancer in the elderly is that cervical cytology is available to women 65 and over who have not had two consecutive negative smears in the previous 10 years (35).

Denmark and Australia--Both the Danish and the Australian governments have issued screening guidelines, although neither has a formal nationwide cervical cancer screening program. The Danish Department of Health recommended in 1986 that screening be done every 3 years. Screening is aimed at women between ages 23 and 59, but all women are invited until age 70 (84). In Australia, the National Health and Medical Research Council issued a report on the frequency of cervical cytology in 1984; it recommended that women be screened every 3 years from the start of sexual activity onward (129).

Utilization of Screening by the Elderly

Utilization Rates

Utilization of Pap smear screening is lower for elderly than for other women. This pattern may be partly related to the fact that many of today's elderly women were already past childbearing, and no longer seeing an obstetrician/gynecologist, when Pap smear screening became widespread. Among women in general, both the proportion of women who have ever been screened and the proportion who have been screened recently has been growing over time. Elderly women, however, continue to have lower utilization by either measure.

Slightly more than one-half (52 percent) of elderly women have had a Pap smear within the past 3 years (55).[8] Utilization has increased over time but still remains lower than in younger age groups. 1n One study, the proportion of women aged 60 to 79 who had had a Pap test within the past 2 years rose from 38 percent in 1973 to 43 percent in 1985. Nonetheless, the 1985 screening rates were still only two-thirds as high as the rate in younger women (89). A second study, based on a 1986 national telephone survey, shows similarly dramatic differences in the use of routine Pap smears between older and younger women (table 10) (61). The decrease in utilization associated with age in this study cannot be attributed to a clinical decision to withhold preventive care from women already ill, since the results were unchanged when the investigators controlled for health status.

A sizable group of elderly women who have never been screened for cervical cancer persists. Estimates of the number of U.S. elderly women who have never been screened range from 24 to 61 percent (86,150,169,172). In a 1986 survey, 11 percent of elderly women said that they had never had Pap smears, nearly double the 6 percent rate for women in general (61). In a 1980 telephone survey of Maryland women in non-metro -politan communities, 23 percent of women aged 65 and older reported never having had a Pap test and an additional 28 percent reported not having had one within the past 5 years (26). These results, although not generalizable to metropolitan communities, are consistent with the findings from the 1986 survey.

Table 10--Utilization of Routine Pap Smear Screening

Received last Pap smear	Age group 20-39	40-64	65 and older
Within past year.	68%	49%	30%
Within past 3 years (if age 20-64) or past 5 years (if age 65 0r older)	91%	73%	59%

SOURCE: Adapted from R.A. Hayward, M. Shapiro, H.F. Freeman et al., Who Gets Screened for Cervical and Breast Cancer?" Arch. Intern. Med. 148:1177-1181, 1988.

8 Because of the data coding practices followed by the National Health Interview Survey (NHIS), on which this figure is based, "within the past 3 years" actually means "within the past 3 years and 11 months. "

Correlates of Utilization in the Elderly

The factors a.ssociated with increased risk of cervical cancer are also associated with low utilization of screening for the disease. Elderly women who refuse screening are probably at higher risk than those who are screened, as they are older, nonwhite, and not previously screened (86). Elderly black women living in non-metropolitan areas have particularly low screening rates (73); in one study, 68 percent of the women in this category had never had a Pap smear (6).[9] Elderly Hispanic women also have very low utilization rates (157).

Women with health insurance, and women with private insurance supplements to Medicare, are more likely to have had a recent Pap smear than less insured and uninsured women (55,61,176). Many insurance policies do not cover preventive care, so these findings are probably not due solely to coverage of preventive services. Rather, having health insurance may be correlated with other factors such as greater affluence, greater concern with health, or lower overall out-of-pocket health expenditures that are themselves related to higher use of preventive services. Educational level and income have also been found to be related to the probability of having had a recent test (61).

Going to a physician increases the probability of being tested, but it does not ensure screening. In one study, among older women who had never had a Pap test, 82 percent had had a recent physician contact (89). In another study, the type of provider was associated with the regularity and the recency of Pap testing: having a gynecologist as the usual source of care was associated with a greater probability of receiving regular Pap-tests (26). Relatively few elderly women, however, have a gynecologist as their usual source of medical care (only 1 percent of women aged 65 to 74 in this study, for instance), and some elderly women receive most of their medical care from specialists who rarely provide gynecological care (e.g., carbiologists (26). Among younger women, gynecologists perform most Pap smears; for elderly women, however, the proportion of smears performed by gynecologists is less than one-half (46 percent). Internists and family practitioners perform most of the rest (166).

It has long been assumed that elderly women would be hard to recruit for screening (133). However, a New York study (172) found that Pap smear screening was acceptable to elderly women attending a municipal hospital clinic: there was only a 25 percent no-show rate for scheduled visits exclusively for Pap tests, and none of the patients offered screening during a primary medical care visit refused it. Outreach programs, using mailed letters or telephone calls to invite women to come in for a screening appointment, have increased Pap smear utilization in both younger and older women in England (l17,132). These strategies may well be effective in elderly American women as well, although recruitment of older women to cancer screening is not necessarily inexpensive (75).

CONCLUSIONS

Pap smear screening, combined with appropriate treatment, can reduce the incidence of invasive cervical cancer and the mortality from the disease in the general population. Elderly women are as likely as younger women to develop invasive cervical cancer, and they are considerably more likely to die from the disease. Thus, routine Pap smear screening of elderly women holds potential for extending substantial health benefits to this population.

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9 In an analysis of 1982 NHIS data, race did not have an independent effect on utilization of cervical cancer screening among elderly women (55). Observed race differences in other studies may well be explained by factors such as income and education.

Screening in elderly women, however, has some characteristics that might yield different results from screening in younger populations. First, there appears to be less CIN and CIS in elderly women. This finding may be in part an artifact of lower screening rates in elderly women. It is possible, however, that either more of these lesions progress to invasive cancer in elderly women, or that progression is faster, or both. This suggests that to detect cervical cancer at a preinvasive state, an optimal screening program for older women would emphasize outreach to previously unscreened women and may include more frequent tests. Second, the potential for inaccurate Pap smears is higher for elderly women, because it is more difficult obtain a sample of cells from the appropriate region of the cervix and because elderly women may have a variety of disorders that can lead to abnormal smears. Thus, ensuring the accuracy of sampling and smear interpretation are also important components of a screening program.

Irrespective of other risk factors, women who have been screened in the past are at lower risk of developing invasive cervical cancer than those who have not been screened. This is presumably due to the detection and treatment of noninvasive cervical neoplasia in screened women. Poor and nonwhite elderly women are particularly likely not to have been previously screened.

Future cohorts of elderly women may have either higher or lower risks of cervical cancer than today's cohort, due to differences in such factors as history of sexuaI activity and hysterectomy rates, and previous use of Pap tests. Little research has been done that elucidates the contributions of different risk factors in the older age group or the natural history of cervical neoplasia in this group.