The Costs and Effectiveness of Cervical Cancer Screening in Elderly Women

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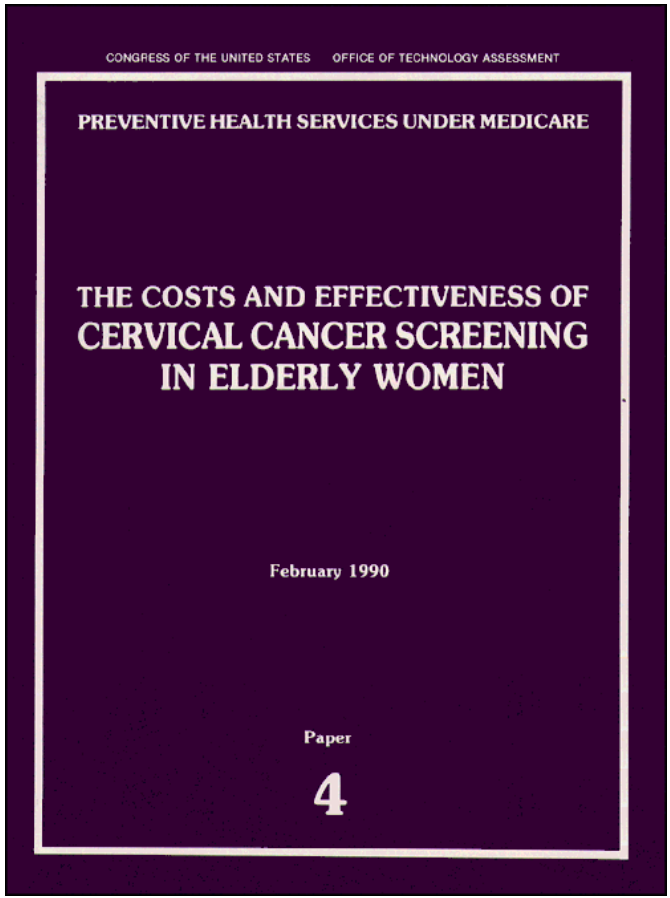

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Costs and Effectiveness of Cervical Cancer Screening in Elderly Women

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Preventive Health Services Under Medicare

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FOREWORD

Interest in health promotion and disease prevention strategies for the elderly has grown in the last ten years, at least partly as a result of the search for ways to moderate the rising costs of health-care in this growing segment of the population. Reflecting this interest, the House Committee on Ways and Means requested that OTA analyze the effectiveness and costs of providing selected preventive health services to the elderly under the Medicare program. The Senate Labor and Human Resources Committee has also requested that OTA provide information on the value of preventive services for the American people. This paper, *Costs and Effectiveness of Cervical Cancer Screening in Elderly Women, is* the fourth in a series of papers being prepared in response to these requests.

Cervical cancer screening with the Pap smear test is a preventive service that is routinely performed on women of all ages but that is much less common among elderly than among younger women. This paper examines what is known about the course of cervical cancer in elderly women; the effectiveness of the Pap test and its accuracy in this age group; the relative costs and effectiveness of different screening test schedules for elderly women; and the implications of these findings for Medicare.

Previous papers in this series on "Preventive Health Services Under Medicare" have assessed screening for open-angle glaucoma, the current use of preventive services by the elderly, and screening for cholesterol. Future papers will assess screening for colorectal cancer and analyze broad issues related to Medicare financing of preventive health services for the elderly.

JOHN H. GIBBONS
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1. SUMMARY

Cancer of the uterine cervix is not a disease restricted to young women. One-fourth of new cases of invasive cervical cancer occur in women age 65 and over; 1,867 elderly women died of this disease in 1986.

Compared to young women, elderly women appear to have lower rates of localized (noninvasive) tumors,[1] but they have higher rates of invasive cervical cancer. Elderly women are also more likely than younger women to have advanced (rather than early) invasive disease at the time of diagnosis.

The prevalence of invasive cervical cancer in elderly women is estimated to be between approximately 2 and 8 per 1,000, or roughly 38,000 to 152,000 women age 65 and over. Incidence is about 0.25 to 0.35 new cases per 1,000 elderly women per year, or about 4,800 to 6,700 new cancers each year. Across all ages, women at high risk of cervical cancer are those who are poor, are nonwhite, were young at age of first intercourse, have had multiple sexual partners, or smoke. Among elderly women, those who have not previously been screened are at especially high risk.

Pap smear screening, combined with appropriate treatment, is an effective method of reducing mortality and morbidity from cervical cancer. In areas where it has been introduced, Pap smear screening has generally been associated with lower mortality from the disease. Case-control studies have found that women who have been screened are two to ten times less likely than others to develop cervical cancer. The protection associated with prior screening is found in elderly women as well as among younger women. Elderly women, however, are less likely to be screened than younger women and have seen less reduction in mortality rates than other groups. Future cohorts of elderly women may be better-screened, as the current group of younger women (with higher screening rates) ages.

Although elderly women as a group would reap benefits from cervical cancer screening, the implications of screening elderly women are different from those for younger women. Pap smears probably yield **a** higher proportion of both false positive and false negative tests in elderly women. Pap smears from elderly women are sometimes inadequate due to anatomical changes associated with age, which may increase the number of false negative test results. Also, some conditions that are prevalent in older women can lead to false positive test results. No studies directly comparing the accuracy of the Pap test in elderly and nonelderly women have been performed.

Medicare coverage of Pap smear screening is one possible measure to increase utilization of this test among elderly women. Until very recently, however, Medicare paid for Pap smears only as a diagnostic test (e.g., after symptoms of cervical cancer developed).[2] One consideration in the implementation of a screening benefit is the relative cost-effectiveness of different Pap smear screening schedules for elderly women. The cost-effectiveness model in this paper simulated the costs (to the health care system) and the benefits of Pap smear screening for a hypothetical cohort of women who enter the system at age 65. The results of the model indicate that Pap smear screening in elderly women does not appear to be very costly for

1 The finding that elderly women have low rates of noninvasive tuners relative to their overall rate of invasive cancer may be due in part to lower screening (i. e., less opportunity to detect such symptomless tuners) in older women.

2 The Omnibus Reconciliation Act of 1989 extended Medicare coverage to Pap smear screening. Tests are reimbursable if a woman has not had a Medicare-covered test within 3 years. The Secretary of the Department of Health and Human Services has the option to make high-risk women eligible for more frequent coverage. The benefit takes effect July 1, 1990.

the potential years of life saved from this technology, although it is unlikely to actually save health care costs.

Under base case assumptions, the model found that a single screening of women at age 65, when they became eligible for Medicare, would save 14,400 life years per 1 million women screened (discounted at 5 percent) and would cost the health care system $1,666 Per year of life saved.[3] The incremental cost per year of life saved is least for 5-year screening ($1 ,453) and is progressively greater as screening frequency increases. It amounts to $5,956 per life-year saved for the incremental effects of a 3-year screening cycle over a 5-year cycle, and rises to $39,693 for annual screening. The model considers only direct cancer-related health care costs and the benefits of lives saved. Potential benefits such as employment and disability-free days, and costs such as future medical costs incurred by extending life, are not included.

The cost-effectiveness of cervical cancer screening under base-case assumptions is comparable to other preventive services for elderly individuals. The cost-effectiveness of Pap tests every 3 years is similar to that of vaccination against pneumococcal pneumonia (136,155); the cost-effectiveness of annual Pap tests is comparable to annual mammogram screening for breast cancer in elderly women (156).

The cost-effectiveness ratio for Pap smear screening depends heavily on the extent to which high-risk, rather than low-risk, women are screened. Low-risk women derive some benefit from screening, but at very high cost to the health care system. Screening only high-risk women, on the other hand, has a very low cost per life-year saved. This difference has implications for the results of the new Medicare benefit that extends coverage to all elderly women. The cost per life-year saved by screening could be considerably reduced if such a benefit were combined with measures to raise the utilization of the benefit by high-risk women above the average rate for the population as a whole (even though the resultant higher utilization would raise total program costs). Because the cost of screening is also highly sensitive to the accuracy of the test, increased investment in laboratory accuracy would likewise increase program effectiveness and reduce the cost per year of life saved.

Cervical cancer is only one of many gynecological diseases that can affect elderly women. Endometrial cancer, for example, is particularly prevalent in this age group (79). A negative Pap smear does not necessarily protect against other uterine cancers. The results of this paper cannot be used to draw any conclusions about the general need for gynecological care in elderly women.

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3 "Cost per year of life saved" is a measure that enables direct comparisons of different health interventions (in this case, cervical cancer screening at different time intervals). In this analysis, the medical costs of each screening program--including screening, diagnosis, treatment, and identification of women who had false-positive screening test--were weighed against the benefits of preventing deaths due to cervical cancer in women whose disease was detected by the screening program.

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.

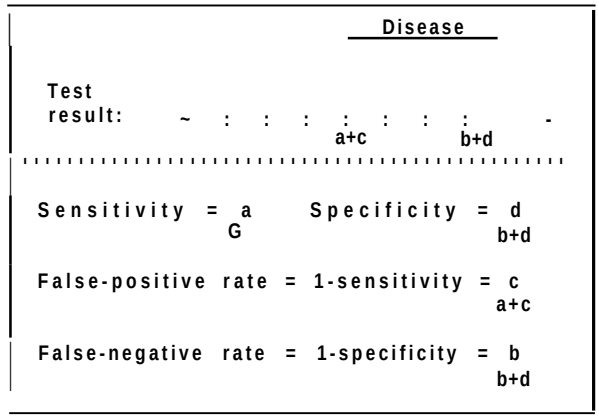
In some cases, efforts to minimize evaluation errors may increase sampling errors. For example, lubricating jelly is generally not recommended for use when a Pap smear is taken because it is believed to diminish cellular detail, making accurate evaluation of the smear difficult. In elderly women, however, 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.

INTRODUCTION

Given that screening can be an effective method of reducing morbidity and mortality from cervical cancer in elderly women, what are the actual likely costs and outcomes that would result from screening women in this group? This chapter describes a cost-effectiveness analysis that assesses the health and cost impacts of different Pap smear screening alternatives for elderly women who are screened. The chapter then examines some of the implications of the model results for the Medicare program.

THE COST-EFFECTIVENESS MODEL

Description

The model examines the relative costs and effectiveness of four different screening alternatives:

- one-time screening at age 65,
- screening every 5 years (beginning at age 65),
- screening every 3 years, and
- annual screening.

A Markov model (described in app. E) is used to simulate the process of screening, diagnosis, and treatment in a hypothetical population of one million women, beginning at age 65. Because one purpose of the model was to lend insight into the usefulness of a Medicare benefit, and because Medicare has no records on most individuals before they reach age 65, the model assumes that nothing is known about the specific screening history of any individuals before that age.

Five states of health are included in the model and are labeled as follows:

- healthy,
- CIN (corresponding to cervical intrae - pithelia neoplasia (CIN) grades 1 and 2--mild and moderate dysplasia),
- CIS (corresponding to CIN grade 3--severe dysplasia and carcinoma *in situ* (CIS)),
- early invasive cervical cancer (EICC, corresponding to stage I cancer), and
- late invasive cervical cancer (LICC, corresponding to stages II, III, and IV).

Within each state of health, two possible substates exist; a woman's condition may be *unrecognized (i.e.,* not yet brought to the attention of the medical system) or *recognized (i.e.,* diagnosed through screening or through the diagnostic evaluation of symptoms). (Following the logic that "recognized" indicates further contact with the medical system, "healthy-recognized" is the label given in the model to healthy women who have false-positive Pap smear results and thus undergo diagnostic workups.) An additional state is included to represent deaths as the model progresses.

The simulation program tracks the progress of the hypothetical cohort of 1 million 65-year-old women until they reach age 109. The remaining survivors are assumed to die before reaching age 110. Each iteration of the model corresponds to 1 year. Running tallies are maintained of the number of smears performed, the number of cases diagnosed at each disease stage, and overall cohort survival.

A significant limitation of the Markov model as it is applied here is that all tumors are assumed to have a constant probability of moving from one state to another in any given time period. In real life there are likely to be multiple populations of tumors with different progression rates depending on etiology, host factors, and so forth. Cruciaaly, a screening program will be most sensitive to finding the slowly progressing lesions (length bias), leading to an overestimate of the program's effectiveness in preventing

mortality. The importance of this issue in interpreting the model results is discussed at the end of this chapter.

Assumptions

Model Inputs

A Markov model simulation requires two sets of inputs (app. E). First, one must specify the proportion of subjects in a cohort falling into each state at the outset--i. e., the proportion of 65-year-old women who are healthy, have CIN, etc. In this model, the proportion of women who begin the model in a state other than healthy corresponds to the prevalence of CIN, CIS, EICC, and LICC in women at age 65. The probability of starting in the healthy state is simply one minus the total of the other probabilities. All women begin the model in an unrecognized substate.

Second, one must specify, for each state, the probability that a woman will move to a different state (e.g., from CIN to CIS) during each iteration of the model (i.e., per year). Not all movements between states can occur; no cases can move out of the dead state, for example. Only the following types of transitions are allowed in this model:

- *recognition* --transition from an unrecognized state to the corresponding recognized state (through screening or diagnosis);
- clearance--transition from one healthy substate to the other by ascertaining that a Pap smear result was a false positive (somewhat counterintuitively, this corresponds to transition from "healthy-recognized" to "healthy-unrecognized");
- *progression* --transition to the next most advanced disease state (e.g., CIN to CIS);
- *regression or cure--permitted* only for transition from CIN or CIS to the healthy state; and
- death--transition to the dead state from any other state.

In any year, women who do not make one of these transitions remain in their current state.

The specific numbers used as inputs to the model are derived from the medical studies described in chapter 2. For most relevant aspects of cervical cancer in elderly women, no definitive studies or unified consensus exists. Thus, to enhance confidence in the results of this model, a range of estimates for each data element was obtained. A base case was chosen to represent the "best estimate" of the true value of the data item. A high estimate and a low estimate are chosen as well, in order to test the sensitivity of the base-case results to the model assumptions. Such sensitivity analyses can enhance confidence in the overall conclusions of the simulation and identify the areas where uncertainty has the greatest implications. The various estimates are presented in table 11 and discussed briefly below. Appendix F presents the rationale for selecting specific estimates in greater detail.

Recognition Probabilities--For women with disease, the probability of transition from an unrecognized to a recognized state in the model is dependent on the sensitivity of the Pap test.[1] For healthy women, "recognition" depends on the specificity of the test--i.e., the rate at which healthy women are falsely identified as having disease. Base-case rates of sensitivity and specificity used in the model are within the range of estimates reported in the literature, but they are from the low end of that range to accommodate the likelihood that real-world accuracy for Pap smears from elderly women is somewhat lower than the test accuracy found in carefully monitored studies and studies of younger women.

Women with CIN and CIS can have their disease recognized only through screening. Invasive cancer, however, may also become recognized as a result of symptoms. Reliable

1 The actual probability for women with CIN and CIS is the product of test sensitivity and survival probability; for women with EICC and LICC, the rate of development of symptoms is an added factor.

Table n--Cost-Effectiveness Model Input Data Assumptions

		Data assumptions		
		Lou	Base	High
Pap smear sensitivity and specificity				
Sensitivity for:	CIN	.50	.75	.00
	CIS/EICC/LICC	.50	.75	.82
Specificity		.87	.95	.99
Annual probability of recognizing disease due to symptoms				
EICC		.07	.12	.27
LICC		.80	.80	.80
Initial state distribution for Pap smear simulation				
HEALTHY		.99013	.98721	.97940
CIN		.00380	.00480	.00580
CIS		.00239	.00239	.00620
EICC		.00081	.00280	.00559
LICC		.00287	.00280	.00301
Age-group-specific mortality rates for invasive cervical cancer				
EICC mortality at age:	65-69	.076618	.076618	.076618
	70-74	.070786	.070786	.070786
	75-79	.078677	.078677	.078677
	80-108	.138621	.138621	.138621
	109	1.0	1.0	1.0
LICC mortality at age:	65-69	.151742	.151742	.151742
	70-74	.172282	.172282	.172282
	75-79	.217248	.217248	.217248
	80-84	.281017	.281017	.281017
	85-108	.331627	.331627	.331627
	109	1.0	1.0	1.0
Annual probabilities of progression between states (per 1,000 cases)				
HEALTHY --> CIN		.94	3.28	5.41
CIN --> CIS		73.6	178.0	267.0
CIS --> EICC		181.0	261.0	632.0
EICC --> LICC		220.0	390.0	860.0
Annual regression rate (per 1,000 cases)				
CIN		5.4	38.1	265.0
CIS		0.0	0.0	201.0
Annual cure rate (Per 100 cases)				
CIN		85.0	95.0	98.0
CIS		90.0	98.0	98.0

Key: CIN--cervical intraepithelial neoplasia (grades 1 and 2)
CIS--carcinoma in situ and severe dysplasia
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for sources of information and basis for individual data assumptions.

data on the rates of symptom development are not available. The assumptions regarding the likelihood of symptom development are based on data on the stage distribution of cancers at diagnosis, the probability of progressing from EICC to LICC, and the assumption that the great majority of women with LICC will develop symptoms within a year (app. F).

Clearance- -Clearance occurs when a woman with a false-positive test undergoes a comprehensive diagnostic workup. It is assumed that all false positives are identified in this workup.[2]

Progression, Regression/Cure, and Death Probabilities--Some research suggests that the probability of progressing from one state of neoplasia to the next is dependent on age (32). Base-case estimates in the model are thus derived from age-dependent data reported in the literature. The age-dependent assumption may not be correct; however, the high and low estimates of progression probabilities encompass a range of probabilities that includes data from other age groups.

Women with CIN or CIS may exhibit spontaneous regression to the healthy state. Women with recognized disease may revert to the healthy state subsequent to treatment (cure). Women with CIS are actually considered to be slightly more likely to be cured by a single treatment than women with CIN, because more women with CIS undergo very aggressive treatment (e.g., total hysterectomy). Consequently, there is a slight increase in the number of cases in which the lesion is entirely removed with a single treatment.

Death rates in the model for women in healthy, CIN, or CIS states are based on national, age-specific, all-cause mortality data (164). They are considered highly reliable assumptions and do not appear in table 11.

The situation for invasive cancer--EICC and LICC--is different. Although some women with EICC are probably cured, data to estimate the probability of this are not available. This model therefore does not permit transitions from the invasive cancer states back to earlier states. Consequently, the model probably slightly overestimates morbidity from invasive cancer; once a woman moves into the EICC state, she will be categorized as having invasive cancer until she dies. This does not affect her chance of survival in the model, however. The death probabilities in the model for women with invasive cancer are based on all-cause mortality data specific to the cohorts of women diagnosed in each stage of cervical cancer. Thus, for a woman with EICC, the statistical likelihood of dying in the model depends only on the fact that she was once diagnosed with EICC, not on the fact that the model continues to classify her in that category.

Service and Cost Assumptions

Each woman in the model diagnosed with CIN, CIS, EICC, and LICC incurs the costs of diagnosis, treatment, and followup associated with that state. At any given screening frequency, a single iteration of the model (representing the passage of a year of time) is accompanied by a specific number of women newly diagnosed in each state. These women then begin to accrue the costs associated with those diagnoses. At the end of the simulation, the total costs associated with each screening frequency can be tallied and compared.

The costs of screening itself and of clearing false-positive cases are also included in the total costs for each screening frequency. In the model, a "positive" test is any

2 A special feature of this model is that the healthy- recognized state is a "virtual" state: after entering that state and being tallied (so that costs of work-up can be assessed), these women are returned to the healthy-unrecognized state immediately, rather than waiting for the next year.

Pap smear result that leads to a further investigation of the possibility of neoplasia. A "false-positive" test is any so-defined positive smear in which the investigation does not lead to a diagnosis of neoplasia, even if some other condition is diagnosed and followed up. This model considers neither the additional costs nor the additional benefits incurred after this point from the incidental diagnosis of other conditions. The cost of a workup to clear a false positive is equivalent to the diagnostic segment of care for CIN.

To calculate the average cost per woman in each state (CIN, CIS, EICC, and LICC), a set of services related to the diagnosis, treatment, and followup of each state were specified. The specified protocol is based on current oncological practice, supplemented by observations of members of an expert panel from their clinical experience (app. C). Modifications were made in the indicated protocol based on statistical data from the National Hospital Discharge Survey, which made possible an analysis of the proportion of hospitalized elderly women with a given diagnosis who actually received specific services. It must be emphasized that the resultant modified protocol is not, and is not intended to be, an example of an ideal protocol for treating cervical neoplasia. Rather, it is an approximation of actual current practice.

Table 12 summarizes the total costs for all services described below.[3] The itemized components of these costs and the calculation of total cost for each service package (e.g., treatment of CIS) are detailed in appendix F.

Table 12--Summary of Cost Estimates for Different Components of Ca

Component	Diagnosis/ treatment	Followup	Total
CIN.	$ 669.65	$ 432.71	$1,102.36
CIS.	3,925.96	432.71	4,358.67
EICC.	8,033.70	1,182.76	9,215.76
LICC.	12,232.00	1,126.76	13,358.76
False positives:	$ 575.51	$ --	$ 575.51
Screening:	$ 11.37 (base estimate)		
	11.37 (low estimate)		
	43.25 (high estimate)		

[a]Cost per woman with indicated condition when it occurs. (Costs as presented in this table are undiscounted; they are discounted at the point in the model where they are incurred.)

KEY: CIN--cervical intraepithelial neoplasia
CIS--carcinoma in situ
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for calculation of individual costs.

Screening --All women are screened in the model (except in the no-screening scenario). The updated Medicare average allowed charge for a simple Pap smear and associated specimen collection fee ($11.37) is used as the assumed cost of the screening service for both the base case and the low estimate.[4] The high-cost estimate for screening includes the cost of a limited visit to a gynecologist as well as the cost of the test itself. If the result of Pap smear screening is

3 The estimate of the total cost of late cancer care, $13,266, is lower than estimates by other analysts based on 1974-1981 data from the Continuous Medicare History File (5). Their analysis would lead to an estimated total cost of approximately $7,000 for a woman dying of cervical cancer 2 years after diagnosis. Their estimates are not directly usable in this cost-effectiveness analysis because they do not distinguish between cases diagnosed in early versus late stages, as is required for this model. In addition, changes in clinical practices, substitution of outpatient for inpatient locations, and so forth, make it desirable to avoid reliance on data from the 1970s.

4 The Medicare average allowed charge for a service is used as the basis for Medicare payments to health care providers; Medicare pays a proportion of the allowed charge for all covered services. Actual physician and laboratory charges may be higher than the Medicare allowed charge.

negative, the patient receives no further service, and she is returned to the population with the expectation of routine rescreening at the time interval under study (e. g., in 5 years).

Diagnosis--If the result of the screening is positive for abnormal cells, a COlPOSCOPY is done (assumed to require an office visit). Subsequent procedures depend on the adequacy and results of COlPOSCOPY, as follows:

- If a satisfactory view is obtained at colposcopy, then positive cases undergo a directed biopsy. Negative cases repeat the Pap test. If it, too, is negative, the case is returned to the population, but if it is positive, ionization is performed. This is an inhospital procedure.
- If colposcopy does not provide satisfactory visualization of the suspect area, ionization is done. If the finding is negative, the Pap test is repeated, and if that is positive, other biopsies are done; if the Pap test is negative, the patient is returned to the population. If the conization finding is positive, the case is diagnosed as CIN, CIS, or invasive cancer.

This is the extent of the diagnostic workup for women with false-positive tests and for women with CIN or CIS. Women with invasive cancer must also undergo a staging workup to determine the extent to which the cancer has spread. The staging protocol includes chest X-ray, pelvic computed tomography scan, sigmoidoscopy, barium enema, cystoscopy, intravenous urography, and blood tests (complete blood count, blood urea nitrogen, and creatinine determination).[5] Most of this protocol can be completed on an outpatient basis, although a minority of women (20 percent of those with EICC and 30 percent with LICC) receive the workup as hospital inpatients.

Treatment--For CIN, treatment options include cryosurgery, cauterization, and laser surgery, while for CIS the options are therapeutic ionization or hysterectomy. It is assumed that all true-positive CIN cases, and all CIS, EICC, and LICC cases, are treated. The assumed frequency with which various procedures are undertaken is drawn from existing hospital discharge data on patients with cervical cancer (app. D).

EICC treatment options are implantation of radioactive agents and/or hysterectomy. LICC options include distant radiation, chemotherapy, pelvic exenteration, or combinations of these. Some advanced cases are admitted to hospitals for supportive terminal care. (This protocol probably underestimates the actual total costs of LICC, since it does not include some relevant outpatient services--e. g., the cost of drugs to reduce pain.)

Followup Services and Costs--Each condition that requires treatment is assumed to have attendant 5-year followup costs. The services associated with followup of different disease states are adapted from Mandelblatt and Fahs (91).[6] The specific services and associated costs are presented in detail in appendix D for each disease state. In summary, the protocol for 5-year followup of each state is as follows:

- *CIN and* CIS--office visits and annual Pap smears for all patients. A small proportion of patients undergo repeat treatments (cryosurgery or ionization) during the first followup year.
- ElCC--office visits and various diagnostic tests, including intravenous

5 The use of ultrasound evaluation in place of some other tests is gaining favor in some institutions, but since the practice is apparently not yet widespread and there are no data on its frequency, it is not reflected in the cost assumptions of this model.

6 In pricing the followup services, clinic visits in their protocol are replaced by physician office visits for applicability to the general population of elderly women.

pyelograms (IVPS), chest X-rays, and pelvic sonograms. Numbers of visits and tests are greatest in the first year.
- LICC--office visits, IVPS, and chest X-rays in followup years 1 through 3; office visits, an IVP, a chest X-ray, and a pelvic sonogram in each of years 4 and 5.

Followup accounts for 8 percent of the total cost of LICC, for 12 percent of EICC, and for 9 percent of CIS costs. Since CIN evaluation is not very costly compared to evaluation of these other stages, followup amounts to 38 percent of total cost per CIN case.

Results

This model calculates the health care costs associated with screening, diagnosis, and treatment of cervical neoplasia at each alternative screening frequency. The benefits calculated include only the years of life saved by implementing screening. Other potential costs (e.g., cost of medical care for conditions unrelated to cervical cancer in those life-years saved) and other benefits (e.g., disability days avoided) are not considered. Both costs and life-years saved are discounted in the reported results.'

The results of the cost-effectiveness model under base-case assumptions are shown in tables 13 through 15. They are presented for 3, 5, and 7 percent discount rates. The discussion below focuses on the base-case results for a 5-percent discount rate.

Health Effects of Screening

In the base case, 14,400 discounted life years are gained for the model cohort of one million women by instituting a single screening at age 65 (table 13). There are successive increments in discounted life-years gained as the intensity (frequency) of screening is increased, although the size of the increase declines at frequencies greater than 5 years. In progressing from a 5-year to a 3-year schedule, for example, the incremental gain is reduced to 7,000 life-years. There is some gain at every increase in screening frequency, however, so total life-years of the cohort are greatest at the most frequent screening schedule. Annual screening adds 50,000 more years of life than no screening at all, or an average of 18 more days of life per woman in the cohort.

Table 13--Model Results: Life-Years Saved (Base-Case Assumptions)[a]

Discount rate and screening schedule	Years of life of cohort (in thousands)	
	Total	Additional
3% discount rate		
No screening	13,364.9	·
One-time at 65	13,384.2	19:3
Every 5 years	13,416.1	31.9
Every 3 years	13,425.8	12.7
Every year	13,435.2	9.4
5% discount rate		
No screening	11,383.1	·
One-time at 65	11,397.5	14.4
Every 5 years	11,419.3	21.8
Every 3 years	11,426.3	7.0
Every year	11,433.1	6.8
7% discount rate		
No screening	9,877.4	·
One-time at 65	9,888.4	11.0
Every 5 years	9,903.5	15.1
Every 3 years	9,908.6	5.1
Every year	9,913.7	5.1

'Per 1 million women beginning at age 65,

SOURCE: Office of Technology Assessment, 1990.

The added years are expected to be of good quality, because they are obtained through the prevention of late-stage cancer cases, not just through extending life for women with late-stage disease. (As table 14 shows, the number of cases of LICC decreases from 23,500 with no screening to

7 Discounting accommodates the economic assumption that something of value received today is worth more than that same thing received later. A 5 percent discount rate assumes that a $100 benefit (or cost) 1 year from now is equal to a $95 benefit (or cost) today. Discounting thus displays all benefits or costs in their present value.

Table 14--Model Results: Numbers of Smears Taken and Cases Detected (Base-Case Assumptions)[a,b]

	Number		Cases			
	Smears (millions)	False positives	CIN	CIS	EICC	LICC
No screening	--	--	--	--	34,461	23,532
One-time at 65	1.0	49,361	3,600	1,306	30,825	20,211
Every 5 years	4.1	199,570	29,257	8,180	14,281	8,162
Every 3 years	6.4	317,340	38,829	7,705	9,731	5,854
Every year	18.3	910,141	53,824	3,511	4,524	4,099

[a]The same actual numbers of cases accrue for each screening alternative regardless. Only the ultimate value of those expressed as life-years saved, is discounted.
[b]Per 1 million women beginning at age 65.

KEY: CIN--cervical intraepithelial neoplasia; EICC--early invasive cervical cancer
CIS--carcinoma in situ; LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990.

4,100 cases with annual screening.) Women live longer because they are cancer-free, or because they have early rather than late cancer. The cost of increasing years of cancer-free life among some members of the group, however, is increased detection and treatment of CIN. Some women whose CIN is detected and treated would not have gone on to develop invasive cervical cancer in their lifetimes. For these women, screening does not improve the quality of life; rather, it brings with it only the psychological costs and physical discomfort of undergoing the diagnostic and treatment procedures. This problem is greatest with annual screening, where the greatest number of CIN cases are detected.

costs

The costs associated with cervical cancer, including screening, diagnosis, treatment, and identification of false positives, are shown in detail in table 15. Total costs of services are higher with screening than without it, and they increase as the frequency of screening increases. The total cost of cervical cancer care for the cohort (of 1 million women) in the absence of screening is $218 million in the base case. By comparison, the cost associated with the least-intensive screening schedule--one-time screening at age 65--is $242 million, an incremental cost of $24 million. Total costs increase as the screening schedule intensifies and rise dramatically for annual screening, which has a total cost of $585 million (an incremental increase of $270 million over an every-3-year screening schedule).

The relative cost-effectiveness of screening at various intervals depends on whether the increase in life-years gained as screening frequency increases is more rapid than the rise in total costs associated with more frequent screening. Comparison of costs and effects of different schedules produces a cost-effectiveness ratio showing the added cost per year of life gained by screening (table 16). In the base case this amount is $1,666 for a one-time screen, but it increases with frequency of Pap testing, so that moving from a 5-year to a 3-year schedule costs $5,956 per additional discounted life-year gained. Annual screening costs considerably more--$39,693 per discounted life-year added to the cohort's life expectancy.

Sensitivity Analyses

Favorable/Unfavorable Cases--This analysis tests the sensitivity of the model results to changing the base-case assumptions

Table 15--Model Results: Costs (Base-Case Assumptions)[a]

Discount rate and screening schedule	cost (in millions) Screening	Confirmation of false positives	Cost of care (in millions) CIN	CIS	EICC	LICC	Total costs (in millions)
3% discount rate							
No screening	$--	$--	$--	$--	$49	$212	$ 261
One-time at 65	11	28	4	6	54	177	281
Every 5 years	36	89	23	27	52	84	311
Every 3 years	56	139	31	26	42	64	358
Every year	156	392	44	13	24	48	677
5% discount rate							
No screening	$--	$--	$--	$--	$40	$178	$218
One-time at 65	11	28	4		46	147	242
Every 5 years	31	78	20	23	45	77	273
Every 3 years		120		22	38		315
Every year	132	333	37	12	23	48	585
7% discount rate							
No screening	$--	$-	$--	$ --	$33	$153	$ 186
One-time at 65	11	28	4	6	40	125	214
Every 5 years	28	69	17	20	40	72	245
Every 3 years	42	105	23	20	34	59	282
Every year	114	288	32	11	23	47	516

[a]Per 1 million women beginning at age 65.

KEY: CIN--cervical intraepithelial neoplasia, EICC--early invasive cervical cancer
CIS--carcinoma in situ, LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990.

Table 16--Cost-Effectiveness of Screening Under Alternative Screening Assumptions: Base Case (5% Discount Rate)

Screening schedule	Discounted life-years' (in thousands) Cohort	Added	Costs (in millions) Total	Added	Cost-effectiveness ratio (added cost per life-year gained)
No screening	11,383.1		$217.79		
One-time at 65	11,397.5	14.4	241.78	$23.99	$ 1,666
Every 5 years	11,419.3	21.8	273.46	31.68	1,453
Every 3 years	11,426.3	7.0	315.15	41.69	5,956
Every year	11,433.1	6.8	585.06	269.91	39,693

[a]Per 1 million women beginning at age 65.

SOURCE: Office of Technology Assessment, 1990.

to more extreme high and low estimates (under a 5-percent discount rate). It includes:

- a "favorable" case in which all high and low input estimates most favorable to screening (e.g., high test accuracy, high prevalence) are combined; and
- an "unfavorable" case that combines all assumptions most unfavorable to screening.[8]

The specific set of high and low assumptions used for each case are presented in table 17; results are presented in table 18. Varying all assumptions in a direction favorable to screening results in absolute savings for all increases in Pap test frequency except for shifting from 3 years to 1 year. In addition, the gain in life years is substantially greater than in the base case. Compared to no screening, even a single screening gains 29,600 years of life. In contrast, if unfavorable assumptions are used, the greatest incremental gain occurs in going from no screening to a single screen but results in the addition of only 2,500 years of life. More frequent screening results in some additional gains, but at very high cost; at annual screening, the incremental cost per life-year gained is nearly $800,000.

High Risk/Low Risk Populations--In a further analysis, the model was applied separately to hypothetical cohorts of high-risk and low-risk women.

- The "high-risk" case includes assumptions of high incidence, prevalence, and progression rates and low regression rates (table 17). The low rate for symptom development for early cancer was also used, representing lower ability or willingness to enter the medical system after the development of mild symptoms of cancer. All other probabilities are as in the base case.
- The "low-risk" case assumes low incidence, prevalence, and progression rates; and high regression and symptomaticity rates. Other assumptions are as in the base case.

Marked differences in outcome were found for the two groups (table 18). For high-risk women, the gain in discounted life years was substantial throughout, and 5- and 3-year schedules result in actual cost savings. Even annual testing would cost less than $6,500 per incremental life-year saved. For low-risk women, gains were small for all but one-time testing. One-time testing yielded a cost-effectiveness ratio of $11,666 per life-year gained; cost-effectiveness ratios for more frequent intervals range from over $73,000 to nearly $500,000.

The "high-risk" and "low-risk" groups in the model do not directly correspond with known risk factors for individuals (e.g., past history of multiple sexual partners, no prior screening). The set of assumptions used to define these groups in the model, however, are those that most likely underlie higher real-world risk. A lack of prior screening, for example, means that any existing disease has not been detected; thus, elderly women with this risk factor would have higher average prevalence rates of neoplasia (one of the inputs for the high-risk group in the model).

Individual Sensitivity Analyses--In order to test the robustness of the clinical and economic assumptions used in the baseline model, one-way sensitivity analyses were performed for the worst-case assumption (either high or low estimate, depending on the parameter) for individual model parameters. For the previously described sensitivity analyses, the results compared the relative cost-effectiveness of screening under different screening schedules. To judge the effect of varying each individual parameter, however, all variables except the individual parameter of interest -- including the screening schedule -- are held constant. Thus, a single screening schedule must be chosen for the

8 High estimates of progression rates may be either favorable or unfavorable to screening, depending on how rapidly progression is assumed to occur in the base case. In this model, it turns out that lower estimates of progression rates are unfavorable, while higher estimates are favorable (table 17).

Table 17--Cost-Effectiveness Model Input Data Assumptions: Selected Sensitivity Analyses

	Data assumptions			
	Favorable/unfavorable[a]		High risk/low risk[b]	
Pap smear sensitivity and specificity				
Sensitivity for: CIN	.80	.50	.75	.75
CIS/EICC/LICC	.82	.50	.75	.75
Specificity	.99	.87	.95	.95
Annual probability of recognizing disease due to symptoms				
EICC	.07	.27	.07	.27
LICC	.80	.80	.80	.80
Initial state distribution for Pap smear simulation				
HEALTHY	.97940	.99013	.99013	.97940
CIN	.00580	.00380	.00380	.00580
CIS	.00620	.00239	.00239	.00620
EICC	.00559	.00081	.00081	.00559
LICC	.00301	.00287	.00287	.00301
Mortality rates for invasive cervical cancer				
(Same as base case for all alternatives--see table 9)				
Annual rate of progression between states (per 1,000 cases)				
HEALTHY --> CIN	5.41	0.94	5.41	0.94
CIN --> CIS	267.0	73.6	267.	73.6
CIS --> EICC	632.0	181.0	632.	181.0
EICC --> LICC	860.0	220.0	860.	220.0
Annual regression rate (Per 1,000 cases)				
CIN	5.4	265.0	5.4	265.0
CIS	0.0	201.0	0.0	201.0
Annual cure rate (Der 100 cases)				
CIN	98.0	85.0	95.0	95.0
CIS	98.0	90.0	98.0	98.0

[a]The 'favorable" sensitivity analysis combines all high and low assumptions most favorable to screening.
[b]The "unfavorable~ sensitivity analysis combines all assumptions least favorable to screening. The 'high risk~case assumes high incidence, prevalence, and progression rates and low regression rates, while the "low risk" case uses opposite assumptions for these factors. Other assumptions (e.g., test accuracy) are as in the base case.

Key: CIN--cervical intraepithelial neoplasia
CIS--carcinoma in situ
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for sources of information and basis for individual data assumptions.

Table 18--Cost-Effectiveness of Screening Under Alternative Screening Assumptions: Selected Sensitivity Analyses (5% Discount Rate)[a]

Screening schedule	Discounted life-years[a] (in thousands) Cohort	Added	costs (in millions) Total	Added	Cost-effectiveness ratio (added cost per life-year gained)
Favorable case					
No screening	11,264.3		$ 553.75	$ --.-"	$ ...
One-time at 65..	11,293.9	29.6	531.18	-22.57	*
Every 5 years	11,343.3	49.4	436.33	-94.85	*
Every 3 years	11,366.9	23.6	400.54	-35.79	*
Every 1 year.	11,395.0	28.1	430.27	29.73	1,058
Unfavorable case					
No screening	11,439.5	·	$ 52.87	$ -----	$ ...
One-time at 65..	11,442.0	2.5	173.09	120.22	48,088
Every 5 years	11,442.8	0.8	382.37	209.28	261,600
Every 3 years	11,443.3	0.5	557.19	174.82	349,640
Every 1 year.	11,444.4	1.1	1,434.46	877.27	797,518
High-risk women					
No screening	11,264.3	·	$ 553.75	$ -----	$ ---
One-time at 65..	11,292.3	28.0	554.95	1.20	42
Every 5 years	11,338.9	46.6	504.34	-50.61	*
Every 3 years	11,362.1	23.2	502.80	-1.54	*
Every 1 year.	11,392.3	30.2	697.41	194.61	6,444
low-risk women					
No screening	11,439.5	·	$ 52.87	$ -----	$ ...
One-time at 65..	11,443.3	3.8	97.20	44.33	11,666
Every 5 years	11,444.3	1.0	170.54	73.34	73,340
Every 3 years	11,444.8	0.5	230.80	60.26	120,520
Every 1 year.	11,445.4	0.6	530.42	299.62	499,367

*Cost-saving.

[a]Per 1 million women beginning at age 65.

SOURCE: Office of Technology Assessment, 1990.

analysis. Results for the one-way sensitivity analyses below are based on comparing a 3-year screening schedule with no screening. They can be contrasted with the analogous comparison under the base case, where 3-year screening (compared to no screening) costs $2,254 per life-year gained. (Note that this figure is substantially different from the figure presented earlier, which was the incremental cost-effectiveness of 3-year compared to 5-year screening.)

- Test Accuracy--Low estimates for expected rates of sensitivity and specificity affect the efficiency of the program considerably. With the low assumptions, comparing a 3-year screening schedule to no screening, 34,200 life years are gained for the cohort at an added cost of over $303 million, or $8,866 per life-year gained. In other words, if test accuracy deteriorated from base-case to low-case estimate--all else equal--the deterioration in test accuracy would cost nearly $7,000 more per life-year saved than what could otherwise have been achieved.
- Disease Prevalence--Lower prevalence rates have minimal effect. This happens because the model depends for the most part on prevalence rates only at initiation of the screening program.
- Disease Incidence and Progression--The model is much more sensitive to as-

sumptions regarding annual progression probabilities (including the probability of progressing from no disease to disease, that is, the incidence rate). The "worst-case" assumptions of progression probabilities result in a cost-effectiveness ratio of $11,971 per year of life saved in going from no screening to a 3-year cycle. It is the sensitivity of the model results to disease incidence and progression that is responsible for a large part of the much lower cost per life-year saved of screening high-risk women.

- Disease Regression and Cure--Estimates of low cure rates have a minimal effect on the results. However, the high estimates of annual regression probabilities raise the cost-effectiveness ratio substantially, with a rise to $8,851 for 3-year screening.
- Rate of Symptom Development--Assuming a lower rate of symptom development in early and late invasive cancer has minimal effect on cost-effectiveness ratios.

Conclusions

The cost-effectiveness model employed here examined the question: Given that a woman, beginning at age 65, gets screened for cervical cancer, what is the relative cost effectiveness of different screening schedules? The model found that, under base-case assumptions (5-percent discount rate), the lowest cost per life-year saved for screening elderly women is obtained with an every 5-year screening frequency, which costs $1,453 per life-year saved. The incremental cost per year of life saved is progressively greater as screening frequency increases, amounting to $5,956 per life year for a 3-year screening cycle (compared to a 5-year cycle) and rising to $39,693 for annual screening. These cost-effectiveness ratios are comparable to other preventive health services for the elderly that have been legislatively mandated, such as the vaccine used to prevent pneumococcal pneumonia and mammography to prevent breast cancer (136,155,156).

It is likely that these findings underestimate somewhat the true cost per life-year saved of screening elderly women. The model assumes a constant probability of moving from one state to another during any given time period, which probably leads to an overestimation of screening benefits. In reality, tumors progress at varying speeds. Since screening programs are more likely to detect slow-growing tumors than fast-growing ones, [9] and since slow-growing tumors are presumably less likely than fast-growing ones to be fatal, the real benefits of screening are probably not as great as those predicted by this model.

Comparing some of the implications of this model to the estimates of other researchers does indeed suggest that this model overestimates the effectiveness of screening, although not dramatically so. The lifetime incidence of cervical cancer that this model predicts under the base case is about 3.5 percent for elderly women receiving no screening and about 1.4 percent for elderly women being screened every 3 years. Some other researchers, using data from the National Cancer Institute's database, have estimated a lifetime incidence for elderly women of less than 1 percent under existing screening conditions (where only one-half of elderly women have been screened within 5 years) (128). An overestimate in this model of the total lifetime likelihood of developing cancer would lead to a corresponding overestimate of lives saved from screening.

Results from the model suggest that the cost per life-year saved for high-risk women who receive screening is quite low (about $1,000 for annual screening and cost-saving for less frequent schedules), while the cost-effectiveness ratio for low-risk women is substantially higher (even for one-time screening). These results have major implications for any generalized screening program. For any given age group, the lowest-risk women have generally had the highest utiliza-

9 **See discussion of** length **bias (ch. 2., box C).**

tion of Pap smear screening programs. If this experience holds true for elderly women as a group, the cost per life-year saved is likely to be highest if the implementation of the benefit does not change the mix of women receiving Pap smears (i. e., mostly low-risk women being screened). If the proportion of screened women who are high-risk increases, the cost per life-year saved will decline, making the program more cost-effective. Thus, investing in outreach to increase utilization by high-risk women could reduce the incremental cost per year of life saved. (Total costs could even decrease if all screened women are high-risk, since for this group screening actually saves costs at 3- and 5-year screening frequencies.)

The cost-effectiveness model presented here is very sensitive to the accuracy of the Pap smear and certain assumptions about the natural history of disease. Estimates of lower and upper bounds for the cost-effectiveness ratios, incorporating these and other factors, are provided by the "favorable" and "unfavorable" sensitivity analyses that incorporate the high- and low-probability estimates that as a group are most favorable and least favorable to screening. The results of these scenarios imply that, under very optimistic assumptions, screening could pay for itself; under pessimistic assumptions, screening yields a positive benefit, but only at relatively high cost.

Considerable uncertainty regarding the epidemiology of cervical cancer in elderly women still exists, even about things so basic as whether the known risk factors predict risk in elderly women to the same extent as in younger women. Additionally, less is known about the natural history of the disease in the elderly than in younger populations. If the development of human papilloma virus (HPV) typing technology proves to predict cancerous outcomes more accurately than the Pap test alone, it will be particularly important to study the prevalence and predictive value of HPV infection in elderly women.

IMPLICATIONS FOR MEDICARE

Coverage Considerations

As of July 1, 1990, Medicare will pay for Pap smear screening tests up to every 3 years. More frequent screening of high-risk women is permitted under the law at the discretion of the Secretary of the Department of Health and Human Services (DHHS).

Medicare has always paid a proportion of the costs of cervical cancer. With no screening, under the baseline assumptions of the model used here, the lifetime financial costs of diagnosis, treatment, and followup of cervical cancer are estimated to average $218 per 65-year-old woman (in present dollars).

With Medicare coverage of Pap smear screening, costs to the program will almost certainly increase. The amount of increase (and the realized benefit) depends on: 1) the frequency of screening covered by the program, and 2) the extent to which beneficiaries utilize the service.

The frequency of the benefit is fundamental to a coverage decision. The cost-effectiveness analysis presented here does not have a "most" cost-effective solution, since additional benefits continue to accrue at each more frequent screening level, but it is generally consistent with the recently enacted benefit. The rapid rise in cost per life-year saved when screening frequency is increased from every 3 years to annually (in the baseline case) makes annual screening slightly more difficult to justify than less frequent screening for the overall elderly population. For high-risk women, however, even annual screening yields substantial benefits at modest cost per life-year gained. (In contrast, for low-risk women, very frequent screening yields virtually no incremental benefits over less frequent screening.)

Two different approaches are theoretically available to consider the different needs and potential benefits for women at different levels of risk of developing cervical cancer. The first approach is to set a Medicare benefit for which all elderly women are eligible, leaving it to each woman and her physician to determine the most appropriate actual screening strategy for that woman. This approach could be supplemented with outreach programs targeted towards high-risk women, since these women are less likely to participate otherwise but reap the greatest benefit from screening. Outreach in this case could range from educational programs to direct financial incentives, such as free screening at public health clinics.

A second approach is to differentiate in a Medicare benefit itself between high- and low-risk women, through a proxy of risk. One potential proxy of risk is a record of previous screening; thus, for example, Medicare might pay for screening at some specified frequency, but only until a woman had a Medicare-documented history of screening (e.g., up to a maximum of 3 tests). A second potential proxy of risk is evidence of low income; thus, Medicare might differentiate between women who are and are not dually eligible for Medicare and Medicaid when providing benefits. Medicare might pay for both the visit and the screening test for women who are also Medicaid-eligible, for example, but pay only for the test itself for other women. These two proxies -- number of previous screens under Medicare and eligibility for other programs, such as Medicaid or Supplemental Security Income-- could be combined in various ways as well.

The existing new law combines elements of both approaches. A general benefit is set by law, but the law empowers DHHS to provide differential benefits to high- and low-risk women. Whether DHHS acts on this option may depend in part on the administrative difficulty of a differential benefit. Administrative concerns are not trivial; any new benefit for which eligibility depends on factors such as time since last screen, total number of past screens, and eligibility for other non-Medicare programs can rapidly become very complex and costly to administer. Minimizing the number of different factors on which the benefit depends would reduce this potential problem.

Quality and Reimbursement Considerations

The relative costs and effectiveness of Pap smear screening depend on the accuracy of the test as it is performed and evaluated in everyday practice.[10] Fewer false positives mean fewer unnecessary followup procedures; fewer false negatives mean fewer women diagnosed during the later stages of invasive cancer, when treatment costs are greatest and cure rates lowest. Improved accuracy may raise some costs, too, since more women with the disease (including those with CIN and CIS) will be diagnosed and treated.

Measures to improve Pap smear accuracy, and particularly those to improve the quality of cytologic evaluation, have their own costs. To make evaluation more accurate, for example, a laboratory might implement strategies such as:

- monitoring/testing programs to evaluate the proficiency of cytotechnologists,
- requiring cytotechnologists or pathologists to re-evaluate a proportion of negative slides,
- limiting the number of slides per day cytotechnologists can examine, and
- continuing education programs for cytotechnologists.

All of these strategies have been considered in the current debate of how to improve laboratory accuracy. In 1988, for example,

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10 A recent study of laboratory accuracy suggests that there is considerable room for improvement. Eight of eighteen laboratories surveyed by the American Society of Cytotechnology were found to have critical deficiencies in their cytology operations (171).

the Health Care Financing Administration proposed a set of requirements, including many of these features, that laboratories must meet in order to qualify for Medicare reimbursement (53 FR 29591). The proposal would also require that laboratory reports to physicians identify inadequate smears, employ detailed descriptions of abnormal smears, and include followup recommendations.

Whether voluntary or mandated, such strategies would likely raise provider costs, which in turn would probably raise the cost of screening to Medicare. This investment would likely improve the cost-effectiveness of screening, although it would raise overall program costs. (Note that it is not absolutely certain that implementation of these strategies would raise costs; e.g., a laboratory beset with costly lawsuits as a consequence of errors might conceivably see a net saving as a consequence of implementing quality-improving strategies.)

Some conflicts may arise between Medicare efforts to improve accuracy of Pap smears and the Medicare reimbursement structure. At present, reimbursement is structured to reward quantity rather than quality; laboratories (or physicians) are paid a set fee per smear, and laboratories reap the greatest profit by encouraging their cytotechnologists to process a maximum number of smears per day. Under this system, fear of medical liability lawsuits and physician dissatisfaction are the only counteracting pressures to improve quality. Strategies to improve evaluation accuracy might require raising Medicare reimbursement rates per smear if the current reimbursement structure were maintained.

Resource Considerations

Medicare coverage of routine Pap smear screening would almost certainly increase the utilization of the test and require more laboratory services to evaluate the additional smears. However, a perceived shortage of cytotechnologists already exists (163). Market responses to increased demand for cytotechnology services, such as raising salaries to draw people into the profession, would probably raise screening costs to Medicare. If Medicare reimbursement rates did not rise, an alternative result would likely be long lag times between sampling and evaluation, with consequent delays in diagnosis for women with positive tests.

Strategies to improve the quality of Pap smear evaluation have additional implications for the availability of services. Limiting the number of slides per day that cytotechnologists could evaluate would increase evaluation time per slide, presumably improving accuracy, but it would also increase the need for cytotechnologists. Again, increased screening costs to Medicare would probably result.

Automated cytologic evaluation of Pap smears might reduce the number of cytologists needed, easing the perceived shortage of these professionals. Such technology is under investigation (149), but its accuracy compared to manual cytologic evaluations is not yet established.

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Advisory Panel members provide valuable guidance during the preparation of OTA reports. However, the presence of an individual on the Advisory Panel does not mean that individual necessarily agrees with or endorses the conclusions of this particular paper.

Appendix B: Acknowledgments

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Appendix C: Expert Panel

Although the literature on cervical cancer is voluminous, information on this disease as it specifically relates to elderly women is scarce. To supplement the literature review that formed the basis of this paper and the assumptions used in the cost-effectiveness model, the contractors convened a small panel of experts to discuss the literature and to elicit information based on the clinical experience of these experts. The panel, consisting of epidemiologists, pathologists, and gynecologic oncologists, focused primarily on three areas:

- the duration of the various states of cervical neoplasia,
- the probability of progression or regression from each of the preinvasive states, and
- diagnostic and treatment protocols for each state.

Other factors that might affect the yield of screening in elderly women, such as characteristics of the Pap test in this age group, utilization of screening age-specific rates of disease, and cohort effects, were also discussed.

Prior to the meeting, each expert was furnished with a synopsis of the relevant literature and was asked to fill out a questionnaire based on his or her interpretation of that literature and personal clinical experience. The panel then met for 3 hours and discussed their initial responses to the questionnaire, after which each expert again independently filled out the same questionnaire. The discussion emphasized identifying a reasonable range for model assumptions and did not specifically attempt to come to consensus on any issue. A list of participants follows.

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Appendix D: Review of Estimates of Progression Probabilities and Duration of States of Cervical Neoplasia

This appendix discusses the major studies yielding estimates of the duration of the various states of cervical neoplasia, the probability of progressing from one state to the next, and the probability of regressing to a previous state. The studies are summarized in chapter 2(tables 4, 5, and 6).

Duration of States of Cervical Neoplasia

The first major study of the natural history of cervical neoplasia in the medical literature is that of Petersen (107), in which a number of women with a diagnosis of cervical intraepithelial neoplasia (CIN) were followed without intervention for a number of years. The researchers observed that the average duration of carcinoma *in situ* (CIS) in these women was 3.7 years, with the time from onset of CIS to onset of invasive cancer ranging from less than 1 year to nearly 9 years in individual women.

Withholding treatment from women diagnosed with CIN rapidly became unacceptable, so subsequent researchers have attempted to estimate the duration of the states of cervical neoplasia in various other ways. One method has been to assume that the process of cervical cancer can be approximated by a Markov process, a type of model that uses a given set of probabilities to relate one state to the next (app. E). Observable variables can be used as inputs to such a model and used to estimate the durations of the various states. A homogeneous model assumes the same transition probabilities for all age groups; a nonhomogeneous model allows the probabilities to vary depending on the group to which they apply.

Barron and Richart used a homogeneous Markov process to assess the duration of CIN using two very different data sets (7,8,9). The first of these was a prospective followup of 557 women in Virginia and New York with known CIN, whose diagnosis was based on 3 successive abnormal Pap smears. Women in the study were followed every 1 to 4 months without intervention if their status was unchanged. The researchers attempted to minimize diagnostic errors by using clearly delineated diagnostic criteria, requiring three smears with CIN for admission to the study, and reviewing smears for reliability and accuracy. Accordingly, the inter-reader reliability in classifying smears was 95 percent, and the Pap smear diagnoses agreed with the colposcopic and ultimate histological diagnoses. Some important information about the sample is not presented in the published accounts: the distribution by age and race of study participants, the comparative characteristics of women who participated and those who refused participation, and the profile of all women with abnormal smears in the institutions studied. The authors found no evidence that transition from one state to another was age-related, but few older women were represented in the sample (the median age was 26, and the maximum age was 65) (8). The median duration of CIN (including severe dysplasia) derived from this population was 3.7 years; the mean duration was 5.7 years (l14).

The second population that Barron and Richart used to estimate duration of CIN was a sample of 11,814 previously unscreened asymptomatic women iiving in Barbados, West Indies, who attended family planning clinics between 1965 and 1968 (9). The sample included 171 women aged 60 to 64.

However, the model only used prevalence data from women aged 20 to 39 to determine the duration of CIN. The resulting estimates were similar to those yielded by the original model. Although this study is based on a population that probably differs from the general U.S. population in risk of cervical neoplasia, the consistency of results between the two studies supports the validity of these researchers' estimates.

In contrast, Coppleson and Brown (32) attempted to demonstrate that the results of a homogeneous Markov model, which assumes that transition probabilities are independent of age, did not fit observed data. They used data collected by Bibbo et al. and age-specific incidence rates for invasive cervical cancer from the Third National Cancer Survey for their estimates, and they used a non-homogeneous Markov model to simulate a process that would yield these real-world results.

The published data used by Coppleson and Brown had some limitations. Bibbo et al.'s series was based on 148,735 women attending the University of Chicago and Planned Parenthood clinics (16). Most of the women were young; only 12 percent of the sample was over age 49. The mean age of this subsample of 17,133 women was given as 65, but no information on the actual age distribution was published. For their model, Coppleson and Brown assumed all of these women to be the average age-- i.e., 65.

Based on their models, Coppleson and Brown estimated the average duration of CIS to be 17 years in women under 65 and 4 years in women aged 65 and over (132). Their findings are valuable because the researchers expressly examined the possibility of differences between age groups, and they concluded that a real difference in the behavior of the disease probably does exist. However, there are several caveats to their findings. Their assumption that all women over 49 were age 65 may invalidate their conclusions for older women, since even if the *average* age of this group were 65, using the actual distribution of ages would give different results from assuming that *all* women were age 65. The effect of this assumption is probably to underestimate the duration of disease states in older women. In addition, several of the assumptions made to fit the model to observed data are at variance with many other researchers' beliefs about the natural history of the disease. For example, Coppleson and Brown assumed that CIN prior to CIS (i.e., dysplasia) was a transient condition, lasting less than one year, and that CIS regressed to normal in a large proportion of cases. In summary, while it may be true that a homogeneous model does not fit the observed natural history of the disease, this analysis does not resolve the issue.

Dunn (40) and Kashgarian and Dunn (69) drew upon the relationship between prevalence and incidence to estimate the duration of a given state of cervical neoplasia. In his paper, Dunn (4 O) divided the sum of all age-specific prevalence rates for a given state by the sum of all age-specific incidence rates for that state to derive the duration of the state. Kashgarian and Dunn (69) used an equivalent method that did not depend on pre-determined age ranges over which age-specific rates were calculated. They estimated duration by first graphing the incidence of each state (CIS, preclinical invasive cancer, and clinical invasive cancer), 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 CIS 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.

The analyses of these researchers used data for 110,000 white women screened in Memphis (40) and 106,000 person-years of observation of white women and an unspecified number of black women from

Memphis and Shelby counties, Tennessee (69). In both of these samples women aged 20 to 39 were over-represented and women aged 55 to 74 were under-represented. Incidence rates were determined from the result of the third screening test. The literature reports did not specify diagnostic criteria for cytology, although most smears were read at one university laboratory. The authors concluded that older women and black women had shorter durations of CIS than other women. Their estimates for black and white women were 8.5 and 10.7 years, respectively (69). For white women, they estimated the duration of CIS to be between 5 and 16 years for young women and to be 1 year for women aged 65 and over (69).

Difficulties in true ascertainment of a particular disease state due to cytology and misclassification may affect the accuracy of estimates of duration derived in this manner. In addition, estimates derived from this formulation will only be correct if the incidence and prevalence rates over the time of measurement are constant and if both are measured from the same state in the disease process. If prevalence rates are increasing or if screening rates differ, these conditions may not hold true. Also, these types of estimates assume similar population mortality rates for women at all ages. For elderly women, who have higher mortality rates than younger women, this assumption may underestimate the true duration of cervical neoplasia.

However, other authors, using similar methods applied to different data sets, have derived estimates of duration that are similar to those of Kashgarian and Dunn, arguing for the validity of this method. Barron et al. applied this method to two data sets: 1) the incidence and prevalence of CIS in British Columbia, Canada, and 2) the prevalence of CIS in Barbados, West Indies. They examined these two sets of data in two ways: first by using the simple relationship between prevalence and incidence described above, and second by examining the equivalent areas under the curves on graphs of the incidence of each stage at each age. They concluded that the duration of CIS is an age-independent variable with upper and lower limits of 3 to 10 years, respectively(7).

Fidler et al. likewise estimated the duration of CIS in two ways: 1) from the relationship between observed prevalence and incidence among women participating in the British Columbia screening program, and 2) from the difference in mean ages of incidence of CIS and preclinical invasive cancer in this population (46). Age-specific rates were presented for this series, but the number of elderly women was small, yielding estimates with a wide range of error. In 1966, 22 percent of the female population in British Columbia was age 60 or over, but this age group represented only 8.5 percent of women screened (46). The estimate of the duration of CIS using the first method is between 6 and 9.5 years, compared to 12 years using the second method.

Another method of estimating the duration of neoplasia is to determine the modal age-specific incidence rates (the modal number of cases per age group). The Canadian Task Force presented such estimates using data from the British Columbian population (22). As with the data used by most other researchers, these data are cross-sectional and may obscure differences among cohorts. Also, estimates obtained as a result of subtracting modal, or even mean, ages of incidence only yield a correct estimate if the durations of all states being considered are equal. This is not likely to be true since the probability of ascertainment is a function of the duration of the lesion (7). The estimates derived in this manner agree the least with estimates from other methodologies, and they are most likely overestimates.

The uncertainties about the duration of cervical neoplasia in elderly women arise primarily from the lack of data on women in this age group. The critical question in assessing the duration of each state of cervical neoplasia is whether the duration of disease

is, or is not, dependent on age. Although Coppleson and Brown's analysis suggested that duration of different states was indeed different in the elderly than in the younger population, there is still little direct evidence to support or refute this hypothesis. The hypothesis is biologically plausible based on current knowledge of the interactions between age and hormonal and immune factors (see ch.2}

Probability of Progression and Regression of Each State

The probabilities of remaining in a given state, progressing to the next state, or regressing to the prior state are difficult to determine for cervical cancer. The best estimates of early disease are based on groups of women with CIN and CIS[1] who were followed without intervention. In one such series, Barron and Richart followed 557 women with CIN (8) and collected data on the distributions of grades of CIN after the initial and two followup exams. Using a Markov model with these data as inputs, the authors estimated that after 10 years 66 percent of all CIN lesions will progress to CIS, 28 percent will remain in CIN, and 6 percent will revert to normal. Regression to normal only occurred from very mild or mild CIN, and the overall probability of progression to CIS increased with the severity of dysplasia (8}

In contrast, Fox (48) followed 278 women with CIN and noted that 31 percent regressed to normal, 9 percent remained in CIN, and 60 percent progressed to CIS. This high regression rate may be due in part to misclassification, as only one smear interpreted as CIN was necessary for inclusion in the study; several women 'regressed" after termination of pregnancy or completion of anti-infection treatment. In addition, 13 percent of the women whose smears originally returned to normal subsequently developed CIN.

The "re-development" of CIN after regression to normal has been noted in other series as well (147). In fact, in one series, among women over age 45 whose initial CIN lesions 'regressed," 40 percent recurred (147). All these factors suggest that estimates of the regression rate of CIN have often been overstated, due to misclassification biases. In contrast, three smears interpreted as CIN were necessary for inclusion in Barron and Richart's series, which should minimize this type of bias.

A Swedish study of 894 women age 15 to 72 with CIN, who were followed for an average of over 4 years, found that 54 percent of lesions regressed, 16 percent persisted and 30 percent progressed (lOO). A number of patients with "persisting CIN" in this study had periods of normal smears for more than 12 months before being rediagnosed as having CIN.

Evidence on the relationship between regression rates and age is mixed. One study noted a lower regression rate for older than for younger women. In this study, women under age 45 with CIN had a regression rate of 38 percent per year, compared to 29 percent per year for women age 45 and over (147). Another study, however, found that fewer lesions progressed, and more regressed, in older women than in young women (100).

The difference in rates of regression noted in nonbiopsy studies compared to biopsy studies suggests that the act of establishing the diagnosis can produce a cure, and that the act of measurement often alters the results (8). Nasiell and colleagues (100)

1 As noted in ch. 2, CIN as used in this report include mild and moderate dysplasia; CIS generally includes CIS and severe dysplasia, because these latter two conditions are hard to distinguish. Barren and Richart, however, specifically attempted to separate different levels of dysplasia and CIS. In the discussion of their studies, CIN includes severe dysplasia; CIS includes only carcinoma in situ.

found that significantly more biopsied than nonbiopsied lesions disappeared during followup (50 v. 57 percent), and fewer biopsied lesions progressed (25 v. 27 percent). Thus, different biopsy rates may be one reason studies report varying results. In addition, nonuniformity of diagnostic criteria and observer variability contribute to the wide range of reported probabilities.

Confounding these difficulties in determining the "true" course of cervical neoplasia in elderly women is the lack of age-specific observational data. The main source of findings regarding age-specific information is the research of Coppleson and Brown, which found that an age-dependent model of disease progression fit actual incidence and prevalence data best (32). The researchers concluded that there is no regression from the state of CIS and that the probability of disease progression from CIS to invasive cancer increases with age. For CIN, the probability of progression did not vary with age in their model. As discussed above, however, their conclusions have some uncertainties due to limitations of the underlying data. Also, the older women in their data set had lower screening rates than young women, which may have resulted in older women being detected at the end of a given state more often than younger women. This could bias the model to predict a higher probability of disease progression in the elderly. Still, as with the duration of disease states, a higher probability of disease progression is biologically plausible in older women.

Appendix E: Markov Models[1]

A Markov model describes the movements of members of a population through a set of states. A simple Markov model requires only two sets of information:

- the distribution of the population among the defined states at the initiation of the model; and
- for each state, the probability that any individual in that state will move into a different state (transition probabilities). In a simple Markov model, these probabilities remain the same with each iteration of the model. In the Markov model used in chapter 3, some probabilities change with successive iterations (e.g., the probability that women will die increases as the cohort grows older).

The transition probabilities can be portrayed in a matrix. For example, imagine a Markov model in which two states exist: healthy and cancer. Assume that in any given period, the chance of a healthy person getting cancer is 10 percent, and the chance of remaining healthy is 90 percent. For people with cancer, the chance of being cured (becoming healthy) during this period is 50 percent, and the probability of continuing to have cancer is also 50 percent. This situation is summarized in the following matrix:

		Period 2	
		Healthy	Cancer
Period	Healthy	0.9	0.1
	Cancer	.	0.5

Now, assume that there are 100 people in the population, and that initially (at the beginning of the model) 90 are healthy and 10 have cancer. Applying the above probabilities, the distribution of the population after one iteration of the model--i. e., in period 2--would be:

Healthy: (90 x 0.9) + (lo x 0.5) =
81 + 5 = 86 people

Cancer: (90 x 0.1) + (lo x 0.5) =
9 + 5 = 14 people

In this simple example, applying the transition probabilities successively to the population distribution from each previous iteration of the model, the population soon reaches a stable distribution:

Percent of	Period				
population that:	1	2	3	4	5
Is healthy	90	86	84	84	84
Has cancer	10	14	16	16	16

(In the model used in chapter 3, the population is artificially required to be stable by imposing the requirement that all women still alive at age 109 die in that iteration of the model (before reaching age 110).)

Markov models rely on certain assumptions that affect their application. Most important for the model applied in chapter 3 is that the probability that an individual will move into a different state depends only on her present state. A simple Markov model has no memory; a person's chance of having cancer in the next period in the example above depends only on his or her health in the current period. Also, the model can be applied only where there are mutually exclusive and exhaustive categories; an individual cannot be represented in two categories at once.

The conditions of Pap smear screening for elderly women are generally amenable to simulation with a Markov model. In the model used in the cost-effectiveness analysis (ch. 3), states of health are defined to be mutually exclusive and exhaustive as they relate to cervical cancer. The initial population

1 The information in this appendix is drawn from E. Stokey and R. Zeckhauser, A primer for policy Analysis (New York: W.W. Norton & Co., 1978).

distribution for the model is the existing prevalence of disease; the transition probabilities are mortality rates and rates for identification, progression, regression, and cure of disease. The purpose of the model as applied here is not to define a stable population distribution, but to track the costs and cases of cervical cancer through the lifetime of the defined cohort of women.

The most troublesome aspect of Markov modeling for cervical cancer screening is the assumption that the transition probabilities are the same for all individuals in each state. Some of the implications of this underlying assumption are discussed in the text.

Appendix F: Basis for Input Assumptions and Calculation of Cost Components in the Cost-Effectiveness Model

Data Input Assumptions

For the cost-effectiveness model employed in chapter 3, several methods were used to choose base, high, and low estimates, Typically, after exclusion of irrelevant and seriously flawed studies, only a few studies remained. Where a single study was clearly more applicable to the elderly population than other studies, it was used as the base case; in other cases, the base case was derived from a study whose results were in the middle of the range of study findings available. For low and high estimates, the lowest and highest values from available studies were generally used. In some cases where a single study served as the base case, computed 95 percent confidence limits served as the extremes. Where no applicable studies are available at all, assumptions were based on the opinions of the expert panel (see app. C).

The sources and rationale for the individual estimates used in the model and presented in table 11 (ch. 3) are discussed in detail below.

Initial Conditions

- Cervical intraepithelial neoplasia (CIN--grades 1 and 2): Most initial conditions for CIN and carcinoma *in situ* are drawn directly from results in studies published in the literature. The prevalence of CIN at age 64 in the base case is drawn from Stern's study of women in a Los Angeles clinic (146), the more recent of the two large reported studies of dysplasia prevalence in this age group. The less recent study, which reported lower prevalence, was used directly as the source for the low estimate and indirectly as the source of the high estimate (the high estimate was the upper bound of the 95 percent confidence interval around the reported figure) (145).
- Carcinoma *in situ (CIS)/severe* dysplasia: Two studies are reported in the literature that measured the prevalence of CIS in older women and whose results are applicable to the initiation of the model. The base-case prevalence is drawn from a study of British Columbian women (46), the study with the largest reported sample of women in this age group that measured this parameter. This figure was also used as the low estimate. The high estimate is drawn from the second study, which reported a substantially higher prevalence (40).
- Early and late invasive cervical cancer (EICC, LICC): The prevalence of EICC and LICC are not reported in the literature in the way those terms are defined for the model. For this model, the reported overall prevalence of invasive cancer was combined with the reported fractions of cancers in the early or late stages to produce a stage-specific prevalence at the initiation of the model. Base and high estimates of the prevalence of invasive cancer are drawn from Dunn (42); low estimates are drawn from Mandelblatt et al. (92). Stage distributions of cancer at presentation are drawn from Fidler et al. (46) for the base case, Dickinson et al. (37) for the high estimate, and from data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)[1] database for the low case (158).

Transition Probabilities

Death--Age-specific general population mortality probabilities (164) are applied for women in the healthy, CIN, and CIS states. A weighted average of the race-specific figures for each age is used, reflecting the racial

1 The SEER data base includes results of a cancer registry maintained in 9 different regions in the United States (16).

distribution of American women in 1980 (164). In the EICC and LICC states, mortality probabilities are taken from overall age-group specific cancer survival data (including deaths from other causes among cancer patients) in the National Cancer Institute's SEER (1978-1984) database (158). A weighted average of race-specific rates was applied to these mortality probabilities as well. Because the sources for these mortality probabilities are considered highly reliable, high and low estimates for sensitivity analysis were not made.

Progression Probabilities--The relationship of non-mortality transition probabilities to epidemiologic data is not straightforward, since standard epidemiologic statistics (mean duration, median duration, survival probability) do not always correspond directly to the terms of the model. With some simple assumptions and mathematical manipulation, however, the available epidemiologic statistics can be re-stated as annual probabilities of transition from one stage of disease to the next, the data items necessary for the model.[2] Only age-dependent progression probabilities (i.e., estimates derived from samples of older women) are used, because the extreme high and low assumptions bracket the available age-independent progression probabilities.

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2 Let p = annual transition probabi1ity, m = median duration, x = mean duration, and S_n = n-year survival probability. Assume that the distribution of transition times is exponential, and let r denote the rate constant of the exponential distribution. Then:

$$p = 1 - \exp(-r) \quad \text{(Eq. 1)}$$
$$m = (\ln 2) / r \quad \text{(Eq. 2)}$$
$$x = 1 / r \quad \text{(Eq. 3)}$$
$$S_n = \exp(-n \times r) = 1 - (1-p)^n \quad \text{(Eq. 4)}$$

Equation 1, 2, 3, and 4 can be used to determine r, depending on the statistics available, and the required probability, p, can then be calculated from equation 1. Since only those who do not die can undergo further state transitions, the actual transition probability used in the model is (1-f) x p, where f is the mortality probability. (For further information about these equations and exponential survival distributions in medical prognosis see Beck, Pauker & Kassirer (10).)

The base-case probability assumption for the progression from healthy to CIN is drawn from Stern (146), the only published study found that reported information on the incidence of dysplasia specifically for elderly women. Probabilities for progression to CIS and to EICC are drawn from Coppleson and Brown's simulation analysis of screening in elderly women (32).

High estimates of the incidence of CIN and the annual rate of progression from CIN to CIS are extrapolations from the base case, since few alternative estimates exist. High incidence of CIN is based on a 95 percent upper confidence bound of the reported estimate; high progression to CIS is calculated as 50 percent greater than the base-case value (since a confidence interval could not be applied to this estimate). The high estimate of progression from CIS to EICC is derived from the data presented by Kashgarian and Dunn (69).

Low estimates of CIN incidence and progression to CIS are derived from preliminary data on women being screened in British Columbia (96). These estimates are lower than the estimates that would result from extrapolations like those made to arrive at high estimates, so they were considered a more appropriate low assumption. The low estimate for progression to EICC is drawn from Dunn (42).

No published estimates are available on the annual progression rate from EICC to LICC. Consequently, the base, low, and high estimates were all based on the opinions of the expert panel (see app. C).

Regression **or Cure**--Women with CIN or CIS may exhibit spontaneous regression to the healthy state, but the rates of regression reported in the literature vary enormously. For the base case, the regression rate for CIN of 38.1 per 1,000 women with disease reported by Campion et al. (121) was used. The high estimate (265.0) is drawn from Robertson et al. (1 18), and the low estimate

(5.4) is drawn from Richart and Barron (1 14). For regression of CIS, the base and low estimates of zero were derived from the personal observations reported by members of the expert panel (app. C). The high estimate is drawn from Kinlen (71).

Women with recognized CIN and CIS may revert to the healthy state subsequent to treatment (cure). Cure is actually considered slightly more likely for women with CIS than women with CIN in the model, because it is assumed that in actual practice women with CIS receive more aggressive treatment, and thus it is more likely that the entire lesion will be removed with the initial treatment. Assumptions of cure rates used in the model are derived from conclusions of cure rates from four sources: 1) the opinions and experiences of members of the expert panel (app. C); 2) Creasman (34); 3) Shingleton and Orr (130); and 4) Nelson et al. (102).

The situation for EICC and LICC is different. Although some women with EICC are probably cured, data to estimate the probability of this are not available. This model therefore does not permit transitions from the invasive cancer states back to earlier stages. Consequently, the model will overestimate morbidity from invasive cancer; once a woman moves into the EICC stage, she will be categorized as having invasive cancer until she dies. This does not affect her chance of survival in the model, however. The death probabilities are based on all-cause mortality data in cohorts of women diagnosed in each stage; thus, in the model, a woman's statistical likelihood of dying depends only on the fact that she was diagnosed with EICC, not on the fact that the model continues to classify her in that category.

Recognition--Transition to a recognized state results either from screening or from diagnostic evaluation of symptoms.

The former possibility occurs only in years for which screening is designated in the program under study. Not all women will avail themselves of the screening opportunity, and among those who do, some women with disease will have false-negative smears. The overall transition probability is the product of the survival probability, the utilization probability, and the stage-specific Pap smear sensitivity.

Most Pap smear sensitivity results reported in the literature are within the range of 60 to 85 percent, with the majority of these finding sensitivities of 80 to 85 percent. One study reported very low sensitivity (35 percent) (122) and two studies reported sensitivities of over 90 percent (14,1 14). Most of these studies probably overstate real-world test accuracy, especially for elderly women. The model thus uses a low sensitivity estimate of 50 percent for all disease states (lower than that found in the bulk of studies, but higher than the lowest reported rate); it uses a base estimate of 75 percent for all disease states (within the range of the bulk of studies, but in the lower part of that range). The high-case estimate is in the upper range of the bulk of studies; in the high case, sensitivity is also permitted to be higher for invasive cancer than for non-invasive neoplasia (82 and 80 percent, respectively). This possibility is suggested in the results found by Boyes et al. (20) based on screening in the British Columbian population.

Symptoms do not usually arise from CIN or CIS. Invasive cancer, on the other hand, eventually becomes symptomatic in most cases. By combining the assumption that 80 percent of all women with late cancer who have not yet developed symptoms will do so within 1 year,[3] with the estimates used for the annual probability of progression from early to late cancer, it is possible to approximate numerically what the annual hazard of

3 Although this 80 percent assumption is entirely arbitrary, the true rate is almost certainly very high. Also, changing this assumption makes virtually no difference to model results unless the nunber is very low.

developing symptoms with early cancer must be to produce the observed distribution of stages among diagnosed women. The results of this calculation are used as the annual probability of recognition of EICC due to symptoms. High and low symptomaticity rates combine high and low progression probability rates with the 80 percent assumption.

Clearance- -In this model, "clearance" refers to the uncovering of false-positive Pap smear results among healthy women, which depends on the specificity of the Pap smear. As with sensitivity, specificity results presented in the literature probably overstate real-world test specificity for Pap smears from elderly women. Three studies report specificities of 99 percent or greater; one study reports a specificity of slightly under 95 percent. The model thus uses 99 percent as the high estimate of Pap smear specificity, 95 percent as the base-case estimate, and a much lower rate--87 percent--as a low estimate that might obtain under conditions of mediocre laboratory quality.

Cost Assumptions

The protocols of service described in chapter 3 were applied in the cost-effectiveness model to data from the National Hospital Discharge Survey (NHDS) to identify the in-hospital services used in each phase of care for cases with abnormal findings (either asymptomatic screened cases or symptomatic cases presenting for care). The NHDS data used included patients aged 65 and over who were discharged between 1984 and 1987 with a diagnosis of either malignant neoplasm of the cervix or CIS. Length of stay, discharge status, and surgical and non-surgical procedures coded from the face sheet of the medical record were printed out. Only those cases with malignant neoplasm or CIS as the first-listed diagnosis were used. The resulting set of data on 210 women was used as an indicator of services received by patients with diagnoses of invasive cervical cancer (ICC) in different stages of disease, and with CIS, according to current practices.

The NHDS data showed that the basic oncologic protocols for different stages of disease could be approximately matched to the service experience of admitted cases. The cost estimates used in this analysis followed the actual survey data with several modifications. The following describes features of this set of calculations.

- An assortment of pelvic surgical procedures that were received by ICC and CIS patients and interpreted to be related to the cancer diagnosis (although, unlike cervical biopsy, ionization, and hysterectomy, they were not in the basic protocol) were included in the inpatient care used in the cost estimation in chapter 3.
- In early cancer, patients receiving total or radical hysterectomies were considered to have received the more expensive radical (Wertheim) procedure that would constitute definitive treatment. CIS patients with hysterectomies were considered to have received the less expensive total hysterectomy operation.
- Bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tubes) was not priced. It was usually coded in conjunction with a hysterectomy and was assumed to be included in the price of this procedure.[4]
- Doses of chemotherapy or radiation therapy were derived from lengths of stay for those receiving these services.
- Prices of services were derived as follows:

  - Hospital costs were based on 1986 statistics published by the American Hospital Association for all community hospitals. The given average expense per inpatient day was updated by applying the National Hospital Input Price Index (provided by the Office of

4 Based on the experience of Enpire Blue Cross/Blue Shield, the Medicare Part B carrier in the New York City area, a separate fee is not usually paid when these two procedures are done together.

the Actuary of the Health Care Financing Administration (HCFA).)[5]

- Fees for professional and clinical services were provided by HCFA, which supplied 1986 average allowed charges under Medicare for a list of procedures in the basic protocol for cervical cancer diagnosis and treatment in and out of the hospital. In addition, certain additional services (an assortment of pelvic surgical procedures that were received by elderly ICC and CIS patients in the NHDS and were interpreted to be related to the cervical cancer diagnosis, plus charges for different types of physician visits), were priced from 1987 Medicare average allowed charges. All prices were updated to 1988 by applying the Consumer Price Index component for professional medical services.

Quantity information for specific services (supplied by HCFA), together with Medicare allowed charges, was used to weigh prices when several types of biopsy or treatment were combined to develop per case averages in the cost estimates.

The basis for the cost figures applied in the model is presented in tables 19 through 26. Table 19 shows the prices for specific component procedures with their sources and the points in the calculations where each price figure was used. These components--e.g., the cost of a hospital visit, the cost of a particular procedure--are then combined in tables 20 through 26 into average cost figures per women with that condition for the appropriate package of services (e.g., diagnosis of CIS, treatment of EICC, followup of CIN).

In the tables, many procedures are prorated according to the proportion of women in that disease state category assumed to receive them. Thus, for example, in table 20, all women with CIN undergo colposcopy at the diagnostic workup, so the per-patient cost is the full amount of the procedure. Only one-third of women are assumed to receive a repeat Pap test, however, the attributable per-patient cost of this component is one-third of the cost of a smear. The proportion of women receiving various services is drawn largely from the NHDS data and represents an approximation of the proportion of women receiving various services under current medical practice.

5 This index, published in the Federal Register, excludes capital items and medical fees from the priced market basket.

Table 19--Prices for Services Related to Cervical Cancer

Service	Unit price	Source[a]	1988[b] Update	Where used i n estimation (see table number)
Office visit- -extended	$ 33.00	HCFA 1987	$35.23	20, 23, 25
Office visit- -intermediate..	25.00	HCFA 1987	26.69	20, 21, 23, 24, 25, 26
Hospital visit--initial comprehensive.	77.00	HCFA 1987	82.20	20, 21, 22, 23, 24, 25
Hospital visit--subsequent brief	20.00	HCFA 1987	21.35	20, 21, 22, 23, 24, 25
Hospital day.	500.81	AHA 1986	545.78	20, 21, 22, 23, 24, 25
Pap test.	7.35	HCFA 1986	8.37	20, 25
Colposcopy.....	46.76	HCFA 1986	53.22	
Colposcopy w/biopsy	84.10	HCFA 1986	95.71	
weighted average			71.56	20, 21, 23, 24
Chest X-ray	20.46	HCFA 1986	23.20	23, 26
Pelvic computed tomography scan.	119.48	HCFA 1986	136.00	23
Sigmoidoscopy.	119.66	HCFA 1986	136.20	23
Barium enema	40.71	HCFA 1986	46.34	23
Cystoscopy...	170.71	HCFA 1986	194.31	23
Intravenous pyelogram.	44.45	HCFA 1986	50.59	23, 26
Complete blood count	7.00	HCFA 1987	7.47	23
Blood urea nitrogen	7.00	HCFA 1987	7.47	23
Creatinine-blood	7.00	HCFA 1987	7.47	23
PeLvic sonogram	47.74	HCFA 1986	54.34	26
Cervical biopsy	40.43	HCFA 1986	46.02	20, 22
Other biopsies:				
cul de sac.	51.00	HCFA 1987	54.44	
uterus	53.00	HCFA 1987	56.58	
vagina	50.11	HCFA 1986	57.04	
vulva	50.85	HCFA 1986	57.88	
weighted average			56.33[d]/58.33[e]	20, 22
Dilation and curettage	251.84	HCFA 1986	286.66	21, 22, 23
Ionization	249.12	HCFA 1986	283.56	20, 21, 22, 23, 25
CIN treatments:				
cauterization	40.40	HCFA 1986	45.99	23
cryosurgery	64.29	HCFA 1986	73.18	21, 23, 25
laser surgery	165.99	HCFA 1987	177.20	
weighted average			58.91	20
Hysterectomy-totaL	933.10	HCFA 1986	1,062.03	21
Hysterectomy- radical..	1,525.56	HCFA 1986	1,729.50	23
Pelvic exenteration.	2,213.59	HCFA 1986	2,509.51	24
Bilateral oophorectomy.	373.00	HCFA 1987	398.39	23
Culdotomy	68.00	HCFA 1987	72.59	23
Dilation of cervical canal	39.00	HCFA 1987	41.63	23
Excision-vagina	95.52	HCFA 1986	108.73	23
Excision-vulva	69.77	HCFA 1986	79.42	21
Hysterectomy	370.00	HCFA 1987	394.99	23
Incision of cervix	42.00	HCFA 1987	44.84	23
Obliteration of vagina	470.00	HCFA 1987	501.75	21, 23
Repair-cystocele	408.00	HCFA 1987	435.56	21
Repair-cystocele/rectoce[e.	509.00	HCFA 1987	543.38	21
Unilateral oophorectomy.	373.00	HCFA 1987	389.19	23
Unilatera(salpingo-oophorectomy.	449.00	HCFA 1987	479.33	21
Vaginotomy	103.50	HCFA 1987	110.49	23
Radium implant[f].	70.49	HCFA 1986	80.23	23
Teleradiation	47.65	HCFA 1987	50.84	24
Chemotherapy	24.75	HCFA 1986	28.17	24
ExternaL radiation	44.70	HCFA 1986	50.87	24

ABBREVIATIONS: AHA = American Hospital Association; CIN = cervical intraepithelial neoplasia; HCFA = Health Care Financing Agency.

[a]AHA, 1986 data from American Hospital Association, Hospital Statistics 1987 Edition (Chicago, IL: American Hospital Association, 1989); HCFA 1986 and 1987 data from Part B Medicare Annua[Data System provided by M. McMuLLan Health Care Financing Administration, Baltimore, MO, personal communications, 1988; and W.J. Sobaski, Health Care Financing Ackninis-, tration, Baltimore, MD, personal communications. 1989.

[b]Based on comsumer price index for professional medical services (in medical care component) from Bureau of Labor Statistics; National Hospital Input Index from HeaLth Care Financing Administration, Office of the Actuary.

[c]Based on weighted average of allowed charges for the following: biopsy of uterus (l), vagina (4), CUL de sac (l), vulva ,(1), (1986 charges updated to 1988).

[d]Used for diagnostic admission.

[e]Used for diagnosis and treatment.

[f]Based on 44 cases from the NationaL Hospital Discharge Survey of elderly women receiving in-hospital care for cervical cancer.

SOURCE: Office of Technology Assessment, 1990.

Table 20--Estimated Costs of Diagnosing and Treating Cervical Intraepithelial Neoplasia (CIN-grades 1 and 2)

Service	Calculation of total cost[a]	Proportion of CIN cases receiving service	Average cost per person with CIN
Colposcopy	$98.25 procedure = $71.56 physician visit =$26.69	100%	$98.25
Repeat Pap test	$8.37	33%	$ 2.79
Ionization	$1,195.11 procedure = $283.56 hospital stay (1.5 days) = $818.67 initial inpatient physician visit = $82.20 additional inpatient visits (.5) = $10.67	30%	$358.44
Cervical biopsy	%6.02	62%	$28.53
Other biopsies	$87.50 (1.5 x $58.33)	100%	$87.50
	Subtotal		$57S.51
Treatment by cautery, cryosurgery or laser surgery	$94.14 procedure = $58.91 office visit = $35.23	100%	$94.14
	Total		$669.65

ABBREVIATION: CIN = cervical intraepithelial neoplasia.

[a]See table 19 for sources of component costs.

SOURCE: Office of Technology Assessment, 1990.

Table 21--Estimated Costs of Diagnosing and Treating Carcinoma **In** Situ

Service	Calculation of total cost[a]	Proportion of CIS cases receiving service[b]	Average cost per person with CIS
COlpOSCOpy	$98.25 service = $71.56 visit = $26.69	100%	$ 98.25
Total hysterectomy	$1,062.03	43%	$ 456.67
Ionization	$283.56	35%	$ 99.25
Dilation and curettage	$286.66	30%	$ 86.00
Other surgery	$340.44	35%	$ 119.15
Hospital stay	$2,892.63 (5.3 days x 545.78)	100%	$2,892.63
Initial physician visit	$82.20	100%	$ 82.20
Additional physician visits	$91.81 (4.3 x$21.35)	100%	$ 91.81
Total			$3,925.%

ABBREVIATION: CIS = carcinoma in situ.

aSee table 19 for sources of component costs.
All services except colposcopy are in-hospital services; proportions of cases receiving in-hospital services are based on 23 cases from the National Hospital Discharge Survey of elderly women receiving in-hospital care for CIS.
cIncludes cryosurgery, excision of vulva, obliteration of vagina, repair of cystocele, repair of cystocele and rectocele, and unilateral salpingo-oophorectomy.

SOURCE: Office of Technology Assessment, 1990.

Table 22--Estimated Costs of Diagnostic Admission for Cervical Cancer

Service	Calculation of total cost	Proportion of cervical cancer cases receiving service[a]	Average cost per person with cervical cancer
Dilation and curettage	$286.66	59%	$ 169.13
Cervical biopsy	$46.02	5.9%	$ 27.15
Other biopsies	$56.33	2.6%	$ 14.65
Ionization	$283.56	15%	$ 42.53
Hospital stay	$3,656.73 (6.7 days x 545.78)	100%	$3,656.73
Initial inpatient physician visit	$82.20	100%	$ 82.20
Additional inpatient physician visits	$121.70 (5.7x $21.35)	100%	$ 121.70
Total			$4,114.09

~See table 19 for sources of component costs.

[a]Based on 27 cases from the National Hospital Discharge Survey of elderly women with diagnostic admissions for cervical cancer.

SOURCE: Office of Technology Assessment, 1990.

Table 23--Estimated Costs of Diagnosing and Treating Early Invasive Cervical Cancer

Service package	Calculation of total cost[a]	Proportion of EICC cases receiving service[b]	Average cost per person with EICC
Outpatient services	Colposcopy:		
	service = $71.56		
	visit = $26.69		
	$98.25	100%	$ 98.25
	Staging:		
	Chest X-ray = $ 23.29		
	Pelvic coopted tomography scan = $136.00		
	Sigmoidoscopy = $136.20		
	Barium enema = $ 46.34		
	Cystoscopy = $194.31		
	Intravenous pyelogram = $ 50.59		
	Extended office visit = $ 35.23		
	Complete blood count = $ 7.47		
	Blood urea nitrogen = $ 7.47		
	Creatinine-blood = $ 7.47		
	$644.37	100%	$ 644.37
	Sub-total		$ 742.62
Inpatient services	Diagnostic admission[c] = $4,114.09	20%	$ 822.82
	Radioactive substance implant = $ 80.23	50%	$ 40.12
	Radical hysterectomy = $1,729.50	30%	$ 518.85
	Other surgery = $ 126.62	59%	$ 74.71
	Dilation and curettage = $ 286.66	11%	$ 31.53
	Ionization = S 283.56	5%	$ 14.18
	Hospital stay (10.1 days) = $5,512.38	100%	$ 5,512.38
	Physician visits = $ 82.20 ($21.35 x 9.1)	100%	$ 82.20
	Additional inpatient physician visits = $ 194.29 (9.1 days)	100%	194.29
	sub-total		$7,291.08
Total			**$8,033.70**

ABBRIVIATION cc = early Invasive cervical cancer.

[a] See table 19 for sources of cost components.
[b] Based on 44 cases from the National Hospital Discharge Survey of elderly women receiving care for EICC.
[c] See table 22 for source of costs.
[d] Includes bilateral oophorectomy, cauterization, cryosurgery, culdotomy, dilation of cervix, excision of lesion-vagina, hysterotomy, incision of cervix, obliteration of vagina, unilateral oophorectomy, vaginotomy.

SOURCE: Office of Technology Assessment, 1990.

Table 24--Estimated Costs of Diagnosing and Treating Late Invasive Cervical Cancer

Service package	Calculation of total cost[a]	Proportion of LICC cases receiving service	Average cost per person with LICC
Outpatient diagnostic workup	Colposcopy[b] = $ 98.25	100%	$ 98.25
	Staging[c] = $644.37	100%	$ 644.37
	Subtotal		**$ 742.62**
Inpatient services[d]	Diagnostic admission[h] = $4,114.09	30%	$1,234.23
	Chemotherapy (2 days)[e] = $ 61.95	23%	$ 14.25
	Teleradiation[c] (2.7 days)[f] = $ 136.86	14%	$ 26.26
	Other external radiation (20.3 days)[g] = $1,032.60	4%	$ 41.31
	Pelvic exenteration = $2,509.51	2%	$ 50.19
	Hospital stay (7.4 days) = $4,038.77	100%	$4,038.77
	Initial physician visit = $ 82.20	100%	$ 218.84
	Additional physician visits (6.4) = $ 136.64	100%	$ 136.64
	Subtotal		**$5,760.49**
Further treatment	Second admission excluding pelvic exenteration = $4,339.43	100%	$ 4,339.43
	Outpatient radiotherapy (30 visits) = $1,526.10	100%	$ 1,526.10
Total			**$12,232.00**

ABBREVIATION: LICC = late invasive cervical cancer.

[a] See table 19 for sources of cost components.
[b] See table 20 for cost of components.
[c] See table 23 for cost of components.
[d] Based on 116 cases from the National Hospital Discharge Survey of elderly women receiving in-hospital care for late cervical cancer.
[e] Based on length of stay for cases with chemotherapy and weighted average of allowed charges for different types of chemotherapy.
[f] Based on length of stay for cases with teleradiation.
[g] Based on length of stay for cases with other external radiation.
[h] See table 22 for cost of components.

Source: Office of Technology Assessment, 1990.

Table 25--Estimated Costs of Followup Care for CIN and CIS

Service package	Calculation	Proportion of total cost[a]	Proportion of CIN and CIS cases receiving service	Average cost per person with CIN and CIS
Followup year 1	4 office visits x $ 26.69		100%	$ 106.76
	1 Pap smear x $ 8.37		100%	$ 8.37
	Cryosurgery: service = $ 73.18 visit = $ 35.23 $ 108.41		10%	$ 10.84
	Ionization: Procecdure = $ 283.56 hospital stay (1.5 days) = $818.67 physician visits (during hospital stay) = $ 92.88 $1,196.11		5%	$ 59.74
	Subtotal			$ 185.71
Followup years 2 through 5	2 office visits annually x $ 26.69		100%	$213.52
	1 Pap smear annually x $ 8.37		100%	$ 33.48
	Subtotal			$247.00
Total				$ 432.71

ABBREVIATION: CIN = cervical intraepithelial neoplasia and CIS = carcinoma in situ.

[a]See table 19 for sources of cost components.

SOURCE: Office of Technology Assessment, 1990.

Table 26--Estimated Costs of Followup Care for Invasive Cervical Cancer

Service package	Calculation of total cost[a]	Proportion of ICC cases receiving service	Average cost per person with ICC
Early cancer followup year 1	4 office visits x $26.69 = $106.76 2 intravenous pyelograms x $50.59 = $101.18 2 chest x-rays x $23.29 = $46.58 2 pelvic sonograms x $54.34 = $108.68		
	cost.....$363.20	100%	$ 363.20
Early cancer followup years 2 through 5	2 office visits annually x $26.69 = $53.38 1 intravenous pyelograms x $50.59 = $ 50.59 2 chest x-rays x $23.29 = $ 46.58 1 pelvic sonogram x $54.34 = $54.34		
	Annual cost. $204.89	100% (x 4 years)	$ 819.56
	Total, followup care for early invasive cervical wincer....--. . . . . ------		**S1,182.76**
Late cancer followup years 1 through 3	4 office visits annually = $106.76 2 intravenous pyelograms = $101.18 2 chest x-rays = $ 46.58		
	Annual cost. $254.52	100% (x 3 years)	$ 763.56
Late cancer followup years 4 through 5	2 office visits annually = $ 53.38 1 intravenous pyelograms = $ 50.59 1 chest x-ray = $ 46.58 1 pelvic sonogram = $ 54.34		
	Annual cost. $181.60	100% (x 2 years)	$ 363.20
	Total, followup care for late invasive cervical cancer------- . . . . . -------		$1,126.76

ABBREVIATION: ICC = invasive cervical cancer.

[a]See table 19 for sources of cost components.

SOURCE: Office of Technology Assessment, 1990.

ACOG	--American College of Obstetricians and Gynecologists
ACS	--American Cancer Society
AHA	--American Hospital Association
ASCP	--American Society of Clinical Pathologists
CIN	--cervical intraepithelial neoplasia
CIS	--carcinoma *in situ*
D&C	--dilation and curettage
DHHS	--U.S. Department of Health and Human Services
DYS	--dysplasia
EICC	--early invasive cervical cancer
HCFA	--Health Care Financing Administration
HPV	--human papillomavirus
ICC	--invasive cervical cancer
IVP	--intravenous pyelogram
LICC	--late invasive cervical cancer
MDYS	--mild dysplasia
NA	--not available
NCI	--National Cancer Institute
NHDS	--National Hospital Discharge Survey
NHIS	--National Health Interview Survey
NIH	--National Institutes of Health
SEER	--surveillance, epidemiology, and end results
USPSTF	--United States Preventive Services Task Force

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