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Report to the Chairman, Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Operations, U.S. House of Representatives

December 1991

BREAST CANCER, 1971-91

Prevention, Treatment, and Research

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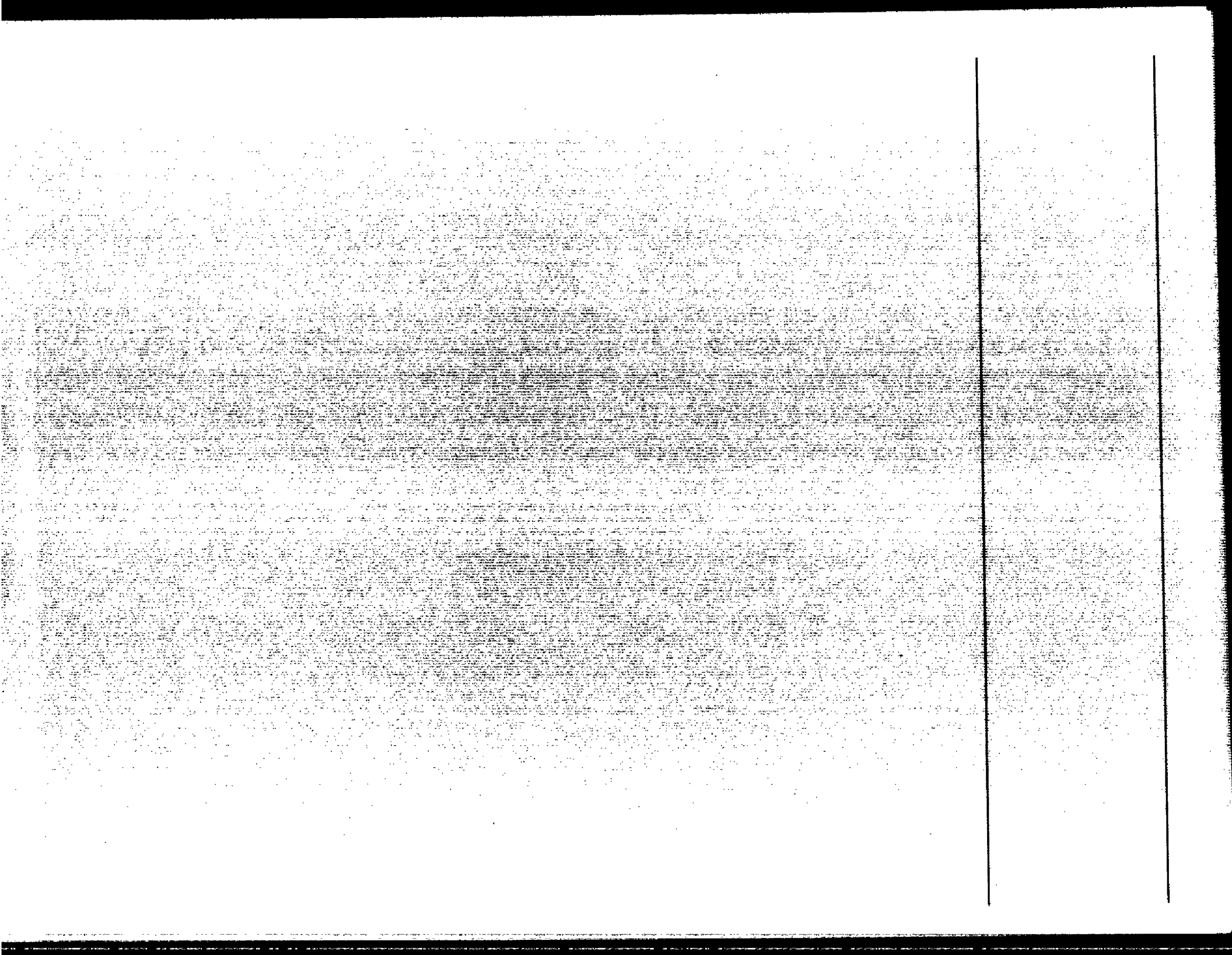

GAO

United States
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Program Evaluation and
Methodology Division

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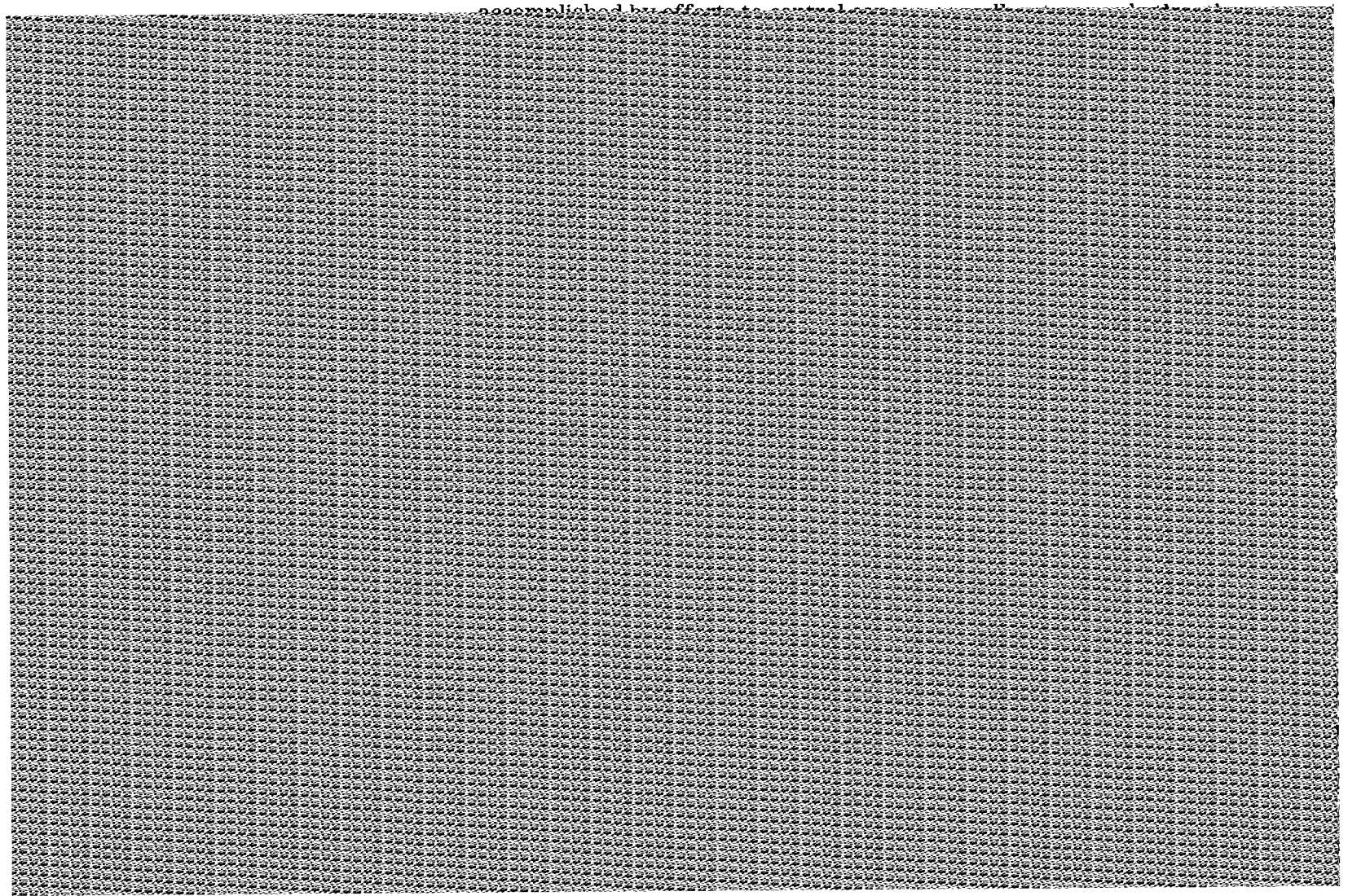
December 11, 1991

The Honorable Ted Weiss
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

On December 23, 1971, President Richard M. Nixon signed into law the National Cancer Act, launching what has been called the "war against cancer." Over the ensuing 20 years, many patients, physicians, and researchers have engaged in heroic efforts and vital skirmishes. Yet at the same time, "the dread disease" often seems to win battles and may even be winning the larger war. As we approach the 20th anniversary of the National Cancer Act, it is appropriate to reflect on what has been accomplished by efforts to control



Prevention Progress

The last 20 years can be summarized both as a period of major advances against breast cancer and as one when the most important indicators of progress have seen no improvement. This contradictory characterization makes it inappropriate to provide simple answers to questions about progress. Rather, to understand both the successes and the failures, it is important to examine the data in detail.

On the negative side, the number of American women newly diagnosed with breast cancer increases each year. The increase in incidence, a gradual trend in the 1970s that accelerated in the 1980s, can be illustrated by any number of statistics. For example, over the 16-year period 1973-88, the years for which data are available,

- the estimated number of new cases of breast cancer diagnosed went from 73,000 to 135,000;
- even after controlling for changes in the population, the rate at which breast cancer was diagnosed went from 82 to 110 cases for every 100,000 women; and
- the estimated annual percentage increase, perhaps the best indicator of change in the incidence of disease, was 1.8 percent per year.

A limitation of these statistics is that they do not provide insight into the critical issue of why incidence is on the rise. Answering this question is important because different answers lead to very different conclusions about "how we are doing." On one hand, the increase in the number of women diagnosed with breast cancer might result from a genuine increase in breast cancer. This would clearly be bad news. On the other hand, it is possible that the "true" amount of breast cancer has not changed. Rather, the increasing numbers could reflect the benefits of increased emphasis on earlier detection and, therefore, would be considered good news.

One way to distinguish between these competing explanations is to look at mortality figures. If the number of women dying of breast cancer is increasing, it is clear that the increases in incidence reflect more disease. When we examined mortality, we found that although more and more women are dying from breast cancer, the adjusted mortality rate (the measure that controls for changes in the population) has remained relatively constant since 1973 (26.8 deaths per 100,000 women in 1973-74 and 27.3 in 1987-88).

Once again, however, interpretations are not simple. Does the rise in incidence combined with stable mortality mean that we are now

detecting many more forms of breast cancer that are readily cured? Or does it mean that there really is much more breast cancer but that this increase has not led to more deaths because of more effective treatments? In reality, both explanations are likely to be part of the truth. As we concluded in our previous report on cancer patient survival, the actual survival of breast cancer patients has improved because management of the disease has improved.[1] At the same time, it is likely that a phenomenon known as length bias (finding more slow-growing disease) has also contributed to the discrepancy between incidence and mortality trends.

The complexity of interpreting the data on incidence and mortality should not obscure our basic findings: More and more women are getting breast cancer and the likelihood is increasing that any woman will be diagnosed with breast cancer in her lifetime. From these findings, we must conclude that there has been no progress in preventing the disease.[2]

Progress in Medical Interventions

On the positive side, the medical management of the disease (that is, the detection, diagnosis, and treatment of breast cancer) has improved. The widespread availability of mammography, a technology for detecting breast cancer that was largely unavailable in the early 1970s, now offers the ability to detect breast cancer while the disease is still early in its development. Based on data from SEER, it seems that the benefits of mammography are being realized. In our examination of tumor size, a factor related to how long the cancer has been present, we found that the average size of breast cancer tumors steadily decreased over the 1977-87 period. A decrease in the size of tumors being detected is clinically significant because treatment when tumors are in the early stages of development greatly increases the patients' chances for survival.

Increasing patients' survival is, arguably, the primary objective of all therapies. However, to assess advances in treatments for breast cancer, it is important to recognize that even in the 1970s many patients were cured and most patients lived for long periods of time. For example, in the mid-1970s three of every four patients survived for at least 5 years after diagnosis. The likely survival of most breast cancer patients means

[1]See U.S. General Accounting Office, Cancer Patient Survival: What Progress Has Been Made? GAO/PEMD-87-13 (Washington, D.C.: March 1987).

[2]There was a modest decline in 1988 in incidence, but it is too early to tell whether this decline signals that the increasing trend has abated to any degree.

that minimizing pain and suffering are also important goals of therapy. It is in this dimension, largely relating to the quality of survival, that we believe the major advances in treatment have occurred. Perhaps most importantly, whereas almost all breast cancer patients were earlier subjected to a disfiguring and disabling form of surgery (known as the Halsted or radical mastectomy), this procedure is rarely performed today. Replacing it is a range of operations that provide equivalent chances for survival while reducing the degree of disability and disfigurement.

In addition to changes in surgery, a greater concern for the quality of life of breast cancer patients is evident today than 20 years ago in such changes as the involvement of patients in decisions regarding therapy and the incorporation of counseling and supportive services into the treatment that is offered to patients.

Survival

We do not have facts, evidence, or hard data to support definitive answers to the question of how best to improve breast cancer patients' survival. Despite the presence of theories about what would accomplish this goal (for example, more widespread dissemination and adoption of state-of-the-art therapies), we could find no empirical evidence to support these ideas.[3] The singular exception is with respect to mammography, where the evidence is compelling that survival would be improved by greater use of the technology.

Prevention Research

The absence of a clear strategy for improving survival argues for the importance of prevention. However, from our review of the literature, we conclude that much remains to be learned about the factors responsible for variations in breast cancer incidence. As a consequence, we see little near-term likelihood that prevention efforts will reduce the incidence of breast cancer. One reason is that most of the important risk factors that have been definitively identified, such as age and heredity, are not amenable to modification. Another is that all the known risk factors account for only 20 to 30 percent of all cases. Until we have a better understanding of the factors that cause breast cancer, efforts to prevent the disease have little chance of success.

[3]In fact, in a previous report we found no survival improvement among a select group of breast cancer patients despite more widespread use of chemotherapy. See U.S. General Accounting Office, Breast Cancer: Patients' Survival, GAO/PEMD-89-9 (Washington, D.C.: February 1989).

Research Support

To compare NIH research funding for breast cancer with funding for five other clinical conditions, we constructed a simple measure of research investment. The data for the most recent year, when adjusted for mortality, show that research expenditures for breast cancer are equivalent to or greater than expenditures for other selected conditions. The singular exception is acquired immune deficiency syndrome (AIDS), for which research expenditures are considerably greater than for breast cancer. Of course, a comparative assessment of one measure of research investment is not a comprehensive assessment of funding levels. Additionally, this comparison should not be construed as an appraisal of the adequacy of funding.

If a theme underlies our findings, it is that the gaps in fundamental knowledge about the etiology of breast cancer (that is, its causes and their mode of operation) are the critical obstacles. Research in this area is a crucial priority. Clearly, efforts to detect, diagnose, and treat the disease would be much more effective if they were linked to knowledge of the disease's etiology. Further, identifying chains of events leading to the onset of breast cancer and learning how to interrupt those sequences are the primary prerequisites for preventive measures.

In conclusion, the facts presented in this report, while showing that many breast cancer patients live longer and better than their predecessors, also show that we do not seem to be winning the war against breast cancer. As we stand on the eve of the 20th anniversary of the National Cancer Act, the expectation is that the coming year will see more women stricken with the disease and more women dying from it than two decades ago. Once again, however, alternative interpretations of these facts are possible. The failure to make inroads against mortality may be a direct result of control efforts that are less than optimal. At the same time, it is equally plausible that the problem lies less in the strategy and tactics than in the intractability of the enemy. If the former is true, it is clear that new approaches to combat breast cancer must be developed and adopted. If the latter, more resources, both in terms of time and money, could help.

We address each of the five questions in greater detail in appendixes I-V. Because we relied extensively on NCI's cancer data, appendix VI describes the SEER program, which has assembled most of the nation's cancer data since 1973. The latest year for which SEER has compiled data is 1988.

We conducted our analysis in Washington, D.C., between March and November 1991 in accordance with generally accepted government auditing standards. It should be noted that we did not verify the SEER data provided by NCI.

As you requested, we did not send this report to the Department of Health and Human Services for comment prior to publication. However, we did meet with officials from NCI and briefed them on our major findings and conclusions. As we arranged with your office, we will send copies of this report to the Secretary of Health and Human Services and the directors of the National Institutes of Health and the National Cancer Institute. We will send copies to others who are interested and make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Robert L. York, Acting Director of Program Evaluation in Human Services Areas, at (202) 275-5885. Other major contributors to this report are listed in appendix VII.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Contents

Tables

Figures

Abbreviations

AIDS	Acquired immune deficiency syndrome
EAPC	Estimated annual percentage change
GAO	U.S. General Accounting Office
NCI	National Cancer Institute
NIH	National Institutes of Health
SEER	Surveillance, Epidemiology, and End Results

Prevention Progress

The first question to be answered is whether progress has been made in the prevention of breast cancer. The most direct indicator of progress in the prevention of a disease is the trend in that disease's incidence. Therefore, we examined incidence rates since 1973 and present our findings in this appendix. We begin with an explanation of differences among crude incidence rates, age-specific incidence rates, and age-adjusted incidence rates, and we present the corresponding rates for breast cancer.

Measures of Disease Frequency

Incidence

Perhaps the most basic measure of disease frequency is the incidence of the disease—that is, a simple count of individuals affected during a given year. For example, for breast cancer, it is estimated that 175,000 American women will be diagnosed with breast cancer during 1991. While useful in planning and providing health services, incidence as a measure has limited utility because it is difficult to make comparisons using only the absolute number of cases of a disease. Usually, adjustments are needed to account for differences such as variation in the populations at risk for incurring the disease. For example, to compare levels of breast cancer in the United States and Canada by simply looking at the total number of new cases in a given year would be misleading. After all, such a comparison ignores the fact that there are many more women at risk in this country.

Incidence Rates

To draw meaningful conclusions about disease frequency from comparisons across different populations, it is necessary to account for both the difference in population sizes and the time period during which data on disease occurrence were collected. Incidence rates accomplish this by controlling for population size at specified times. That is, the incidence rate divides the total number of cases of a disease during a given year by the population at risk during that year. In the case of breast cancer, then, the incidence rate for 1991 would be the number of breast cancers diagnosed in 1991 divided by the number of women in the population during that year. For ease of comparison, this rate is usually expressed per 100,000 persons.

Age-Specific Incidence

Breast cancer incidence rates can be presented for the entire female population (crude rate) or for categories within the population defined on the basis of particular characteristics such as age or race (category-specific rates). For example, age-specific rates represent the number of cases of breast cancer diagnosed in each specified age group divided by the total number of women in that group during a specified time period. Table I.1 presents age-specific incidence rates for breast cancer by 5-year age groups during 1984-88.

Table I.1: Average Annual Age-Specific Incidence Rates for Breast Cancer, 1984-88

Age	Rate per 100,000 women[a]
15-19	0
20-24	0.9
25-29	7.4
30-34	26.7
35-39	66.2
40-44	129.4
45-49	187.4
50-54	220.0
55-59	267.6
60-64	338.9
65-69	390.7
70-74	421.8
75-79	461.4
80-84	451.3
85 and over	411.9

[a]SEER program. Rates are per 100,000 female population of the specified 5-year age group.

Source: National Cancer Institute, Cancer Statistics Review 1973-1988 (Bethesda, Md.: July 1991), table II-40.

Age-Adjusted Incidence

Comparing category-specific rates presents more precise pictures than comparing overall crude rates. However, when there are a large number of categories (as in the case of age), many comparisons must be made: 55-59-year-olds in 1973 compared to 55-59-year-olds in 1988, 60-64-year-olds in 1973 compared to 60-64-year-olds in 1988, and so on. For this reason, it is often useful to have a summary rate for each time period that takes into account specified differences in the population groups. This is done through a procedure called adjustment or standardization. Adjusted rates are statistically constructed summary rates that account for the differences between populations with respect to specified variables. For example, in the case of age, the adjusted incidence

rate would be computed by taking the weighted average of the age-specific incidence rates. The weights for the computations are the fractions of persons in the corresponding age groups of a standard population.[1]

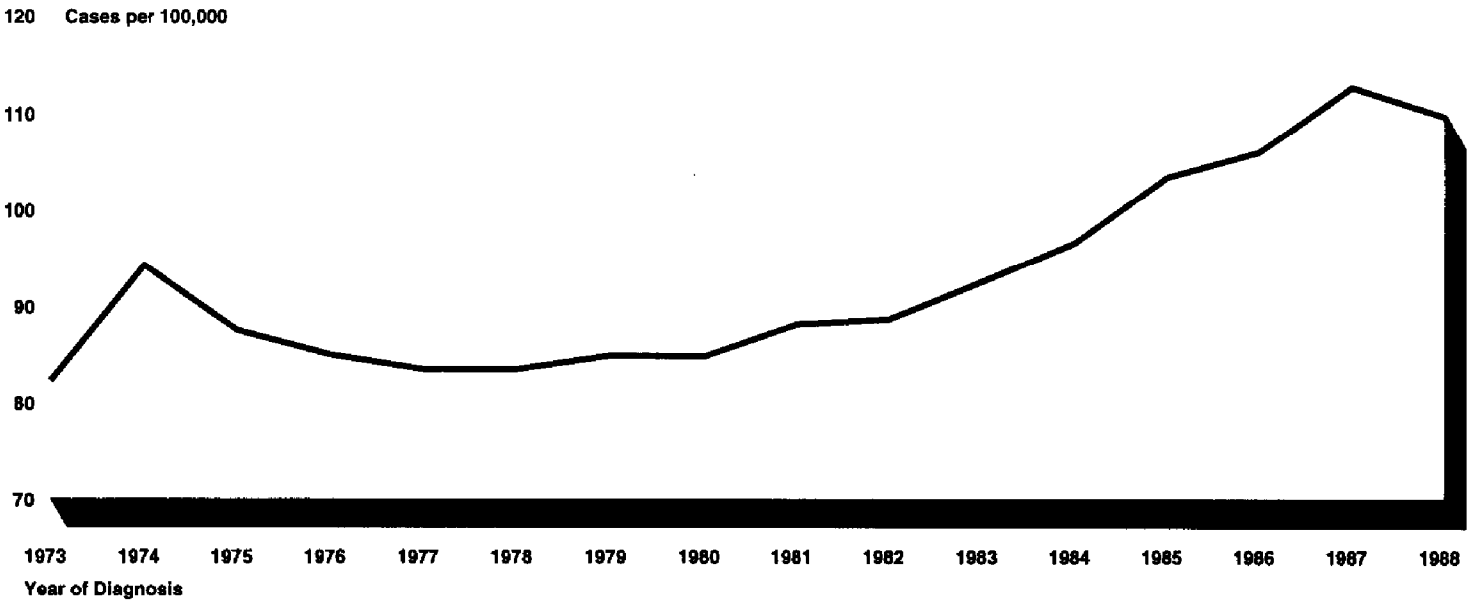
In the case of breast cancer, standardization allows us to use a single statistic, the age-adjusted rate, to convey much of the information in table I.1. The average annual age-adjusted incidence rate for all women during the 5-year period 1984-88 was 105.6 new cases per 100,000 women. This standardized rate represents the hypothetical rate that would have been observed if the 1984-88 population had the same age distribution as the standard, the population in 1970.

Measures of Change

Age-adjusted incidence rates, adjusted to the 1970 population, are plotted by year of diagnosis in figure I.1. Connecting the annual values in the figure highlights both the direction and sharpness of the yearly changes in incidence rates. (A sudden peak in 1974 is largely artifactual and is discussed below.) The incidence of breast cancer in women has been rising quite steadily since 1977 and rose sharply in the 1980s, increasing from 84.8 cases diagnosed per 100,000 women in 1980 to 112.5 in 1987. In 1988, the latest year for which data have been compiled, incidence declined to 109.5. Whether this decline indicates that the trend of increasing incidence has abated to any degree must await the compilation of more data over the next few years.

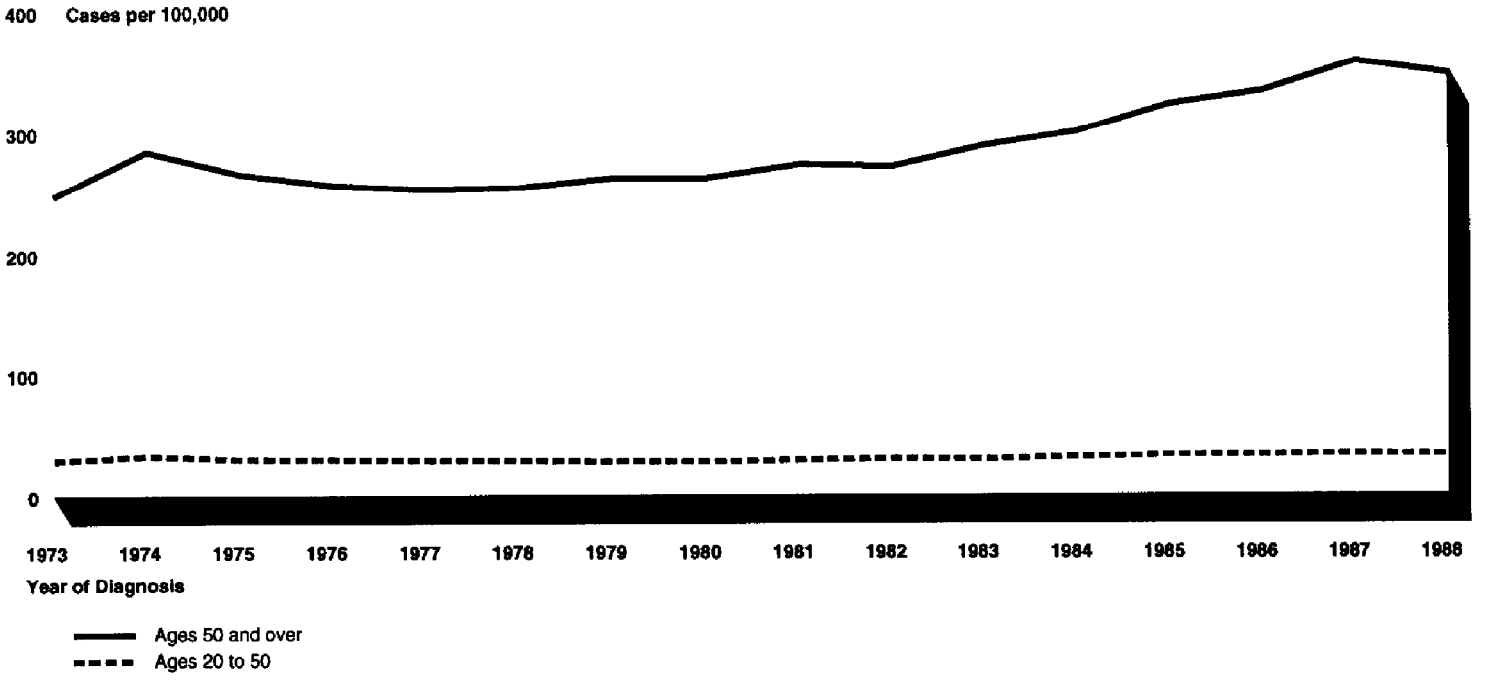
[1]For the standard in computing age-adjusted rates, SEER uses the 1970 U.S. population.

Figure I.1: Breast Cancer Incidence Rates, 1973-88



Breast cancer rates are often reported in the two categories of under 50 years and 50 years or older. This cutoff is used to approximate the differences imposed by menopause, as menopausal status is believed to have etiologic and biologic importance for breast cancer. Age-adjusted incidence rates by year of diagnosis are plotted for these two age groups in figure I.2. Until 1980, the increase in incidence rates concentrated in the postmenopausal age group, but since then the incidence rate has also risen in the premenopausal age group, going from 27.5 cases per 100,000 women in 1980 to 32.8 in 1988.

Figure I.2: Breast Cancer Incidence Rates, 1973-88, by Age Group



Percentage Change

While tables can present specific information about incidence rates and graphs can depict the patterns of data, summary statistics can provide additional information about change in rates. Over the 16-year period 1973-88, the age-adjusted breast cancer incidence rate for U.S. women increased by 25.8 percent. Table I.2 reports the total percentage change over the period for all women and for two age groups. To reduce the effect of year-to-year variation, the percentage change is calculated using the average of the 1973 and 1974 rates and the average of the 1987 and 1988 rates.

Table I.2: Age-Adjusted Incidence Rates for Breast Cancer and 16-Year Trends, 1973-88[a]

Population and age group	Average rate[b] 1973-74	Average rate[b] 1987-88	% change 1973-88	EAPC 1973-88[c]
All women	88.2	111.0	25.8	1.8
Women under 50	30.7	33.1	8.0	0.7
Women 50 and over	265.7	351.1	32.1	2.1

[a]SEER program. Rates are per 100,000 females and are age-adjusted to the 1970 U.S. standard population. Each rate has been age-adjusted by 5-year age groups.

[b]The average rate is the average annual rate over the specified 2-year period.

[c]EAPC is the estimated annual percentage change over the 16-year interval. Each EAPC is significantly different from zero ($p < .05$).

Source: National Cancer Institute, Cancer Statistics Review 1973-1988 (Bethesda, Md.: July 1991), table II-4.

One problem with using total percentage change as an indicator of the true change in breast cancer incidence is that the measure is very sensitive to the incidence rates in the base years. In the case of breast cancer, selecting the appropriate base years presents an especially difficult problem. This is because of the unusual attention given the disease following the announcements in September and October 1974 that the wives of the nation's president and vice president had undergone surgery for breast cancer. The publicity surrounding these celebrated cases is thought to be responsible for an artificial increase in the incidence rates for 1974 in that many more women than usual went for breast exams.

If the average of the rates for 1975 and 1976 were used for the base instead of the average for 1973 and 1974, the base would be lower, resulting in a larger percentage change over the 16-year period. However, some of the cancers detected in 1974 might otherwise have been detected in 1975 and 1976, suggesting that a 1975-76 base is artificially low. Complicating the picture even further is the position that because the publicity about breast cancer occurred in the last quarter of the year, some of the surge in mammography may have spilled over into 1975.

Estimated Annual Percentage Change

Because total percentage change is so sensitive a measure and because the first biennium of available data coincided with an "alerting event"—the aforementioned widely reported surgeries in the fall of 1974—another measure that uses more data in the estimation, and therefore presents a more balanced picture, is needed to capture the trend. The estimated annual percentage change (EAPC), based on linear

regression, is such a measure. Table I.2, cited previously, reports the estimated annual percentage change for the 16-year period 1973-88 for all women and for two age groups.

Over the 16-year period 1973-88, the estimated annual change in breast cancer incidence was a 1.8-percent increase. Thus, for any year in the 1973-88 period, 101.8 women would be diagnosed with breast cancer for every 100 diagnosed in the previous year. For the premenopausal age group, 100.7 would be diagnosed for every 100 diagnosed the previous year; for the postmenopausal age group, 102.1 for every 100 the previous year.[2]

Trends

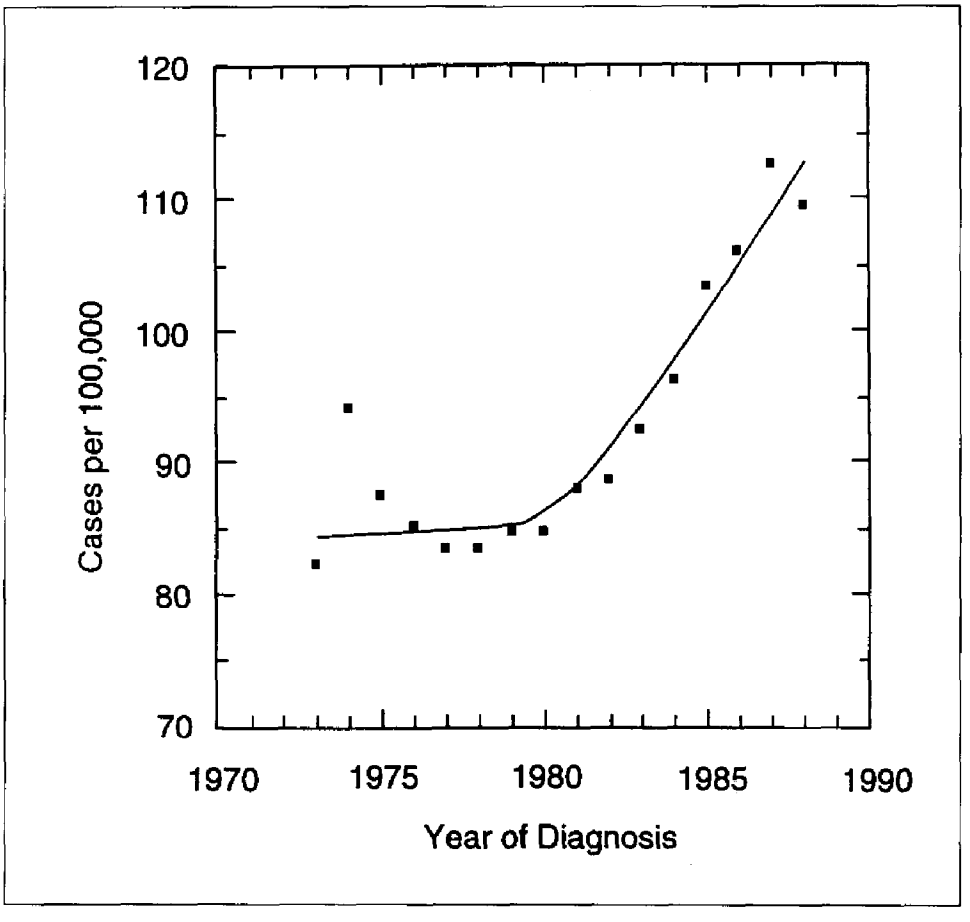
While figure I.1 shows that incidence rates rose from 1977 to 1988, the increase was marked from 1982. Incidence rose 4.3 percent per year during the 6-year period 1982-87, a jump from the previous 1.1 percent per year during 1973-81. For 5-year periods, comparable estimated annual percentage changes for 1982-86 and 1983-87 are 4.6 percent and 4.9 percent, respectively. With the decline in 1988, the estimated annual percentage change for the 5-year period 1984-88 was 3.4 percent.

To highlight the pattern of change in annual incidence, a method of smoothing data (robust locally weighted regression) is used in figure I.3 to superimpose a curve on the data points that were plotted in figure I.1.[3] Whether the 1988 data indicate that the trend of increasing incidence is slowing or merely document a random, short-term decline cannot be determined until data are collected for the next few years. The change in incidence rates in the early 1980s is dramatic.

[2]Because the EAPC over a specified time period is calculated by fitting a straight line through the logarithm of the incidence rates, the computation assumes that the annual percentage change from each previous year's rate is constant throughout the period.

[3]This data-smoothing procedure is also known as LOWESS, locally weighted scatterplot smoother. In the figure, 70 percent of the data points are used to smooth each value on the curve (F = 0.7). William S. Cleveland, The Elements of Graphing Data (Monterey, Calif.: Wadsworth, 1985), pp. 167-79. Using another method, Miller and colleagues plotted the data on a logarithmic scale and fit segmented linear models, identifying a "join point"—a point in time when there is a significant change in the log-linear incidence trend. Their best-fitting model indicated a significant change in the incidence trend after 1982 (95-percent confidence interval = 1982, 1983). Barry A. Miller, Eric J. Feuer, and Benjamin F. Hankey, "The Increasing Incidence of Breast Cancer Since 1982," Cancer Causes and Control, 2 (1991), 68-69.

Figure I.3: Breast Cancer Incidence Rates, 1973-88



We next interpret the trends in breast cancer incidence. However, because our interpretations require reference to mortality data, we first present breast cancer mortality rates.

Mortality

In 1991, 44,500 American women are expected to die of breast cancer. For the 16-year period 1973-88, the estimated annual percentage change in breast cancer mortality among women was a 0.2-percent increase. The EAPC is a 0.4-percent increase for women age 50 and older but a 0.7-percent decrease for women younger than 50. Table I.3 presents mortality rates in greater detail. While incidence rates have been increasing dramatically, improved medical interventions, the subject of appendix II, may have held overall mortality rates fairly steady.

Table I.3: Age-Adjusted Mortality Rates for Breast Cancer and 16-Year Trends, 1973-88[a]

Population and age group	Average rate[b] 1973-74	Average rate[b] 1987-88	% change 1973-88	EAPC 1973-88[c]
All women	26.8	27.3	1.8	0.2
Women under 50	6.9	6.2	−10.5	−0.7
Women 50 and over	88.0	92.2	4.8	0.4

[a]National Center for Health Statistics public use tape. Rates are per 100,000 females and are age-adjusted to the 1970 U.S. standard population. Each rate has been age-adjusted by 5-year age groups.

[b]The average rate is the average annual rate over the specified 2-year period.

[c]EAPC is the estimated annual percentage change over the 16-year interval. Each EAPC is significantly different from zero ($p < .05$).

Source: National Cancer Institute, Cancer Statistics Review, 1973-1988 (Bethesda, Md.: July 1991), table III-4.

Interpretations of Incidence

By all the measures, the incidence of breast cancer is increasing. The increase may indicate a true rise in the frequency with which women are developing breast cancer. However, changes in incidence rates may also reflect changes in breast cancer detection practices. To the extent that the increase in incidence is a function of greater emphasis on detection rather than true increases in the prevalence of breast cancer, measures of incidence are said to be biased. At least two sources of bias related to detection practices may be reflected in the observed increased incidence—lead time bias and length bias.

Lead time bias results from changes in the timing of detection. The consequences of this form of bias for changes in incidence can be shown by the following hypothetical example. Assume that every year 100 new breast cancers begin and that it takes 4 years until symptoms appear. Every year, 100 cases of breast cancer would be recorded. They would be categorized as newly diagnosed even though they started 4 years earlier. With no change in incidence and no change in detection, the incidence would remain stable at 100 per year. However, if there is a campaign to urge women to see their doctors for cancer screening, it is likely that in addition to the 100 cancers that exhibit symptoms, many of the cancers in their third and second years of growth would also be picked up in the course of the examinations. The result would be an increase in reported incidence even without any change in the underlying incidence of the disease (that is, there are still 100 new cases per year).

Closely related to lead time bias is length bias. Length bias refers to the overrepresentation among diagnosed cases of those with a long

presymptomatic phase of disease. This occurs because breast cancer tumors differ in their natural history. They develop at different rates, with the result that tumors with long preclinical phases are more likely to be detected in screening than cancers that progress more rapidly to clinical symptoms. As a consequence, changes in detection practice can result in different types of breast cancer being included in incidence rates. Length bias results from screening that detects types of breast cancer that were not formerly diagnosed and counted as "breast cancer."

We do not know how much of the increase in breast cancer incidence stems from lead time bias or length bias. Certainly, both forms of bias account for some of the dramatic increase that began in the early 1980s. Exactly how much of the increase is "real" (indicative of higher levels of breast cancer) is not known. Further, explanations for any real increase in incidence are largely unsatisfactory in that the majority of women diagnosed with breast cancer continue to have no known risk factors for the disease. As a result of these uncertainties, we conclude that, as NCI states in its most recent statistical review, the increased incidence in breast cancer remains "a major concern" that is unexplained.

Progress in Medical Interventions

To ascertain what has changed in the management of breast cancer, we examine three components of medical intervention in this appendix: (1) detection, (2) diagnosis, and (3) treatment. Our analysis uses multiple measures to gauge change along each of these three dimensions. Much has been written about breast cancer interventions in the medical literature; many of our findings are drawn from it.

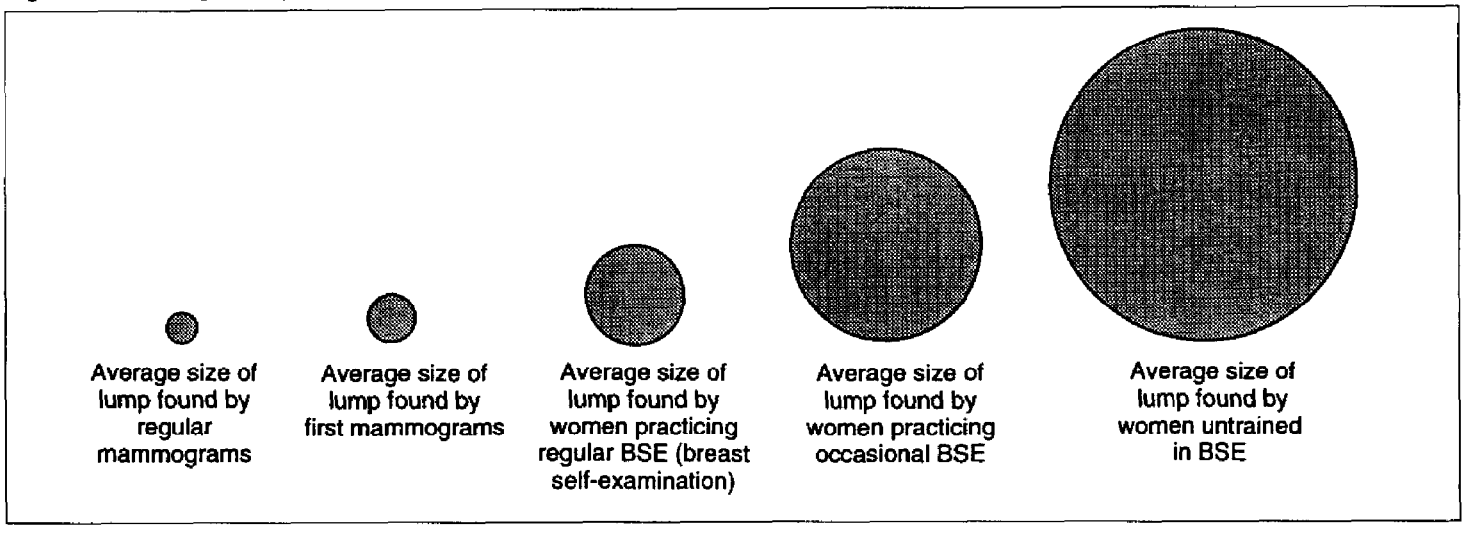
To corroborate reported changes in medical interventions over 20 years, we reviewed patient records from two points in time at one hospital. We selected a community hospital in a large metropolitan area that drew patients from both its urban location and surrounding suburbs, that offered a general, nonspecialized practice, and that held breast cancer patient charts from 1972-74 as well as from current years. Findings from these patient charts provide a window on the past and present at the same institution and complement pertinent technical reports in clinical journals.

Detection

Breast cancer can be detected by self-examination, a physician's physical examination, and mammography. Mammography, an X-ray picture of the internal structure of the breast, is the most promising technique for finding early disease because it can detect small tumors and other breast abnormalities that might be missed during a physical examination. This can be seen from figure II.1, which shows average lump size according to method of detection, contrasting the size lump found by a screening or first mammogram or by regular mammograms or by breast self-examination.[1]

[1]First mammograms or "prevalence examinations" identify larger lesions, which may have been present for some time, simultaneously with smaller tumors. By contrast, regular screening mammography or "incidence examination" is more likely to find smaller tumors, either newer or slower growing, because preexisting larger tumors would have been found at the initial screening. Neither is a definitive test for cancer but detects an abnormality that requires further investigation to establish its nature.

Figure II.1: Average Lump Size by Method of Detection



Source: Breast Health Program of New York, Health After 50, December 1990, p. 2.

The impetus for earlier detection comes from the expectation that early treatment greatly increases the chance for longer survival. Our examination of changes in detection focused on mammography. Specifically, we were concerned with changes in access to the technology, its use, and the effect it has had. The focus on mammography was selected because published studies had indicated that it had the potential to significantly reduce mortality from breast cancer.

Access

Under the question of access, we considered two issues: the availability of the technonolgy (that is, the number of mammographic facilities) and health insurance coverage for the procedure. Supply of equipment can be seen as a measure of physical access to mammography, while coverage benefits can be seen as a measure of the means to access.

Supply

Throughout the 1970s, both the technological standards and the acceptability of the use of mammography were in flux. With the reduction of radiation exposure, improvement of film, and the reporting of results from studies of screening mammography during the late 1970s and early 1980s, the supply of mammography machines began to increase rapidly. A recent study estimated that from 1981 to the end of 1990, almost 10,000 mammography units had been installed. Current estimates are that there are more than enough machines to meet the screening needs of American women.

Coverage

Surveys and information from health insurance trade associations, professional associations, and federal health agencies show that benefits are increasingly designed to encourage screening mammography. Until 1986, most commercial insurance companies did not provide coverage for screening mammograms. By 1990, however, 68 percent of employees with employer-based health insurance were covered for mammography.

The spread of coverage is evident from laws in 33 states that now require third-party coverage of screening mammography. Four more states have laws that require insurers to offer coverage. States first mandated coverage in 1987. State-mandated coverage laws vary in what types of insurance policies and health plans are included, age limits, periodicity of examinations, quality control requirements and equipment standards, and the population base affected by the coverage. In government-sponsored health insurance programs, a 1990 survey identified 17 state Medicaid programs that cover screening mammography, and beginning in 1991, the federal Medicare program covers screening mammography once every 2 years for women beneficiaries 65 and older.

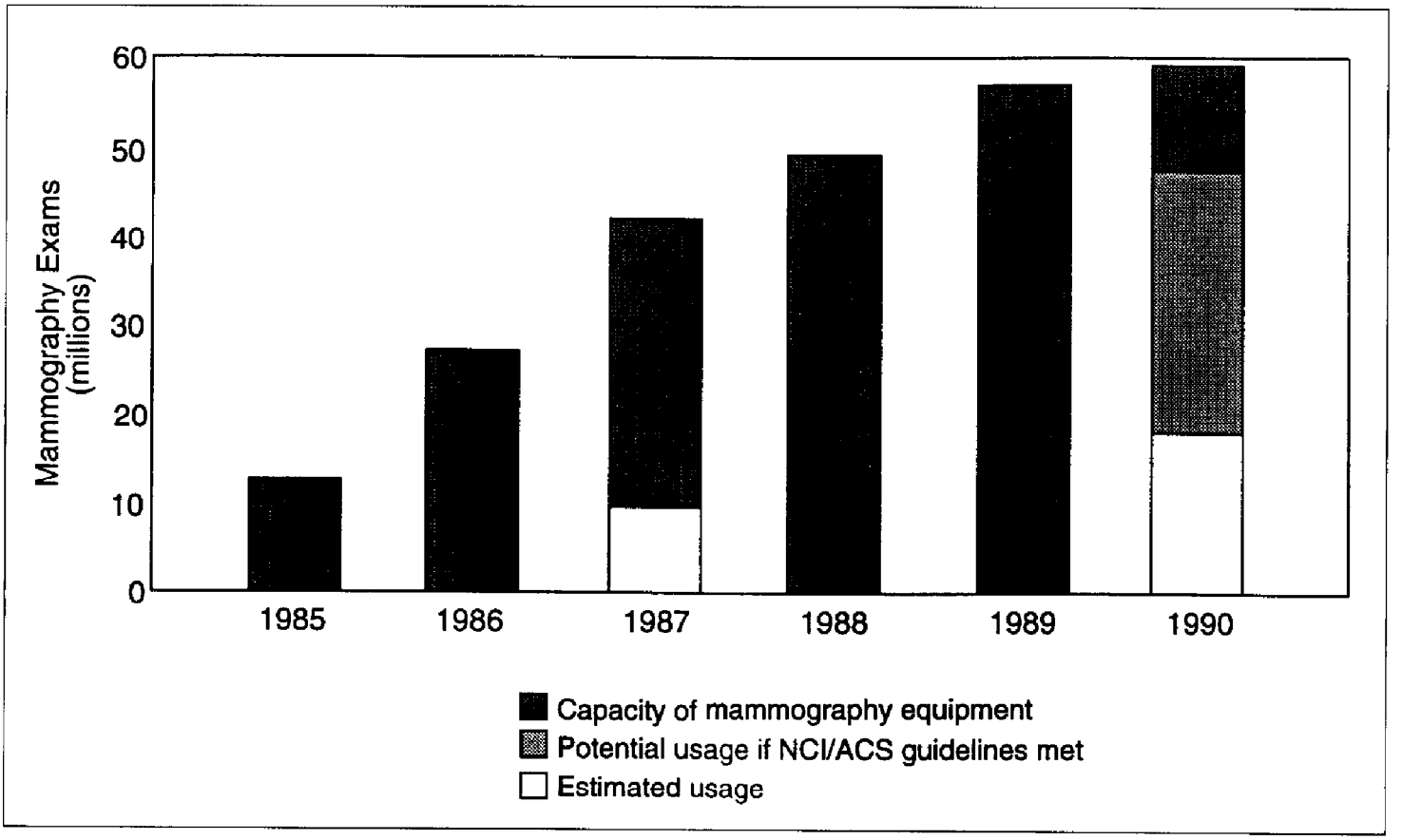
Use

Before 1980, few women in the United States were being screened by mammography. Our review of patients' records showed that in 1972-74, breast cancer was usually detected by physical findings alone, most commonly when the patient found a lump herself or when she was hospitalized for some other condition. When the findings were confirmed by a physician and found suspicious, the patient was referred to a surgeon for further diagnosis and treatment. At this point, mammography may have been performed as a part of the diagnostic workup to help assess lesion size. However, mammography was almost never used in asymptomatic women. Thus, premalignant lesions and early nonpalpable cancers were usually detected only when accompanied by a palpable mass. By contrast, patients' records in the 1990s show that mammography is the usual method of detection. In addition, it is invariably used before deciding on definitive treatment.

Despite recommendations by NCI and medical and health organizations for regular screening mammography, more than half of women over 40 have never had the test. Actual estimates, depending on study design, are that between 15 and 30 percent of women in this age group have had screening mammograms in the year preceding interviews. The irony is that a recent report on mammography showed that the supply of equipment has increased so dramatically that the estimated 1990 capacity was both greater than estimated usage and also greater than potential

need if guidelines issued by the National Cancer Institute and the American Cancer Society for mammography use were met. Figure II.2 reproduces a chart illustrating these findings.

Figure II.2: Mammography Capacity, Need, and Usage



Source: Martin Brown, "U.S. Mammography Capacity Exceeding Usage and Need," Journal of the National Cancer Institute, 83:1 (January 2, 1991), 5.

There are no reliable estimates for national mammography use for all the years indicated in the figure. The source of the 1987 estimate is the National Health Interview Survey, which showed that approximately 21 percent of all women over 40 years of age (approximately 9,800,000 women) had mammography within the previous year; the source of the 1990 use estimate is the Jacobs Institute of Women's Health. The finding of unused capacity is consistent with our 1989 survey of all facilities providing mammography in four states (California, Florida, Idaho, and

Michigan). We found that the majority of facilities performed a comparatively low volume of mammography.[2]

Effect

To determine the effect of the increased use of mammography in detecting early cancers, we compared breast cancer lesion sizes at the time of surgery in annual random samples of SEER cases. If mammography is effective in detecting early breast cancer, an increased use of mammography would be expected to result in the detection of smaller tumors that might not otherwise become clinically apparent for several years. At first, increased mammography would lead to an increase in the number of localized and small tumors; later, to a decrease in the number of advanced and large tumors. Over time the trend in size of tumors detected would move toward a smaller average.[3]

Using 10-percent annual random samples of breast cancer cases from SEER, we calculated that the average tumor size over the 11-year period 1977-87 fell by 26 percent, from 3.6 centimeters in the longest dimension to 2.6 centimeters. This overall percentage change was obtained by using the average of the 1977 and 1978 sizes and the average of the 1986 and 1987 sizes. Table II.1 reports further detail on these data. In 1977, SEER registries began to code tumor size in a form suitable for this analysis. Any inaccuracies in SEER tumor size data are assumed not to be differentially biased.

[2]U.S. General Accounting Office, Screening Mammography: Low-Cost Services Do Not Compromise Quality, GAO/HRD-90-32 (Washington, D.C.: January 1990), pp. 14 and 21.

[3]Although stage at diagnosis (collected by SEER as extent of disease rather than stage specified in the medical record) could provide another measure, it could be biased by changes in stage classifications, staging procedures, and diagnostic techniques.

Table II.1: Mean Breast Cancer Tumor Size

Year of diagnosis	Tumor length mean in centimeters
1977	3.6
1978	3.8
1979	3.4
1980	3.6
1981	3.3
1982	3.2
1983	3.1
1984	3.0
1985	3.1
1986	2.9
1987	2.6

Diagnosis

Once breast cancer is suspected, a series of tests is performed to determine whether the growth is cancerous and, if so, the type of disease and the extent to which it has progressed. These tests are essential in the selection of the most appropriate treatment. In the case of breast cancer, these are the questions that must be answered for selection of appropriate therapy:

- Is the abnormality clearly cancer?
- If so, can cancer be found in other parts of the body?
- If not, what is the likelihood that the disease is contained entirely within the breast?

The first question is answered through a procedure known as biopsy, which involves the removal of suspect tissue from the breast with a surgical knife or needle. Biopsies are performed while the patient is under local or general anesthesia. A pathologist examines the tissue cells under a microscope to determine whether they are cancerous. All the patients in the early period of our hospital chart study underwent surgical biopsies in the hospital prior to definitive breast surgery on the same day. In 1990, because of improvements in both technique and efforts to contain costs, breast biopsies were usually performed on an outpatient basis, often under local anesthesia, sometimes at a hospital, and often at unaffiliated ambulatory surgery facilities. If the biopsy showed cancer, surgery was performed 1 or 2 weeks later.

Several biopsy methods can be used to remove tissue for a pathologist to examine. Size and location of the lump or suspicious area and the

patient's general health are considerations in the choice. A newer low-cost biopsy technique performed as an outpatient procedure, requiring no anesthesia and leaving no scar, is diagnostic fine needle aspiration, in which a hollow needle and syringe remove cell clumps from a mass. This is now often part of the initial diagnosis.

Once the suspicious mass is determined to be cancerous, it is important to determine if cancer is present at any other sites in the body. This is significant because currently there is no cure for breast cancer once it has spread to other organs (the lymph nodes under the arm are not considered "other organs"). This means that if metastatic deposits are discovered (typically in bones or in the lungs), the therapeutic options are limited to palliation or enrollment in research studies.

If no metastatic deposits can be found, it is not conclusive evidence that cancer does not exist somewhere outside the breast. Current thinking is that breast cancer can start as a systemic disease. An essential step in the diagnostic process, therefore, is to distinguish between patients who are likely to have metastases outside the breast and those whose cancers are confined to the breast. This distinction is important because the former group can benefit from chemotherapy or hormonal therapy as adjuvants to surgery, while the latter group can frequently be cured by surgery alone. Many of the developments in recent decades in diagnosis are oriented to distinguishing between these two groups of patients. Although there have been a number of such developments (principally, tests of the DNA in the tumor cells to see how "active" the cancer is), there currently exists little consensus on exactly where to draw the line between high- and low-risk patients. In fact, consensus statements about appropriate treatment for localized breast cancer have become less specific and more uncertain over time.[4]

One development that has helped guide physicians and patients in deciding on appropriate treatments is the development of hormone receptor assays. Some breast cancers depend on the female hormones estrogen and progesterone to grow, while others do not. The assays determine whether the tumor contains a receptor protein that combines with these hormones and can thereby inform the decision as to whether

[4]To seek consensus on medical practice, NIH established a consensus development program in 1977 that brings together scientists, medical practitioners, and informed laypeople to evaluate new or conflicting approaches. Each panel meets for several days, reviewing scientific evidence, seeking consensus on key questions posed in advance of the conference, and drafting a consensus statement that contains recommendations for medical practice. These statements are disseminated through reports in medical journals and directly to practicing physicians. In 1979, 1985, and 1990, consensus statements on breast cancer focused on local disease.

hormonal therapy (principally, the estrogen blocker tamoxifan) would be effective. In the early period, assessment of steroid receptors was not available commercially. The 1990 charts show that estrogen and progesterone receptor assays are now routine after biopsies.

Treatment

Much has changed in the range of treatments available for breast cancer over the last 20 years. Given these changes, we conclude that breast cancer patients are treated better than they were, but it is not clear that they are treated more effectively. To determine changes in treatment, we examined two components of care—the technical and the interpersonal. Technical care is the application of the science and technology of medicine. The interpersonal component of care is the social and psychological interaction between patient and providers, both professional and institutional. For this component, we examined both patient involvement and supportive care.

Technical Component of Care

Procedures

Current treatment for breast cancer typically involves surgery and also may include any combination of radiation, chemotherapy, and hormonal therapy. Breast cancer surgery is the excision of the cancerous lesion, sometimes the breast, and sometimes additional tissue. Radiation treatment is used to achieve local control by destroying cancer cells in the area of the tumor. Chemotherapy is the use of toxic substances to kill cancerous tissue and is largely directed at any cancer cells that exist outside the breast. Estrogen therapy, primarily the antiestrogen agent tamoxifen, is the most frequently used hormonal therapy, particularly for postmenopausal women with receptor positive tumors. Similar to chemotherapy, hormonal therapy is directed at preventing the reoccurrence of cancer following surgical removal of the primary tumor.[5]

Each form of therapy for breast cancer has negative consequences. Surgery often involves loss of the breast; radiation can damage healthy tissues, cause systemic illness, or lead to another cancer; reactions to chemotherapy range from nausea and hair loss to cardiotoxicity, sterility, and even death; and tamoxifan, the treatment with the mildest

[5]Research is currently being conducted as well into the benefits of tamoxifan for preventing breast cancer.

side effects, can cause menopause-like symptoms. In spite of many successes, a large proportion of cancer therapy is unsuccessful.

To examine changes in surgery in the last 20 years, it is important to distinguish between the different surgical procedures performed during that period. Lumpectomy refers to removal of the cancer and a margin of surrounding normal breast tissue. Synonyms include partial mastectomy, quadrantectomy, wide excision, and tumorectomy. These terms may imply removal of different amounts of normal breast tissue. Simple mastectomy refers to removal of all breast tissue only. Its main synonym is total mastectomy. Modified radical mastectomy goes beyond the simple mastectomy and removes the axillary lymph nodes. Synonyms are total mastectomy and (or with) axillary dissection and extended simple mastectomy. The most extensive operations for breast cancer are referred to as radical mastectomy and extended radical mastectomy and involve removing the breast, the axillary nodes, the lymph nodes in the chest wall, and the pectoral muscles.

In addition to surgery, almost half of all breast cancer patients are treated with some combination of chemotherapy, radiation therapy, or hormonal therapy. This is especially true for early-stage cancer patients. These patients will receive a moderate dose of radiation to the primary tumor bed if they elect breast-conserving surgery. In addition, systemic therapy (that is, chemotherapy or hormonal therapy) will be recommended for most patients with localized tumors independent of whether they elect lumpectomy or mastectomy as their surgical option.

Practice Patterns

In an earlier report, we found that these major changes occurred in the treatment of breast cancer from 1950 to 1982:

- a decline in the number of radical mastectomies being performed;
- the reorientation of when radiation therapy should be used, with less extensive use in general; the exception is for patients with early disease who undergo breast conservation procedures;
- the advent of multimodal chemotherapy as adjuvant to surgery for early stage cancer; and
- the development of synthetic "anti-estrogen" drugs.[6]

[6]U.S. General Accounting Office, Cancer Patient Survival: What Progress Has Been Made? GAO/PEMD-87-13 (Washington, D.C.: March 1987), p. 43.

The review of hospital charts confirmed those findings. The Halsted radical mastectomy, already uncommon in the 1972 charts, was not present in the 1990 charts, while lumpectomy, found in only a handful of the 1972 charts, was more frequent in the 1990 charts. Now modified radical mastectomy and lumpectomy with axillary lymph node dissection are the most frequent types of surgery.

In 1972, postoperative radiation was used by some hospitals, especially in more advanced cases in doses considered heavy by today's standards. The 1990 charts show that radiation therapy is routinely ordered for patients undergoing lumpectomy. In the early 1970s, chemotherapy and hormonal therapy were used for patients with advanced-stage or recurrent disease but not for patients whose early-stage treatment left them asymptomatic. Today they are used in the months after surgery to destroy areas of undetectable malignant spread.

We compared the blend of different forms of treatment—primarily surgery and adjuvant therapy following surgery, whether chemotherapy, hormonal therapy, radiation, or some combination of these—in all SEER breast cancer cases. Surgery only is the most frequently occurring treatment modality and shows little change between 1974 and 1988, with frequencies of 60 and 59 percent, respectively. Next in frequency is the combination of surgery with radiation. This combination shows changes over time, dropping from 20 percent in 1974 to 12 percent in 1988. The other most frequent combinations are surgery with chemotherapy and surgery with hormonal treatment. Both categories have increased in frequency from just over 1 percent in 1974 to 6 and 7 percent in 1988.

Interpersonal Component of Care

Treating the patient involves considerably more than technical care. The interpersonal component of care refers to how responsive and attentive providers are in interacting with the patient. Although we reported the shift away from the Halsted radical mastectomy under the technical component of care, that change came about because of the interaction of the technical component with the interpersonal component of care. We think this is beneficial. In this section, our interest lies in ascertaining to what further extent patient involvement and supportive care have changed.

Patient Involvement

Through the interpersonal relationship, the patient communicates not only information necessary for arriving at a diagnosis but also preferences necessary for selecting the most suitable course of care. We focused on the trend from one-step biopsy-surgery procedures to two-

step procedures as an indicator of patient involvement. While the change in surgical practice patterns has accompanied other changes in the technical component of care, it reveals a significant change in the interpersonal component of care.

In a one-step procedure, a biopsy to determine if cancer is present and definitive surgery to remove the cancer are performed under one anesthesia without waking the patient. A two-step procedure, in which a biopsy is performed first and surgery is delayed for one or more days, allows the patient to consider treatment alternatives after a definitive diagnosis.

In the early 1970s, the date of the first positive biopsy was always the date of definitive treatment. In 1990, the one-step procedure was rare. Discussion between patients and physicians about treatment options may not always be recorded, and the quality of recording may vary among physicians. Nevertheless, the case records often reflect substantive preoperative discussions of therapy options with patients, although many records include merely a signed form indicating routine discussion, perhaps in the context of securing informed consent for surgery.

Supportive Care

Supportive care for breast cancer patients includes several types of physical therapy, psychological counseling, social services, and peer support groups intended to help women adapt to their surgery and cope with anxiety or depression. We looked at postmastectomy support groups in the hospital patient records we examined.

The 1972 charts give no indications that patients received postoperative social services. In contrast, nearly all the 1990 charts document social worker visits with patients and include referral to Reach to Recovery, an exercise and peer support program operated by the American Cancer Society. Because of the much shorter hospital stays now associated with breast cancer surgery and the increase in outpatient adjuvant therapy, Reach to Recovery, Encore (a similar program), and other supportive services take on added importance in contributing to the failure or success of technical care, maximizing patient welfare, and improving the quality of survival.

Survival

With the singular exception of more extensive use of mammography, there is little in the way of facts, evidence, or hard data to support definitive answers to the question of what can be done to improve breast cancer survival rates. In this appendix, we first discuss breast cancer survival rates and then present suggestions commonly made for improving these rates. In brief, these are to increase access to the full range of improved medical interventions: Too many women do not get mammograms, too many patients are not assigned to appropriate treatments, and too many patients do not get state-of-the-art surgery, adjuvant therapy, and support services.

Survival Rates

The relative survival rate represents the likelihood that patients will not die from causes associated specifically with their cancer within some specified time after diagnosis. This involves adjusting the observed survival rate for expected mortality, taking into account, as appropriate, the age, sex, and calendar year of diagnosis. Relative survival rates for breast cancer patients have shown a small improvement. The 5-year relative survival rate is 77.0 percent for patients diagnosed during the 1981-83 period, the latest period for which SEER has assembled 5-year follow-up data. By contrast, patients diagnosed during the 1974-76 period had a 74.1-percent 5-year relative survival rate. (The difference in rates between 1974-76 and 1981-83 is statistically significant, $p < .05$.)

In our March 1987 report entitled Cancer Patient Survival: What Progress Has Been Made? we examined published survival rates in terms of their accuracy, meaningfulness, and utility as measures of progress.[1] We identified a number of biases that can artificially inflate the actual improvement in patient survival and recommended that the Secretary of the Department of Health and Human Services include a description of the potential sources of bias likely to cloud the interpretation of survival rates in future annual cancer statistics reviews. Our reservations about survival rates as indicators of progress remain. It is important to note, however, that whatever the reason, a breast cancer patient today has a higher probability of 5-year survival than a patient 20 years ago.

[1]U.S. General Accounting Office, Cancer Patient Survival: What Progress Has Been Made? GAO/PEMD-87-13 (Washington, D.C.: March 1987).

Improved Interventions

Detection

The efficacy of screening mammography is well established for middle-aged and older women. There is no doubt that under ideal conditions, screening asymptomatic women by periodic mammography examinations reduces breast cancer mortality. Women who use it may experience a 30-percent reduction in mortality.[2] However, as we saw in appendix II, screening mammography continues to be underused. The low use may help explain why breast cancer mortality rates have not declined overall and leads to the view that screening mammography can be effective in reducing total mortality from breast cancer only if it is applied to a much greater portion of the population. Questions remain about how to implement mammography screening and to reduce the negative consequences. The latter include the cost of screening programs, false negatives and false positives, radiation exposure, and unnecessary diagnosis and treatment (both costly and potentially harmful). Nevertheless, mammographic screening offers the best prospects for detecting breast cancer, and its wider use should improve survival rates.

Diagnosis

As we pointed out in appendix II, although the purpose of diagnosis is to aid in the selection of appropriate treatment, in many instances there is no consensus on what constitutes the most appropriate treatment. The lack of consensus can be seen from the series of NIH consensus statements about appropriate treatment for local disease, which have become less specific and more uncertain over time. Although the medical profession knows more about a greater variety of treatments than formerly, with increased knowledge has come a greater degree of caution in how definitive to be in advising physicians on the choice of treatment.

Treatment

Survival rates for breast cancer patients might improve, some argue, if new treatments were disseminated and adopted widely in general practice. For example, survival is increasing for patients with less common cancers in part because a large fraction of patients with rare cancers are enrolled in clinical trials, with the consequence that the results of trials

[2]U.S. General Accounting Office, Screening Mammography: Low-Cost Services Do Not Compromise Quality, GAO/HRD-90-32 (Washington, D.C.: January 1990), p. 10.

are interpreted, put into practice, and reach most patients nearly simultaneously. Of course, such rapid and concurrent identification, diffusion, adoption, and implementation of trial results is more difficult for the much larger number of patients who have more common cancers like breast cancer. One of our previous studies showed that many patients with common cancers for whom new treatments are appropriate do not receive state-of-the-art treatments.[3] Dissemination and adoption of new cancer treatments face many barriers.[4] We have no evidence on how wider dissemination affects survival. However, our only study examining how the survival of breast cancer patients has changed since the introduction of adjuvant chemotherapy found no detectable increase in overall survival among patients who should have benefited from the therapy.[5]

In summary, when looking across detection, diagnosis, and treatment, the evidence is mixed on the ability to improve survival through available methods. Only with respect to mammography is it clear that more extensive use would likely lead to increased patient survival.

The uncertainty about how to "do better" once breast cancer is diagnosed leads naturally to questions about the ability to prevent the disease and underscores the importance of cancer prevention. The issue of prevention serves as the focus of the next appendix.

[3]U.S. General Accounting Office, Cancer Treatment 1975-85: The Use of Breakthrough Treatments for Seven Types of Cancer, GAO/PEMD-88-12BR (Washington, D.C.: January 1988).

[4]U.S. General Accounting Office, Cancer Treatment: National Cancer Institute's Role in Encouraging the Use of Breakthroughs, GAO/PEMD-89-4BR (Washington, D.C.: October 1988).

[5]U.S. General Accounting Office, Breast Cancer: Patients' Survival, GAO/PEMD-89-9 (Washington, D.C.: February 1989).

Prevention Research

Cancer prevention has been defined as

"actions taken to stop or reverse the initial development of malignant neoplasms that would at later stages threaten life or health. This definition includes the identification of high-risk persons and reduction of their exposures, the identification and control of external hazards, and the use of measures to block or reverse the development of lesions among persons already exposed but in whom no cancer is (yet) detectable."[1]

As this definition implies, successful prevention requires knowledge of the "exposures" that increase the risk of a disease. However, as we show below, little is known about the factors responsible for variations of breast cancer incidence in the general population.

Some factors that initiate or promote breast cancer are known, some are suspected, and still others remain unrecognized. There is a growing acceptance, however, that most breast cancers result from the combined effects of multiple exposures and individual susceptibility. This is consistent with multistage models in which different risk factors accelerate the development rates at various stages of carcinogenesis. Some affect early stages as initiators, others act at late stages as promoters, while still others influence both early and late stages. It is generally thought that cumulative exposures, long latency periods, and multistage processes account for the risk of breast cancer. The evidence is based primarily on genetic studies in laboratories and on epidemiologic studies in human populations.

To answer the question of what research is needed to help prevent breast cancer, we address three subsidiary questions in this appendix:

- What is the prevailing knowledge about risk factors for breast cancer?
- What critical hypotheses about risk factors for breast cancer prevention remain to be addressed?
- What kinds of research would be necessary to address these critical questions, and what are the significant obstacles to success in this research?

[1]John C. Bailar III, "The Case for Cancer Prevention," Journal of the National Cancer Institute, 62:4 (April 1979), 727.

Established Risk Factors

We begin answering these questions by reviewing the findings of studies of breast cancer risk factors. Breast cancer has been the object of epidemiologic investigations since before the 1930s, and studies have proliferated since the 1960s. By 1991, more than 800 articles had been published on the subject, including several comprehensive reviews. This massive amount of research has established a number of widely accepted risk factors for this disease that are documented with compelling consistency.

Table IV.1 lists the established risk factors for breast cancer and the approximate magnitude of the increase in risk associated with each of them. The table indicates that with the exception of age, country of birth, and a history of breast cancer in both the mother and a sister, the established risk factors for breast cancer are associated with only modest increases in risk. To provide a perspective on risk, epidemiologists who focused primarily on smoking and lung cancer found relative risks were in the 10- to 30-fold range. An American Cancer Society study estimated that the common established risk factors alone or in combination account for only between 20 and 30 percent of breast cancer cases.

Table IV.1: Established Risk Factors for Breast Cancer

Risk factor	High-risk group	Low-risk group	Magnitude of risk differential[a]
Age	Old	Young	>>>
Country of birth	North America, Northern Europe	Asia, Africa	>>>
Socioeconomic status	High	Low	>>
Marital status	Never married	Ever married	>
Place of residence	Urban	Rural	>
Region of residence	Northern U.S.	Southern U.S.	>
Race			
Age 45 or older	White	Black	>
Younger than 40	Black	White	>
Nulliparous[b]	Yes	No	>
Age at first full-term pregnancy	30 or older	Younger than 20	>>
Oophorectomy premenopausally[c]	No	Yes	>>
Age at menopause	Late	Early	>
Age at menarche	Early	Late	>
Weight postmenopausal	Heavy	Thin	>
History of cancer in one breast	Yes	No	>>
History of benign proliferative lesion	Yes	No	>>
Any first-degree relative with breast cancer	Yes	No	>>
Mother and sister with history of breast cancer	Yes	No	>>>
History of primary cancer in endometrium or ovary	Yes	No	>
Mammographic parenchymal patterns[d]	Dysplastic parenchyma	Normal parenchyma	>>
Radiation to chest	Large doses	Minimal exposure	>>

[a]>>> Indicates relative risk of greater than 4.0.

>> Indicates relative risk of 2.0-4.0.

> Indicates relative risk of 1.1-1.9.

[b]Nulliparous is not having borne offspring.

[c]Oophorectomy is removal of an ovary.

[d]Parenchyma is the essential and distinctive tissue of an organ as distinguished from its supportive framework.

Source: Jennifer L. Kelsey and Marillie D. Gammon, "The Epidemiology of Breast Cancer," CA-A Cancer Journal for Clinicians, 41:3 (May-June 1991), 157.

Methodology

We reviewed the literature to summarize recent gains in knowledge about risk factors. In the contemporary body of research, some investigators have considered potential risk factors that were not well studied in the past while some have sought more detailed knowledge about risk factors previously identified. Our literature review emphasized papers published since 1980 directly relevant to breast cancer risk factors, including reviews of research, reports of empirical studies, and commentaries on the methodologies applied in this area. To locate journal articles, we used standard medical literature search routines, employing computerized bibliographic data bases, literature review articles, journal citations, and consultation with experts.

We evaluated studies by considering various aspects of design quality. Epidemiologic research uses a wide range of designs applied to problems in laboratory, clinical, and population settings. Whatever the nature of a study, a few key design features—such as the admission rule, the method of allocating subjects to treatments, and the use of controls—largely determine the strength of the scientific evidence that results.

Particularly where studies reach divergent conclusions, we examined the research reports to understand differences in study designs, measurement methods, and statistical procedures. Identifying study design characteristics that might result in outcome variations can indicate areas for further investigation.

Areas of Current Research

In the remainder of this appendix, we summarize information extracted from our review of the current literature.

Genetics and Breast Cancer

Occasionally, breast cancer occurs in clusters in families. It was this observation that led to the long-held suspicion that cancer-predisposing genes might be inherited. The evidence for a genetic link is strong enough that researchers are now using genetic markers to identify exactly which gene or genes raise a woman's susceptibility to breast cancer.

A different genetic link can be seen from other cancers, where evidence is mounting that certain genes inside a cell must change before a tumor can grow. Such genetic changes can occur as a result of exposure to

some risk factors or simply by chance. Fifty to 60 genes have been implicated in various kinds of cancers, and scientists now suspect that a mutant form of a particular gene, the p53 gene, may be an almost indispensable element in the cancerous transformation of a healthy cell to a tumor cell. While the p53 gene can help block unruly cell growth as a tumor suppressor, irregularities of the p53 gene have properties of an oncogene (a gene that can play a normal role or can allow or can cause a cell to divide and multiply wildly), transforming normal cells into cancer cells. Recent studies have shown that the p53 gene is overactive in 15 to 20 percent of breast cancer tumors. The bearing of this discovery on breast cancer is not yet clear, but further studies are expected to increase the understanding of how a normal cell is transformed into a malignant cell.

Epidemiologic Research

Most of the established risk factors for breast cancer are associated with only modest increases in risk, factors that have relative risks of only twofold or less. Nevertheless, even though most risk factors have relatively weak effects, the effects can be greater in selected population subgroups. Additionally, it is estimated that the established risk factors alone or in combination account for only between 20 and 30 percent of breast cancer cases. Unfortunately, most of the established risk factors, especially those that substantially increase risk (age, country of birth, and a history of breast cancer in both the mother and a sister) do not lend themselves to preventive measures. Thus, several areas of recent and current research are directed toward identifying preventable causes or at least toward understanding better the risk factors for and etiology of breast cancer.

Caffeine

Caffeine consumption is unrelated to breast cancer risk. Approximately 90 percent of the population consumes coffee, tea, cola, cocoa, and chocolate daily, so even a small increased risk for breast cancer would imply a significant public health problem. Although a few studies have suggested a positive association between caffeine consumption and breast cancer risk, most evidence suggests no association, and caffeine consumption is not now regarded as a possible risk factor.

Cigarette Smoking

The weight of epidemiologic studies suggests that cigarette smoking is not materially related to the risk of breast cancer. Although some studies have suggested a positive association and a few have indicated a negative association (protective effect), the relations have been weak and inconsistent across studies. A meta-analysis of the literature on current smoking and breast cancer risk found a summary odds ratio for

case-control studies of 1.12 and a summary relative risk for cohort studies of 1.14. It is unlikely that cigarette smoking has either a uniform effect or a protective or deleterious effect for breast cancer. Cigarette smoking is not now regarded as a possible risk factor for breast cancer.

Alcohol

Rapidly accumulating evidence indicates a dose-response relation between alcohol consumption and a higher risk of breast cancer. A recent meta-analysis combined the epidemiologic data from 16 studies, analyzed them as two data sets, and for two drinks daily calculated relative risks of 1.4 for case-control data and 1.7 for follow-up data. At levels of approximately two or more drinks daily, the data are strongly supportive of an association. At lower levels of consumption, the association is weaker and more modest. Some studies published after the meta-analysis, both a case-control and a follow-up study, found no association. Authors of one were "skeptical" about combining results from different studies while authors of the other reported that the overall conclusion of the meta-analysis held even after including the findings from their study.

Given the prevalence of alcoholic beverages, even a small elevation in risk has important public health implications. In a public health context, the increased risk that is apparent from these data cannot, however, be considered independently from a protective effect suggested by other studies of modest alcohol consumption against cardiovascular disease, a far more prevalent condition.

Knowledge of the biological mechanism by which alcohol has its effect could elucidate the relationship by clarifying the role of alcohol in breast cancer etiology. The timing and duration of drinking and the type of alcoholic beverage consumed also need further evaluation. For example, a few studies have found that drinking early in life, before age 30, heightens the risk.

Oral Contraceptives

The influence of oral contraceptives on the risk of breast cancer has been studied extensively during the past 25 years. Most studies have found that oral contraceptives neither increase nor decrease the risk for breast cancer in the vast majority of women. Nevertheless, some individual studies suggest that oral contraceptives may increase the risk in certain subgroups of women, such as women who begin using contraceptives at a young age or before their first pregnancy, while other studies do not. No convincing interpretation of the disagreement and inconsistency among studies has been found, so drawing conclusions is difficult. For example, even studies that show subgroup effects are inconsistent

about whether duration of use or timing of use (and whether in relation to age or pregnancy) are decisive factors.

Taken together, these subgroups include a large number of women, but many studies have not found that women in these subgroups are at high risk. Four out of every five American women in their midthirties are using oral contraception or have used it at some time. For many women, the prevention of unintended pregnancy confers a benefit that outweighs risks. It also appears that oral contraceptive use confers benefits in the prevention of ovarian and endometrial cancers and the regulation of menstrual problems but increases risk of diseases of the circulatory system. Thus, should it be demonstrated that the use of oral contraceptives increases the risk of breast cancer, significant public health and psychological ramifications could be expected.

Because oral contraceptives affect hormonal functioning, a profound effect on breast cancer risk might have been anticipated and the failure to demonstrate this seems puzzling. Continued research is needed to resolve apparently contradictory findings about subgroups of users. Of particular interest will be studies that examine women who began using oral contraceptives at a young age and follow them into older age ranges.

Estrogen Replacement Therapy

Since the 1960s, physicians have prescribed estrogen for many women to treat symptoms of menopause and to adjust the estrogen levels of women who have had bilateral oophorectomy, or surgical removal of the ovaries. Studies on the effects of postmenopausal estrogen replacement therapy on the risk of breast cancer are inconsistent, most reporting that estrogen replacement therapy does not increase the risk but many reporting increased risk for certain subgroups. Two studies of large groups of women who used estrogen replacement therapy found that use for 15 to 20 years has a small to moderate effect, with relative risks of around 1.5 to 2.0.

Postmenopausal hormone use has been estimated to involve between 15 and 50 percent of all recently postmenopausal American women, depending on location. In a recent year, enough noncontraceptive estrogens were purchased to treat an estimated 2.3 million postmenopausal women. Thus, even the most conservative estimates show that a sizable number of women would by affected if long-term or high-dose use is found to lead to even a small increase in risk for breast cancer. Any effect of estrogen replacement therapy on breast cancer risk would need

to be weighed against its established protective effect against osteoporosis, the established increased risk for endometrial cancer, and probable decreased risk of coronary heart disease. Additional studies that include large numbers of women who have used estrogen for 15 or more years are needed.

Diet

In 1981, Doll and Peto made the widely cited statement that it may be possible to reduce U.S. breast cancer death rates by as much as 50 percent by dietary means.[2] However, such estimates do not connote established knowledge because studies to test the effectiveness of dietary interventions are not available. Recommendations to reduce the proportion of fat in the diet in order to reduce the risk of breast cancer are based on informed judgment and suggestive evidence from animal experiments and from correlations between national incidence rates and national food production or disappearance rates. In fact, more recently Doll wrote of diet "That it is so important and responsible, perhaps in synergism with other agents, for something between 20 and 70 percent of all cancers is still more a matter of faith than of scientific knowledge."[3]

Vitamin A, beta-carotene, retinol, and other dietary factors have also been considered as either protective or causative for breast cancer in some studies, again with inconsistent or inconclusive results. Data are at present too limited either to refute or to confirm any of these hypotheses with confidence.

For many reasons, epidemiologic confirmation of the low-fat diet hypothesis has been difficult to obtain. Thus the health effects of low-fat diets are not well demonstrated. Taken as a whole, study conclusions are incompatible. Animal studies and correlational studies are contradicted by case-control and cohort studies that have found only weak associations, either positive or negative, or no associations. Case-control and cohort studies have consistently failed to provide evidence of a positive association between dietary fat and the risk of breast cancer.

If the strong positive associations suggested by the international data on dietary fat were true, the weak inverse associations actually seen in the prospective studies would be statistically extremely unlikely. The possibility remains that reducing fat intake to 20 percent of total calories, as

[2]Richard Doll and Richard Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," Journal of the National Cancer Institute, 66:6 (June 1981), 1207.

[3]Richard Doll, "Lifestyle: An Overview," Cancer Detection and Prevention, 14:6 (1990), 591-92.

some advocate, might influence breast cancer rates. It is also possible that dietary fat may be linked to breast cancer through overall caloric intake, body weight, or height or that the timing of the adoption of a low-fat diet may be decisive.

The understanding of the role of diet in breast cancer etiology is now limited. Not only are the roles of specific dietary constituents unclear, but also the age at which they might have an effect is unknown. As dietary hypotheses become better defined and supported, the development of objective markers of diet such as biochemical measures would strengthen studies. It remains unclear whether randomized clinical trials of sufficient size, duration, and degree of compliance can be conducted to evaluate hypotheses that involve major changes in eating patterns, such as a reduction in fat intake. Clinical trials involving nutritional supplements or dietary modification for individuals at high risk may be more feasible.

Radiation

Exposure to radiation increases risk for breast cancer. The health effects of radiation are well demonstrated in studies of atomic bomb survivors and persons with significant medical exposure. Following exposure, radiation-induced breast cancer risk decreases slowly with time for at least 35 years and may remain throughout life. Exposure after age 35 to 40 has only a small effect. The risk from lower exposure levels has not been definitively quantified because a very large exposed population would be needed to estimate risks at very low exposure levels.

The unequivocal recommendation of the National Academy of Sciences 1990 study Health Effects of Exposure to Low Levels of Ionizing Radiation is that women avoid all but necessary screening exposure to radiation. The risk of radiation-induced breast cancer from modern mammography is generally estimated to be small in relation to its benefits. A single mammography examination of each of 250,000 asymptomatic women between ages 40 and 50 might be expected to cause one new breast cancer over their lifetimes. The radiation contribution to breast cancer risk from mammography screening of asymptomatic women is not much at issue. Because very few women receive a significant exposure from other sources, radiation cannot account for a large proportion of breast cancer.

Conclusions

In our review, we found that during the past decade some new potential risk factors have been studied. While some have been dismissed and evidence of an etiologic role has accumulated for others, none are yet considered as established risk factors. For example, caffeine and cigarette consumption are no longer regarded as materially related to breast cancer. Parity, or childbearing, and lactation in certain age groups have emerged as possible protective factors, while delayed childbearing may have greater significance than previously thought. Evidence has accumulated that alcohol consumption and exposure to diethylstilbestrol (DES) during pregnancy are associated with increased risks. Studies are contradictory about the long-term use of oral contraceptives, but some suggest that use for several years at an early age modestly increases the risk of incurring breast cancer before age 35 and perhaps before age 45. A few studies suggest that estrogen replacement therapy for 20 years increases the risk for postmenopausal breast cancer.

Priority areas for further research thus include clarifying the effects of long-term use of oral contraceptives and estrogen replacement therapy. Studies to determine the role of alcohol in breast cancer etiology are needed. Epidemiologic studies will continue to be concerned with diet, although its causal role remains in doubt because many studies have failed to provide evidence of a meaningful association between dietary fat and breast cancer. As dietary hypotheses become better defined and supported, large-scale clinical trials may become more feasible.

It is also likely that risk factors not yet identified are involved in breast cancer etiology. The effects of exposure to some known risk factors may be limited to specific time periods, such as periods of rapid breast development. Also, the effects of exposure to some risk factors, such as radiation, may follow long periods of latency. Progress in understanding the etiology of breast cancer continues to rely substantially on epidemiologic studies, while laboratory genetic studies can be expected to be increasingly important.

Some emerging risk factors may prove more amenable to modification and to preventive measures than the well-established risk factors. In the meantime, known secondary preventive measures such as mammography and breast self-examination should be vigorously pursued.

Research Support

In this appendix, we provide information about how financial support for breast cancer research compares with support for research on other clinical conditions.

Methodology

We compared NIH research funding for several clinical conditions by constructing a measure of research investment. We computed NCI breast cancer research funding in fiscal year 1990 per U.S. breast cancer death during that year. Then we compared this measure with the same measure for lung and prostate cancer and for AIDS and stroke.

Of course, a comparative assessment of one measure of research investment is not a comprehensive assessment of relative research funding levels, which would have to consider additional factors such as potential years of life lost, morbidity, and quality of life. Also, this measure of research investment does not take account of such considerations as the opportunities for scientific advances, the mixture of specific biomedical disciplinary knowledge required, and the availability and interest of individual researchers.

We selected lung cancer because it is the leading cause of cancer mortality for both men and women and because the leading risk factor, smoking, is controllable. We selected prostate cancer because its incidence is similar to that of breast cancer and because it is the most common cancer in males. We selected AIDS because of its growing incidence, its epidemic status, and its priority in federal health policy. We selected stroke because it is prevalent but not communicable and because two of its leading causes, hypertension and diabetes, are treatable.

Data and Findings

NIH indexes each funded grant by its primary, secondary, and sometimes tertiary research emphasis. Thus, retrieval of all project awards primarily concerned with a particular clinical condition would not include all research expenditures directed at that condition. Similarly, retrieval of all project awards concerned at any emphasis level with a particular clinical condition would also include expenditures for research on other conditions. Therefore, we report here NIH research award expenditure

data for all three emphasis levels and expenditure per death ratios calculated for both the narrow and broad expenditure level data. Table V.1 presents the data, sources, and our findings.[1]

Table V.1: NIH Research Expenditures and Mortality for Both Sexes for Selected Conditions, Fiscal Year 1990[a]

Condition	Deaths[b]	Primary expenditure	Primary: death	Expenditure			Total: death
				Secondary	Tertiary	Total	
AIDS	23,630	$360,793,000	$15,268	[c]	[c]	$360,793,000	$15,268
Neoplasms							
Prostate	32,390	11,848,517	366	$19,044,899	$246,329	31,139,745	961
Breast	44,490	67,846,556	1,525	54,655,572	1,538,752	124,040,880	2,788
Lung	137,630	34,679,807	252	42,399,703	1,203,360	78,282,870	569
Stroke	145,640	51,176,146	351	20,200,979	114,621	71,491,746	491

[a]Fiscal year 1990 extramural awards; excludes intramural research.

[b]Twelve months ending with September 1990.

[c]AIDS expenditure figures include all AIDS research, whether primary, secondary, or tertiary.

Source: National Center for Health Statistics, Monthly Vital Statistics Report, 39:10 (February 19, 1991), tables 6 and 7; NIH Division of Financial Management, "Justification of the Budget Estimates, FY 1992," p. 34; and NIH Division of Research Grants, CRISP table 1A, fiscal year 1990, April 5, 1991.

These data show that research expenditures per death are higher for breast cancer than for all the selected clinical conditions except AIDS. NIH research expenditures per breast cancer death in fiscal year 1990 were at least three times larger than expenditures per lung cancer, stroke, or prostate cancer death. The higher expenditures for AIDS research may reflect its newness and, hence, the lack of knowledge about it and correspondingly greater scientific opportunity; in addition, AIDS is a contagious disease, whereas the other conditions are not.

As research expenditures, the figures presented exclude the cost of treatment for the different conditions. In terms of research expenditures, the measures show that breast cancer compares favorably with the other selected conditions. However, this comparison should not be construed as an appraisal of the adequacy of funding.

[1]We also tested whether there was any statistical association between deaths and research expenditures. We used a nonparametric rank order test. Spearman's rank correlation coefficients (rho = −0.3 with primary expenditures only; rho = −0.4 for all expenditures) are not significantly different from 0. A correlation coefficient of 0 would indicate that there is no systematic relationship between rankings and that the number of deaths and the research expenditures are mutually independent.

Data Source: The SEER Program

To determine whether the incidence of breast cancer in American women has changed and to answer other questions posed in this report, we needed data that contained extensive information on characteristics of the disease, patients, and their treatments. The SEER program, initiated by NCI in 1973 and currently the primary source for data on cancer in Americans, provided pertinent data. In this appendix, we describe SEER.

Cancer Registries

SEER collects data from nine population-based cancer registries that cover 9.6 percent of the total U.S. population: five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound). In addition, SEER includes Native American populations in Arizona and 10 rural counties in Georgia. By the end of 1988, the data base contained information on 1.5 million cancer cases diagnosed since 1973. Approximately 120,000 new cases are added annually.

The nine geographic areas included in the SEER data base are not a probability sample of the population and were not selected by some other method that permits valid generalization to the entire United States. Areas were selected primarily for the ability to operate and maintain a population-based cancer reporting system and for their epidemiologically significant population subgroups.

Nevertheless, SEER data are believed representative of overall patterns because the cancer mortality rates for specific sites of cancer and for SEER specific populations are very close to those for the United States as a whole. For example, for all whites, the U.S. mortality from all cancers in 1985 was 167.8 per 100,000 whereas in SEER areas it was 167.5. Additionally, for breast cancer, when all death certificates in the SEER areas for 1985 and 1986 listing breast cancer as the underlying cause (mortality measure) were compared to original diagnoses (incidence measure), 98.7 percent were in agreement. Conversely, when all SEER breast cancer cases diagnosed in 1974 and 1975 (incidence measure) were followed to death through 1986 (mortality measure), 95.7 percent of the death certificates agreed on the underlying cause of death. According to NCI, "with respect to selected demographic and epidemiologic factors, they are reasonably representative subsets of the United States population."[1]

[1]National Cancer Institute, Cancer Statistics Review 1973-1988 (Bethesda, Md.: July 1991), p. I.5.

Patient Records

SEER data rest upon information abstracted from individual patient's hospital charts. Each hospital chart itself is a collection of information on the patient, the physician's notes, descriptions of diagnostic and treatment procedures and findings, and other information. Some diagnostic procedures formerly done in the hospital are now often done in physicians' offices, and nonsurgical treatments (radiation therapy, chemotherapy, and hormonal therapy) are commonly done on an ambulatory basis. The result is that increasingly hospital charts no longer reflect the full course of care, and some of the time some information can be incomplete, contradictory, and ambiguous.

A trained medical record abstractor condenses the information in cancer patient charts and codes it by a set of rules intended to achieve reproducibility and uniformity in the data reduction process over both time and place. Then the codes are entered into a computer system and checked for unlikely and inconsistent data. Finally, the regional registry submits a computer tape to SEER twice each year. Also, the nine registries abstract death certificates for which cancer is listed as the cause of death. When this report was published, the last full annual cohort of patients in SEER were those who were diagnosed in 1988.

Strengths and Weaknesses

A limitation of SEER is that its data do not include information on exposure—occupational history, smoking history, diet, radiation exposure, or residence history. In addition, SEER contains no information on individuals who do not have cancer. The combination of these two omissions means that SEER cannot be used for epidemiological studies of the causes of breast cancer.

Notwithstanding potential weaknesses in data collection and reduction and potential limitations on the ability to generalize from them, statistics derived from SEER data may also be affected and biased by short-term or long-term changes in the populations under study, such as changes in diet or exposure to other risk factors, by technological changes in detection procedures, such as mammography, and by earlier recognition of symptoms, such as through breast self-examination. A major benefit of the SEER population-based registry is that it includes data from the complete range of hospitals serving communities rather than only particular hospitals, some of which may be highly specialized.

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