GAO

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

March 1987

CANCER PATIENT SURVIVAL

What Progress Has Been Made?

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GAO

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Program Evaluation and
Methodology Division

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

Dear Mr. Chairman:

In response to your April 9, 1985, letter, this report focuses on cancer patient survival rates. As you know, considerable controversy exists as to whether the reported improvements in these rates reflect true progress against cancer or whether the improvements are simply the result of "a statistical mirage."

This study specifically examines the survival rates published by the National Cancer Institute in terms of their accuracy, meaningfulness, and utility as measures of progress. The study also determines, for 12 of the most prevalent forms of cancer, whether patient survival has actually improved and, if so, the factors contributing to that improvement.

As we arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of the report. At that time, copies will be sent to the Department of Health and Human Services. We will also make copies available to interested organizations, as appropriate, and to others upon request.

Sincerely yours,

Eleanor Chelimsky
Director

Executive Summary

Purpose

Cancer, as the second leading cause of death in the United States, has been an issue of public concern throughout this century. This report responds to a request by the Subcommittee on Intergovernmental Relations and Human Resources of the House Committee on Government Operations that GAO determine whether progress was made in extending cancer patient survival from 1950 to 1982 In order to answer this general question, the report addresses 5 specific questions·

1. How accurate are the survival rates published by the National Cancer Institute (NCI)?

2. What do survival rates actually measure? (That is, How meaningful are survival rates?)

3. What measurement problems limit our ability to interpret changes in survival rates over time?

4. Did survival rates improve from 1950 to 1982 for specific types of cancer?

5. Where improvements in survival rates occurred, what factors can best account for them?

Background

In order to get some sense of progress made against cancer, different statistics are employed. The three major types are those that tell us how many people get cancer (incidence rates), how many people die from cancer (mortality rates), and how many cancer patients live for a specified period of time (survival rates).

In recent decades, cancer incidence and mortality rates both increased. One hopeful sign of progress against cancer has been a steady increase in reported survival rates. Recently, however, questions have been raised as to whether this improvement in cancer patient survival is the result of advances in the detection and treatment of cancer or simply an artifact of the way survival rates are measured. The resolution of this issue is the focus of this review.

Results in Brief

Advances in the detection and treatment of cancer from 1950 to 1982 have extended patient survival in all but one of 12 cancers GAO examined. GAO concludes, therefore, that progress has been made. However, the extent of improvement in survival for specific cancers is often

not as great as that reported. One reason is that biases artificially inflate the amount of "true" progress.

GAO has also determined that the improvements in patient survival have been most dramatic for the rarer forms of cancer and least dramatic for the more prevalent cancers. As a result, even though the absolute number of lives extended is considerable, this number remains small relative to all cancer patients.

Despite the limited nature of progress in extending the lives of cancer patients, strong evidence exists that the quality of survival for these patients has improved considerably since 1950.

Principal Findings

The accuracy of survival rates seems to have improved with NCI's introduction of the surveillance, epidemiology, and end results (SEER) program in 1972. However, the survival rate provides information on only one aspect of survival, and the interpretation of survival trends is difficult, primarily because of changes in detection practices and what is, or is not, called cancer. These changes introduce a number of biases that can artificially inflate the actual improvement in patient survival. Thus, the published survival rates may not be especially useful by themselves in understanding survival trends.

To learn whether survival has actually improved and, if so, what the major factors are that account for the improvement, GAO focused its attention on 12 types of cancer. For each of these cancers, GAO conducted group interviews at two comprehensive cancer centers identified as possessing expertise in that type of cancer.

These sessions and other evidence assembled indicate that survival has indeed improved for most cancers and that the factors that account for the improvements are earlier detection, improved surgical and radiation procedures, and the advent of chemotherapy. However, major breakthroughs have been infrequent and have come primarily in the treatment of leukemias and lymphomas. Improvements in patient survival for the carcinomas, which constitute approximately 85 percent of all cancer cases, have been slower. A number of recently developed treatments for various carcinomas are too new to have significantly affected the latest published survival rates. One additional finding is that improvements in survival could be achieved through better and more extensive application of existing diagnostic and treatment procedures.

Finally, GAO shows that the extent of progress perceived can differ depending upon the perspective from which it is viewed; the extent of progress is seen as considerably greater from an "absolute" perspective, which focuses upon the number of lives extended, than it is from a "relative" perspective, which focuses upon the proportion of lives extended.

Recommendation

GAO recommends that the secretary of the Department of Health and Human Services (HHS) include a description of the potential sources of bias likely to cloud the interpretation of survival rates in future annual cancer statistics reviews.

Agency Comments

HHS concurred with GAO's recommendation and will implement it in calendar year 1987. HHS also agreed with many of GAO's conclusions, including that survival could be improved through better application of existing treatments and that the quality of life for cancer patients improved from 1950 to 1982. However, HHS did express a number of general concerns with the report. Many of the comments HHS provided are critical of the scope of the study and imply that the focus on survival is overly narrow. HHS believes that the tone of the report is unduly negative, that the methodology contains some weaknesses, and that the absence of quantitative estimates could result in a biased reading of the report. After careful review of the issues HHS raised, GAO does not consider these criticisms valid, for reasons that are explained in chapter 4 and appendix V. GAO's position is reinforced by the majority of independent experts who reviewed a draft of the report and did not share HHS's concerns.

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Abbreviations

ADC	Adenocarcinoma
ALL	Acute lymphocytic leukemia
AML	Acute monocytic leukemia
CAT	Computerized axial tomography
CIS	Carcinoma in situ
CML	Chronic myelocytic or granulocytic leukemia
ERP	End results program
GAO	General Accounting Office
HHS	Department of Health and Human Services
LCC	Large-cell carcinoma
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
SCC	Small-cell carcinoma
SEER	Surveillance, epidemiology, and end results program
SQC	Squamous-cell carcinoma

Introduction

The term "cancer" describes a set of diseases characterized by the unrestricted proliferation of abnormal cells. In 1985, approximately 462,000 Americans died from cancer and 910,000 new cases were diagnosed. Currently, more than $2 billion is spent annually on efforts to combat cancer; more than half of this amount comes from federal funds.

Recently, conflicting opinions have been expressed on how much progress has been made in combating cancer Some believe that many lives are being saved and that, with some cancers, progress has been remarkable; others believe that the reported improvements result primarily from statistical artifacts and that there has been little real progress At the request of the Subcommittee on Intergovernmental Relations and Human Resources of the House Committee on Government Operations, we have attempted to explain and resolve these differences.

In this chapter, we offer a description of cancer that should clarify the terms and concepts used throughout the report. This is followed by a brief overview of federal efforts to combat the disease. We then describe our study's objectives, scope, and methodology. The chapter concludes with an overview of the remainder of the report.

Cancer: Not a Single Disease

The human body's trillions of cells are subdivided into groups and classes to form various tissues and organs and are programmed to carry out appropriate functions As part of the normal bodily processes, most of these cells multiply and divide in a routine manner to replace cells that are lost or destroyed. Cancer originates as a defect that allows cells to start multiplying in an unrestrained fashion These cells, in turn, give rise to an ever-increasing population of similarly unrestrained cells, which typically form a mass of tissue referred to as a "tumor." Not all tumors, however, are considered cancerous or "malignant"; some do not invade normal, neighboring tissue and are called "benign."

During the development of a malignant tumor, cancerous cells break off and travel through the blood stream or the body's lymphatic system. This process, called "metastasis," lodges cancer cells in a wide variety of organs where they can grow into new, malignant tumors.

One important way of categorizing cancers is based on the types of cells from which they originate. Listed below are the 5 major types of cancer as defined by this criterion.

1. Carcinomas (85-90 percent of all cancers). Carcinomas originate from epithelial cells—that is, the cells that make up the tissue that covers and lines all the organs in the body. This type of cancer can occur in almost any organ, including the lungs, stomach, breasts, colon, uterus, and kidneys.

2. Sarcomas (2 percent of all cancers). The body contains cells organized into connective tissue that are found in muscles, bones, fat, lymphatic vessels, and nerves. Sarcomas are tumors that originate from these cells.

3. Leukemias (4 percent of all cancers). White blood cells that combat foreign agents entering the body are a basic component of the body's immune system. Leukemias result from an abnormally high proliferation of white blood cells produced by bone marrow.

4. Lymphomas (5 percent of all cancers). Similar to leukemias, lymphomas are also characterized by an overabundance of white blood cells. The difference between the two disease types is that for lymphomas, the abnormal levels of white blood cells result from overproduction by the spleen and lymph nodes rather than by problems in the bone marrow.

5. Myelomas (rare). In addition to producing white blood cells, bone marrow produces plasma cells. The unrestrained growth of plasma cells is the defining characteristic of myelomas.

Although this classification is not comprehensive (it does not include germ-cell tumors and certain other forms of cancer), it covers the overwhelming majority of cancers and includes all the specific cancers examined in our study.

Cancers are also categorized by the organ in which the abnormal growth originates, referred to as the "primary site." The resulting categories, such as cancer of the lung, breast, or skin, are the most frequently used in presenting statistics on disease patterns or trends. This categorization mixes tumors that have different cell origins; for example, both carcinomas and sarcomas are included in the term "uterine cancer."

The picture becomes even more complex when one considers the considerable variation within cancers of the same primary site, even when they are all carcinomas. A good example is lung cancer. Although the overwhelming majority (90 percent) of lung cancers are carcinomas, there are four major types (small cell, squamous cell, adeno, and large

cell) that differ with respect to such critical factors as etiology, natural history, responsiveness to treatment, and prognosis.

The complexity does not end here, in that cancers obviously differ in how far advanced they are (stage of the disease) and, perhaps less obviously, in the degree of normality (differentiation) exhibited by the cells that constitute the tumors (grade).

Our purpose in listing the criteria used to classify cancers is not only to provide an overview but also to emphasize the fact that cancer is not a single disease but, rather, a term that refers to many, perhaps hundreds, of different diseases. The distinction between diseases is relevant to this report in that, as we show in chapter 3, the extent of progress differs among the various cancers.

The Federal Role

The federal government's role in cancer research began in 1910 when the U.S. Public Health Service conducted a study on cancer through the U.S. Hygienic Laboratory and the Federal Plague Laboratory It was not until 1937, however, that a federal agency was created whose primary responsibility was to focus on cancer. That agency, the National Cancer Institute (NCI), had a total appropriation of $400,000 during its first 2 years. NCI was one of the institutes within the National Institutes of Health, where, despite initiatives to move it, it has remained to this day. The budgetary allotment for the organization has increased to approximately $1 billion per year.

The major federal initiative in the cancer field since the establishment of NCI came with the passage of the National Cancer Act of 1971 (public law 92-218). The legislation authorized an appropriation of $1 59 billion for cancer programs and research over a 3-year period and increased the authorities and responsibilities of the director of NCI. Furthermore, it initiated the national cancer program, established the 23-member national cancer advisory board to replace the national advisory cancer council, and authorized the establishment of 15 new research, training, and demonstration cancer centers. It also provided for cancer control programs, integrated with state and other health agencies for the diagnosis, prevention, and treatment of cancer. In addition, the legislation provided for the collection, analysis, and dissemination of all data useful for the diagnosis, prevention, and treatment of cancer. This included the establishment of an international cancer research data bank, which disseminates the latest research findings.

Upon signing the law in December 1971, President Richard M. Nixon commented

"We would not want to raise false hopes by simply the signing of [this] act, but we can say this· That for those who have cancer, and who are looking for success in this field, they at least can have the assurance that everything that can be done by government, everything that can be done by voluntary agencies in this great, powerful, rich country, now will be done and that will give hope and we hope those hopes will not be disappointed "

Background

"We're not curing much more than we were a generation ago "

"We're saving thousands of lives today that weren't saved 20 years ago "

"There has been disappointingly little progress in curative treatment since the middle of this century."

"Progress has been remarkable in some cancers "

These seemingly contradictory statements, made in recent years by leaders in the cancer field, frame a controversy whose resolution is the primary objective of this investigation.

Progress in controlling cancer can occur along many dimensions (for example, reducing the number of new cases, the number of deaths, or the side effects of treatment). Each of these dimensions has problems in terms of the availability and credibility of information for reaching conclusions. As a result, determining the extent of overall progress in controlling and combating cancer is an undertaking beyond the scope of any single study. Our investigation is restricted, therefore, to only one dimension of progress: the attempt to extend the survival time of cancer patients. This dimension was selected as the focus of our study because of the considerable controversy over whether survival rates have actually improved.

Objectives, Scope, and Methodology

In order to illuminate the issues in the controversy outlined above, we addressed the following questions:

1. How accurate are the survival rates published by NCI?

2. What do survival rates actually measure? (That is, How meaningful are survival rates?)

3. What measurement problems limit the ability to interpret changes in survival rates over time?

4 Did survival rates improve from 1950 to 1982 for specific forms of cancer?

5 Where improvements in survival rates occurred, what factors (for example, treatments, diagnostics, and disease definitions) can best account for them?

The logic underlying the ordering of these questions is straightforward. The first 3 questions concern the statistic used frequently as an indicator of progress, the survival rate, and the answers to these questions provided us with a sense of how usefully it indicates improvement Then we determined whether survival has actually improved over time for specific types of cancer We accomplished this by using both published survival rates and other relevant data.

Changes in cancer patient survival rates, the focus of question 4, can come about for many reasons, including the development of new therapies, changing diagnostic procedures, and shifts in the population falling victim to the disease. Our fifth study question, therefore, is directed at determining what has produced the apparent changes in survival rates. Finally, from our findings for questions 1-5, we looked at whether real progress has been made with respect to cancer patient survival overall

The Scope of the Work We Performed

We discovered in our preliminary investigation that the survival rates discussed in debates on the extent of progress were the survival rates published by NCI.[1] Therefore, we concentrated on NCI's rates to determine their accuracy and meaningfulness (study questions 1-3). The time selected, 1950 to 1982, is based on the earliest and latest dates for which survival data were available when we initiated our review (The majority of the data collection for the project took place during the first 3 months of 1986.)

The determination of whether cancer patient survival has actually improved, and the factors contributing to that improvement (study questions 4 and 5), is best accomplished for each disease The selection

[1]The two primary sources of these rates were the following publications U S Department of Health and Human Services, National Institutes of Health, Cancer Patient Survival Report Number 5 (Washington, D C 1976), NIH publication no 81-992, and U S. Department of Health and Human Services, National Cancer Institute, 1985 Annual Cancer Statistics Review (Washington, D C December 1985)

of the cancers to be included in the study was driven by our interest in focusing on the diseases that affected the largest number of patients. Accordingly, we selected for examination any cancer that was among the top 10 in terms of reported incidence rates in either 1950 or 1982. This criterion yielded 12 cancers: bladder, breast, cervix, colon, lung, endometrial, head and neck, prostate, rectum, and stomach, as well as leukemia and non-Hodgkin's lymphoma.[2] Excluded from this list were a number of cancers, such as Hodgkin's disease and testicular cancer, in which progress has been considerable, according to the National Cancer Institute. At the same time, our focus on the most prevalent diseases excluded some cancers, such as cancers of the esophagus and pancreas, for which little or no progress has been reported.

With respect to whether progress has been made for cancer in general, the scope of this review is restricted primarily to progress in extending cancer patient survival. This does not mean that this is the only, or even the most important, dimension for evaluating progress. Rather, it is the only aspect of progress that we can address in light of our focus in study questions 1-5.

Our Evaluation Methodology

We used a dual approach for addressing the study questions. We determined the utility of cancer survival rates as measures of progress (study questions 1-3) by a methodological review of the specific procedures and data used to compute those rates. We used an information synthesis to answer the other questions. A more detailed description of each approach follows.

Our methodological review assessed the accuracy and meaningfulness of cancer survival rates. This involved our review and evaluation of the data and methods used to estimate cancer survival rates in the following steps:

- documentation of procedures for data collection and computation of survival rates,
- identification of the actual and potential problems with those procedures, and
- evaluation of survival rate accuracy and meaningfulness in light of the problems identified.

[2]The terminology used to refer to the cancers included in the category "head and neck" has changed since 1950, when the category was called "buccal cavity." As will be explained in chapter 3, in this report, cancers of the colon and rectum have been categorized as "colorectal cancer", cancer of the uterus has been categorized as "endometrial cancer."

The first step was accomplished through a review of the "methods" sections of published NCI reports on patient survival, as well as through interviews with NCI officials. We concentrated on data collection procedures and the equation employed by NCI in the computation of its survival rates. (Appendix I shows how survival rates are computed and appendix II describes the current data collection program supported by NCI).

We identified the problems with published survival rates through an extensive review of the literature. We held discussions with critics identified through our readings to ensure that their views were well understood and appropriately represented.

Our final step was a comparison of the information from the first two steps to reach conclusions about the overall accuracy and meaningfulness of the published rates.

An information synthesis was used to address the fourth and fifth study questions, as well as to determine overall progress in cancer patient survival. As with any information synthesis, the key elements involve a determination of what information is to be collected, how the information is to be collected, and how the information is synthesized. Each of these areas is discussed below.

1 Information needs. We considered as relevant any information that could help in reaching conclusions on whether reported survival improvements were real and, if so, the factors contributing to the improvements. Included in this broad category was the following information:

- data on disease trends (that is, incidence, survival, and mortality rates) from 1950 to 1982 for each of the 12 cancers,
- documentary evidence and expert testimony concerning the aspects of disease symptomatology and progression with implications for detection;
- documentary evidence and expert testimony of changes in any aspect of disease management (that is, detection, pretreatment evaluation, and treatment) that could possibly influence survival rates; and
- experts' opinions on whether the reported survival improvements were real or artifactual and the specific factors contributing to the reported improvements.

While some of this information was quantitative (such as data on disease trends), the majority was qualitative (for example, whether screening procedures had changed).

2. Data collection methods. We collected the data on disease trends from NCI documents and gathered the documentary evidence on disease characteristics and on changes in the management of the 12 cancers through an extensive review of the literature, identified through a computer-assisted search of on-line bibliographic files. We completed this work prior to soliciting expert testimony and opinion.

To obtain expert testimony and opinion, we conducted a series of group interviews at national comprehensive cancer centers. Two sessions were held for each cancer type; the individual sessions were held at different cancer centers. The centers we selected for each disease were those we identified as having resident expertise in the specific cancers. Experts in epidemiology, medical oncology, pathology, radiation therapy, and surgery, selected by the cancer center administrations, participated in these sessions.[3]

All the sessions followed a similar format. In each session, we asked panelists whether reported improvements in survival rates were real, and then we asked the experts to discuss the specific changes in the understanding and management of the disease that had taken place since 1950. For each change noted, we asked panelists to indicate what implications it has for patient survival, as well as other implications of the change that they considered important.

3. Synthesis strategy. Much of the information collected was not synthesized but, rather, tabulated. We tabulated the data for the responses to question 5, concerning the factors that contribute to changes in survival for each cancer type. Since we made no attempt to determine the exact magnitude of survival improvement caused by specific factors, we simply indicate the changes in disease management that our expert panels considered relevant.

[3]One exception to this general format was that the sessions on colon and rectum cancer were held jointly, as were those on leukemia and non-Hodgkin's lymphoma (NHL) This was because of the considerable overlap in the recommended participants for the gastrointestinal (colon and rectum) and hematological (leukemia and NHL) cancers Another exception was that three sessions were held for breast cancer and, because of scheduling problems, only one session was conducted for stomach cancer A complete list of the centers visited, the cancer types discussed at each center, and the individuals who participated is contained in appendix III

To determine whether patient survival has actually improved, we needed a synthesis of the facts available and opinions presented. As a starting point for this synthesis, we examined the published survival rates for the 12 cancers of interest, in each case, improvements were reported for the period 1950 to 1982. Our next step was to determine whether there was any evidence to support or question the reported improvements. Toward this end, we addressed three issues.

The first issue was whether the improvements in survival rates were consistent with incidence and mortality trends. As we explain in chapter 2, the survival rate can be thought of as the ratio of survivors to total cases Given this definition, the survival rate should be inversely related to the ratio of deaths to total cases, which can be approximated by the ratio of mortality to incidence This inverse relationship means that as we observe more deaths per case volume—that is, as the ratio increases—the survival rate must decrease in order for the data to be consistent. Similarly, as the ratio of mortality to incidence declines, survival rates should improve. Finally, we would have consistency if survival rates remained stable in the instances in which the mortality-to-incidence ratio did not change over time [4]

The second issue was whether there was any medical reason to assume that an improvement in survival rates should have occurred. That is, were there any changes between 1950 and 1982 in the way the cancers of interest were diagnosed and treated that our expert panels believed improved the survival chances of patients? The presence of such changes would increase our confidence that the reported improvements in survival were real, whereas their absence would obviously make us question their reality.

The concluding section of chapter 2 identifies several types of measurement bias that can artificially inflate the extent of change in survival rates over time Therefore, the third issue that we examined was how prone each of the 12 cancers is to these various forms of bias. For reasons that become clear upon reading the section on bias, addressing this issue required us to pay close attention to whether there were any changes in disease detection, in staging techniques, or in the diagnosis of cancer If change had taken place in one or more of these areas, we concluded that measurement bias could easily exist.

[4]The ratio of mortality to incidence is only an approximation since it assumes that the ways in which cancers are detected and recorded have not changed, which, as we show in chapter 3, is not the case

Since a "yes or no" response was possible for each of these three issues, eight situations could exist. Tables 1.1 and 1.2 show our conclusions regarding whether survival improvements were likely to be real for each of these eight situations. Table 1.1 includes the four cases in which there was no reason to assume measurement bias, and table 1.2 includes the four situations in which such bias was believed to exist.

Table 1.1: Decision Rules When No Measurement Bias Exists

	Survival improvement consistent with incidence and mortality trends	
	Yes	**No**
Change with survival implications occurred in management of disease	Real improvement	Real improvement
No change occurred	Real improvement	Artifactual improvement

Table 1.2: Decision Rules When Measurement Bias Exists

	Survival improvement consistent with incidence and mortality trends	
	Yes	**No**
Change with survival implications occurred in management of disease	Real improvement	Artifactual improvement
No change occurred	Artifactual improvement	Artifactual improvement

As can be seen from tables 1 1 and 1.2, the decision rule was a simple one in that we considered three dimensions· the existence of bias, the consistency of data on survival, incidence and mortality trends, and the changes in the management of the disease that had the potential to extend survival. If two or more of these dimensions supported the position that patient survival had improved, we concluded that it had. Conversely, if the majority of the dimensions indicated that no improvements in survival had taken place, we concluded that none had.

It should be emphasized that our design included elements of subjectivity (for example, selection of participating centers and expert opinion) and is heavily dependent on qualitative data. Therefore, our findings are not as conclusive as those of studies that rely on objective, empirically validated data. However, since a major rationale for conducting this study was the lack of data, we believe that our results constitute the strongest comprehensive evidence to date on what actually occurred in the area of cancer patient survival from 1950 to 1982.

Contributing to our belief in the validity of our findings is the extensive review of this report; we sent copies of the draft report to all 20 national comprehensive cancer centers. By doing so, we provided the opportunity to all centers to comment on our findings, even the centers that did not participate directly in the study.[5] In addition, the write-ups on the 12 specific cancers were sent for comment to the individuals who served on the corresponding expert panels. We believed these reviews were necessary to insure that our characterization of the experts' testimony and opinions was both fair and accurate. Finally, comments were obtained from the Department of Health and Human Services (HHS). Comments from each of these sources have been incorporated into the report. The complete text of the HHS review is reproduced in appendix V

Report Overview

We begin our examination by addressing, in chapter 2, the utility of the cancer survival rate as an indicator of progress in extending patient survival. Chapter 3 provides evidence other than published rates to determine whether survival rates for 12 forms of cancer have actually changed and, if so, why. The issue of how much progress has been made is dealt with in chapter 4, our final chapter, which begins with a review of our major conclusions.

[5]The individuals from the nonparticipating centers are referred to as the "independent" experts or reviewers in the executive summary, chapter 4, and appendix V

Cancer Survival Rates as Measures of Progress

Introduction

In appropriations hearings for the 1985 budget, the director of the National Cancer Institute used the reported improvements in patient survival rates as evidence that progress is being made in controlling cancer. Recently, though, questions have been raised concerning the utility of cancer survival rates for reaching conclusions on the extent of progress. It is this general issue, the utility of the rates, that this chapter focuses on. Specifically, we address our first 3 study questions:

- How accurate are the survival rates published by NCI?
- What do survival rates actually measure? (That is, How meaningful are survival rates?)
- What measurement problems limit our ability to interpret changes in survival rates over time?

These questions concentrate upon the survival rate, which is one of many statistics that can be generated from a form of investigation known as "survival analysis " Survival analysis has two basic approaches. One involves an examination of the time that passes between two events In business applications, this approach might focus on the amount of time between the start-up and demise of a certain type of firm; in education, the concern could be with the interval between entry and exit of students from postgraduate training. In health, this form of survival analysis is often concerned with the interval between disease onset and death

The other approach to survival analysis is one in which the interval is established by the analyst beforehand and the concern is with the number or percentage of individuals who "survive" for that specified period. For cancer, this approach would involve the specification of an interval, typically 5 years, and the determination of the proportion of patients who remain alive at the end of that time. The survival rate is then computed by converting this number to a percentage. For example, if 100 cancer patients were identified and 60 were still alive at the end of the interval, the survival rate would be 60 percent.

This simple form of the survival rate—the percentage of all cases alive at the end of some interval—is referred to as the "observed," or "crude," survival rate. One problem with this rate is that it represents deaths from all causes, such as traffic fatalities and heart attacks, not just from cancer. A more appropriate measure of true survival, the "relative" survival rate, does take into account death from other causes and is defined as "the ratio of a patient group's observed survival to that expected for persons in the general population of the same age, sex,

race, and calendar year of observation." The use of relative survival rates is particularly important for cancer because the population most at risk, the middle-aged and elderly, is at the greatest risk of dying in general.

It is the relative survival rate that is used by NCI in its annual cancer statistics reviews, so that when a 5-year survival rate of 50 percent is reported for a particular cancer, it does not mean that exactly half of all patients with that cancer were alive 5 years following diagnosis. Rather, it indicates that 50 percent of all patients whom we would expect to be alive, after other potential causes of death are accounted for, actually survived. The specifics of how the relative rate is actually computed are complex, and a detailed understanding of the algorithm is not essential for understanding the findings that follow, but, for interested readers, we present the algorithm in appendix I.

How Accurate Are Cancer Survival Rates?

A statistic is considered accurate if it is free of systematic error. Like all other statistics, survival rates are prone to different types of systematic error. Since all statistics are values generated from samples (subsets of populations), some of these errors result from the process by which individuals are selected for inclusion in a sample. In situations in which samples are randomly drawn, differences between the sample value and the true value for the population are said to result from "sampling error." When the selection of cases to be included in a sample occurs in a nonrandom fashion, as happens for the samples from which cancer survival rates are derived, differences between the statistic (the value derived from the sample) and the true population value can result from "coverage error." In the case of survival rates, coverage error could exist if data were collected only in community hospitals, since the patients in those hospitals may differ from cancer patients in general

Another type of statistical error, "measurement error," refers to inaccuracies that result from problems in the way that the measurements are made. For example, indicating that patients have cancer when they do not or that someone died of cancer when the actual cause was stroke would both be considered measurement error.

Since both measurement and coverage error are inexorably linked to the data collection process, it is necessary to review how the data are collected in order to determine the extent of error in the computation of

cancer survival rates. Such reviews are complicated by the fact that survival data for the period of interest, 1950 to 1982, have been collected through three different efforts

Prior to 1956, data on cancer patient survival were drawn from individual registries that collected survival information without regard to comparability between registries. In 1956, NCI organized the end results program (ERP) in an effort to coordinate the collection of survival data. The ERP began with four central registries and 10 hospital registries Although five published reports were based on ERP data, the survival rates from one report to another are not considered comparable, because the registries involved in the program changed over time.

The surveillance, epidemiology, and end results (SEER) program was initiated in 1972 and continues to be the source for current cancer survival data. SEER differs from ERP in a number of important ways that have implications for both measurement and coverage error. With respect to coverage error, the situation seems to have improved with SEER for three reasons. One is that all the registries participating in SEER are based on population rather than institutions. That is, they cover a geographic area and collect data on all the cancer patients in that area. Institution-based registries collect information on only patients within a geographic area who happen to enter a hospital maintaining the registry. The difference between the two types of registries is important because the patients of a hospital may differ from the general class of cancer patients in an area, thereby introducing coverage error.

Coverage error can also occur with population-based registries if the populations covered by those registries differ from the general population. However, SEER data seem less prone to such errors than ERP data, because the SEER population coverage is much broader. While the SEER population is not a scientifically drawn probability sample of the country, it can be argued that the sample is more representative of overall cancer patterns than that of ERP.

Finally, the distinguishing characteristic of SEER that we believe reduces the coverage error associated with its survival rates is the representation of ethnic minorities Unlike ERP, SEER is designed to insure that racial minorities are included in sufficient numbers to allow conclusions about their cancer survival patterns. (A more detailed description of the coverage under SEER is in appendix II.)

SEER differs from ERP in a number of other ways that are significant for reducing threats to the accuracy of survival rates. In our review, we identified a number of specific errors that could reduce the accuracy of survival rates. Errors that relate to the determination of whether a patient has cancer, referred to as "case entry," are listed in table 2.1. Table 2.2 shows potential errors in the determination of patient status at "case exit," or the end of the interval of interest.

Table 2.1: Problems in Case Entry

Problem	Description	Error introduced
False positives	Patients are incorrectly diagnosed as having cancer	If true problem is more lethal than the diagnosed cancer, patient's shorter survival can cause cancer survival rate to be underestimated, if true health problems are less lethal than the diagnosed cancer, patient's longer survival can cause rate to be overestimated
False negatives	Patients with cancer are not diagnosed as having the disease	Missed diagnoses may bias survival rates if the omissions follow a pattern, for example, if the less active or more benign cases are missed, survival rates would be underestimated
Misspecification or nonspecification of primary site	Cancer is diagnosed, but the body site of origin is not specified	Survival rates by site may be higher or lower than the true rate if cases for a particular site are not attributed to that site
Incomplete enumeration	All cases of cancer are not identified	Same as error introduced for problem of false negatives
Redundancy	Cases of cancer are counted twice	If cases that are counted more than once are not random, survival may be biased, since those diagnosed as being serious might be more likely to seek a second opinion, the chances of double-counting would be greater for the worst cases, and this would result in underestimating the cancer survival rate

Table 2.2: Problems in the Determination of End-Point Status

Problem	Description	Error introduced
Losses to follow-up	Inability to determine whether a patient is alive or dead at the end of the interval (usually because the patient cannot be located)	If lost patients have better survival than patients for whom data are available, overall survival rates would be underestimated, if their survival is worse, survival rates would be overestimated
False positive misspecification of cause of death	Cause of death is noted as cancer when it is actually something else	None, because the relative survival rate is not concerned with cause of death
False-negative misspecification of cause of death	Cause of death is noted as something other than cancer when death results from cancer	None, because the relative survival rate is not concerned with cause of death

As can be seen from tables 2.1 and 2.2, there are many potential problems. We begin our discussion with those in table 2.2 because only one problem introduced by end-point status determination could distort survival rates—cases lost to follow-up. To deal with this potential problem,

SEER registries adopt a number of procedures. The nonprofit organizations that, under contract to NCI, consolidate data from the registries for entry into SEER are required to maintain follow-up on all living patients All registries review death certificates and hospital readmissions for patient follow-up, and supplemental follow-up techniques include written contact with the attending physician or the patient and review of Health Care Financing Administration records, diagnostic related group records, and Medicaid records. Some registries have also tried matching voter registration or motor vehicle registration files. One registry, in Puerto Rico, goes so far as to conduct house-to-house interviews.

The SEER program has also introduced procedures to reduce the types of error listed in table 2.1. One of these involves a review of the percentage of cases identified by death certificate only. The assumption is that an unusually high percentage identified by death certificates alone would indicate flaws in case finding, since most cancer patients should be identified as having the disease before they die from it. Most SEER registries do relatively well with death-certificate-only as a measure, yielding 3 percent or less of the cases in each registry.

Another approach to limiting case entry problems under SEER is the use of case-finding "audits" that consist largely of a series of matches These are conducted by registry and NCI staff who visit the registries and participating hospitals and compare registry lists of cases with hospital pathology reports and discharge lists. By making such comparisons, staff can discern problems involving false-positives, false-negatives, and primary site misspecification, as well as errors resulting from incomplete enumeration or redundant case counting. If more than 1 percent of cases are missing from the registry rolls, a more extensive review generally is initiated.

A final example of procedures adopted by SEER to improve data accuracy is a series of consistency checks on the adequacy of abstracting case information. During site visits to registries, staff reabstract records and code and then compare their abstracts with the data submitted to NCI. SEER identifies and reports the source of any errors (abstracting, coding, or computer conversion problems) to the registries.

It should be noted that SEER has other initiatives aimed at insuring the comparability of data and the appropriate training of staff. SEER combines data from 11 population-based registries across the country. Comparability is accomplished by using standard contract provisions for all

the registries that collect specific elements of data for patients. The SEER coding manual outlines the level of detail for specific data elements and describes decision criteria for items such as extent of disease and a primary-site designation for multiple-site cancer patients.

All registry contracts specify the need for a core staff able to perform epidemiologic and other research using registry data and also require that staff attend workshops and training sessions sponsored by NCI. The University of California at San Francisco, under contract to NCI, conducts a training program on registry methodology (abstracting and coding procedures) and also aids in other quality assurance efforts.

The procedures adopted by SEER to limit inaccuracies from coverage and measurement error lead us to conclude that the survival rates derived from SEER data are probably more accurate than other rates. Although we can make no definitive statement as to how accurate current survival rates are, it is important to recognize that most of the debate over these rates does not revolve around the issue of accuracy. Critics charge that even if survival rates were perfectly accurate, their utility for assessing progress remains limited. Why this is so serves as the focus for the remainder of the chapter.

What Do Survival Rates Actually Measure?

As we state in the "objectives, scope, and methodology" section of chapter 1, progress against a disease can occur in any of a number of ways. Reductions in the number of new cases or deaths would certainly constitute progress, as would the diminution of the pain or cost associated with any treatment for that disease. Since progress can occur along many dimensions, it is important to specify exactly which of these dimensions is measured by any specific statistic being used as an indicator of progress.

Two important questions that cannot be answered by studying the survival rate are "How many people have or get cancer?" and "How many people die from cancer?" These questions cannot be answered because they are about absolute numbers ("how many") and because the survival rate, since it is a rate, provides only relative information. This is easily demonstrated with the hypothetical data presented in table 2.3

Table 2.3: Incidence, Mortality, and Survival

Group	Number of cases	Number of survivors	Number of deaths	Survival rate
A	100	60	40	60%
B	200	120	80	60

As can be seen, the survival rate, since it is a proportion, remains the same for both groups, even though the levels are dramatically different: twice as many cases of cancer are diagnosed and twice as many deaths are caused by the disease in group B. Survival rates, therefore, are obviously inappropriate for reaching judgments about progress in reducing the absolute number of cases or deaths.

Also, survival rates do not provide much insight into the actual number or percentage of patients cured of cancer. This limitation is illustrated by any situation in which a patient dies of cancer after the specified survival interval. For example, if we are measuring 5-year survival, any patient who died more than 5 years after the date of diagnosis would be counted as a survivor even though the patient's eventual death was directly attributable to cancer. The relationship between the interval most frequently used—5 years—and cure differs considerably by cancer type For diseases that are rapidly fatal, such as liver, lung, and pancreatic cancer, the 5-year survival rate would be a reasonable approximation of cure rate. For some cancers, such as breast and prostate cancer, periods of 5, 10, and even 15 years may elapse between the time of diagnosis and death, even when the treatment is ineffective and the patient is killed by the cancer For such cancers, the 5-year rate has questionable utility as an indicator of anything other than rates of early relapse

Another limitation of the survival rate is that it provides no information on how long cancer patients live. For example, if the survival rate for a particular cancer is 40 percent, we do not know whether the remaining 60 percent of patients die within the first year of diagnosis, within 4 years of diagnosis, and so on; nor do we know whether the survivors have normal life expectancies or die shortly after the survival interval

One final limitation on the ability of survival rates to inform us about cancer patient survival is that they contain no information on the quality of survival. A patient who spends much of the 5-year period in and out of hospitals, undergoing toxic treatments, and suffering great pain is considered equivalent, from the perspective of a survival rate, to

a patient who never shows any further signs of disease following initial therapy.

These limitations are not cited as evidence that the survival rate has no utility for understanding how well we are controlling cancer; rather, they are intended to caution the reader that survival rates address only one of the many objectives in cancer control—the extension of patient survival. Specifically, a survival rate tells us what percentage of patients live for a specified period from the time of diagnosis or, in other words, the probability of any single patient living for that length of time. Survival rates do not convey much information about cure rates or how long patients live and provide no insight into their quality of life. Using survival rates alone to reach conclusions about general progress is therefore inappropriate, since they can address only one aspect of progress. Even with respect to extending life, changes in survival rates are difficult to interpret.

Problems in Interpreting Changes in Cancer Survival Rates

Data published by NCI and the information collected in the course of our review suggest that, in general, we are detecting cancers earlier than we did in 1950. However, as the hypothetical example presented below illustrates, earlier detection may result in reported improvements in survival rates even when no improvements have actually taken place

Let us assume that a particular type of cancer has a 10-year interval between its onset and the patient's death. In 1950, the majority of patients would wait until symptoms appeared, typically in the sixth year of the disease. Untreated, these patients would live approximately 4 years; thus, the 5-year survival rate computed in 1955 is small. In an effort to combat the disease, a program is begun in 1960 that encourages frequent checkups and, as a result, the cancer of most patients during that year is detected in the fourth year of its progression. When the survival rate is computed again in 1965, the majority of these patients are still alive. As can be seen from this example, even if there were no change in treatment given and patients in both sets continued to die 10 years after disease onset, this situation would increase reported survival rates without the patients diagnosed in 1960 actually living any longer This phenomenon is commonly referred to as "lead-time bias."

As we mention in chapter 1, cancer patients are often categorized by stage, a measure of how far their disease has progressed. To compensate for lead-time bias, survival rates are often published stage by stage However, as was recently pointed out by a group examining the

"staging" of lung cancer patients, even this approach is subject to biased interpretation, because of a phenomenon known as "stage migration," illustrated in figure 2 1.

Figure 2.1: Stage Migration

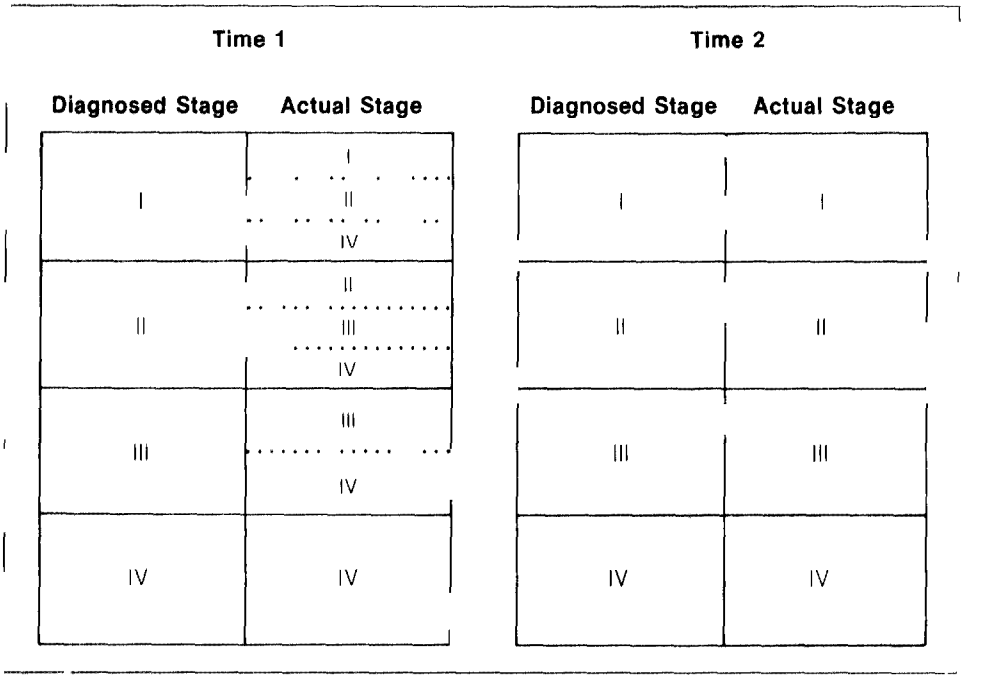

Figure 2.1 shows the distribution of cases by stage for a disease at two time periods At time period 1, some of the cases are inappropriately classified at lower stages than they should be, because of imprecise technologies. For example, some of the cases that are put in stage I really belong in stage II. At time period 2, improved diagnostic techniques allow for more proper stage classification This improves survival at each stage. The reason is that the cases removed from stage I are those whose prognosis is worse relative to the other cases in that stage. Relative to stage II, however, the prognosis of the "migrating" cases is better, so stage II survival also improves. As the migration continues, survival would increase for the other stages as well.

Complicating interpretation even further is a set of problems that result from changes in the characteristics of diseases and patients One of these problems is commonly referred to as "length-time bias." To understand length-time bias, it is important to recognize that not all cancers grow at the same rate and, even within the same disease type (for

example, prostate cancer), the length of time that passes before symptoms become apparent can vary. As a result of this variation, changes in detection practices could result in different types of diseases being included in the computation of survival rates. Should this happen, comparisons of these rates over time would be inappropriate.

The advent of mass screening programs illustrates this point. When no widespread screening takes place, cancers are often diagnosed as a result of some symptom noticed by the patient or physician. With screening, though, one would expect an increase in the number of cancers diagnosed in asymptomatic patients. These cancers may differ considerably from those of patients with symptoms at time of diagnosis, in that some may never progress to a symptomatic stage or may do so only after an extended time. By increasing the number of asymptomatic cases relative to those that already exhibit symptoms, survival rates would improve simply as a result of length-time bias—that is, a change in what is being counted as cancer.

The last problem we mention in interpreting survival rate change is "selection bias," which occurs when the characteristics of cancer patients change. For example, consider comparing survival rates before and after the introduction of a cancer screening program. Not all groups participate equally in screening programs. Typically, it is the better educated segment of the population that is most aware of the advantages of early detection and volunteers to be screened for the disease. This subpopulation is already more likely to be conscious of health protection and to have greater access to medical care. Thus, the patients added by screening may be healthier in general than earlier cancer patients and may have a better prognosis. If this occurs, the characteristics of patients in the before-and-after groups will differ and, as a consequence, the actual change in survival rates may be overestimated or underestimated.

Table 2.4 summarizes the forms of bias that can lead to misinterpretations of changes in survival rates. Throughout chapter 3, frequent references are made to these biases in the discussions of the 12 cancers.

Table 2.4: Biases in the Interpretation of Survival Rate Change

Type of bias	Description	Consequence
Lead time	Change in the point of progression of the disease at which the diagnosis is made	Diagnosing patients earlier in the progression of their cancers extends the interval between diagnosis and death, even if no changes occur in how the cancers are treated
Stage migration	Change in the precision with which patients are categorized in stages	As patients are more precisely classified, many tend to "migrate" to higher stages, thereby improving the survival rates for both the stage they moved from and the one they moved to
Length time	Change in the types of tumors counted as "cancer"	Including tumors with excellent prognoses that were not included at previous times improves survival rates, even if the management of the cancers does not change
Selection	Change in the characteristics of patients included in survival rate computation	If more patients with better prognoses are included, survival rates will increase, and if more patients with poorer prognoses are included, rates will decline, both changes in rates will occur, even if there is no change in the management of the cancers

We began this chapter by stating that improvements in survival rates have been used as evidence that progress is being made against cancer. The contention that higher survival rates indicate improvements in our management of cancer may, in fact, be true. However, we demonstrated that improvements in survival rates may also result from changes in the way that the rates are measured Changes in when measurements are taken and how patients are characterized as well as changes in the types of cancer and patients included in the data on survival can all result in reported improvements in survival rates, even when no improvements have actually occurred. However, NCI does not systematically alert readers of its annual cancer statistics reviews to potential sources of bias that affect changes in survival rates. Thus, published information may overestimate or underestimate the extent of progress in extending cancer patient survival.

Changes in Cancer Management From 1950 to 1982

Introduction

The forms of measurement bias described in chapter 2 make it clear that it is impossible to know whether cancer patient survival changed by simply comparing the reported survival rates for 1950 with those for 1982. To answer this question, we need some sense of how much confidence one should have in any reported changes. In this chapter, we present such information for 12 specific types of cancer: bladder, breast, cervical, colorectal (colon and rectum), endometrial, head and neck, the leukemias, lung, non-Hodgkin's lymphoma, prostate, and stomach. For each cancer, we examine whether the reported survival improvements are consistent with incidence and mortality trends; whether changes in the way the cancer is detected, evaluated, and treated could account for reported improvements in survival; and the forms of measurement bias that may be relevant for the cancer in question. Using this information, we can conclude whether survival rates actually improved. In addition, we can answer our fifth study question: What factors contributed to the improvements in survival?

The structures of the sections on the 12 cancers are similar: all contain a brief overview in which the relevant cancer is described; a discussion of trends in incidence, mortality, and survival rates; a table listing major changes in the management of the disease and the implications of these changes; and a discussion of survival progress that synthesizes all this information and presents our conclusions.

The information on the 12 cancers is drawn from a variety of sources The general descriptions of the diseases come from a number of medical texts and journal articles. Information on incidence, mortality, and survival trends is drawn primarily from NCI statistical publications. The tables on changes in disease management and the implications of these changes are based primarily on comments from our expert panels. Finally, the discussions on survival that conclude our review of each cancer incorporate the contents of previous sections as well as panel comments and literature-based information.

Two changes during the period of interest, the advent of sophisticated imaging devices and improvements in radiation therapy delivery mechanisms, have implications for a wide array of cancers. In order to make the tables on changes in disease management as concise as possible, we begin by discussing these two changes. Although they are not mentioned in the tables, they are included, when relevant, in the discussion at the end of each section.

Crosscutting Changes in Cancer Management

Before therapy is initiated for any form of cancer, it is important to know as much about the specific case as possible. Therefore, once a malignancy is suspected, a series of tests and procedures are performed to determine the cancer type, size, and location and the presence of any metastases. This information is used to select the most appropriate therapeutic approach. One change noted by our expert panels was an improved ability to obtain accurate information, for treatment planning, on the presence and magnitude of cancer in the body. This improvement came primarily as a result of the development of an array of devices and procedures that can detect even minute amounts of cancer cells without the need for surgery. Among the most notable of these technological developments are the computerized axial tomography (CAT) and radionuclide bone scans.

The capabilities of these new imaging technologies, which can show physicians the precise location, size, and shape of tumors, have considerable implications for cancer patient survival in that they can lead to the selection of more appropriate, and thereby more effective, therapies In addition, by improving the ability to detect distant metastases, the imaging technologies may prompt physicians to choose more aggressive therapies that may offer the only real hope of cure. The extent to which survival rates have been improved by these technologies is unclear, though, since most patients with metastatic disease still die, and many patients with localized disease were cured even before the scanning devices were available.

One thing that has certainly improved as a result of CAT and bone scans is the quality of life for cancer patients. For one thing, because these devices allow physicians to gather information without performing surgery, the pretreatment evaluation of cancer patients can now be accomplished with less pain and suffering. Perhaps more important is the improved ability provided by the imaging technologies to identify the cancer patient who has little hope of cure and thereby avoid painful, and ultimately futile, therapies.

Another change in cancer management that has relevance for many different types of cancer is the improved ability to deliver large doses of radiation directly to a tumor while sparing surrounding tissue. This improvement comes as a result of numerous technological advances in the field of radiation therapy, including the introduction of new radioactive materials and improved delivery mechanisms for intracavitary and interstitial implants. The most significant advance in this area, however,

has been the development of the high-energy devices that allow for larger doses of radiation and more precise targeting.

The ability to deliver tumoricidal doses while sparing surrounding tissue has allowed for the irradiation of tumors that were previously inaccessible. Since radiation is known to effect cures in a considerable number of tumor types, the changes in radiation devices have extended survival for some of the patients suffering from them.

One additional benefit of the new radiation devices is that they have greatly reduced the complications associated with therapy, many of them quite serious. An example of this is the reduction in the number of colostomies required as a result of irradiation of the pelvic area.

We discuss the extent to which the new imaging and radiation technologies have affected each of the 12 cancers more fully in the sections that follow.

Bladder Cancer

Overview

In 1985, an estimated 40,000 persons in the United States developed bladder cancer, and approximately 11,000 persons died from the disease. The (urinary) bladder serves as the repository for urine on its route from the kidneys out of the body. The lining of the organ is referred to as a "transitional epithelium" because each of its several layers is formed by a transformation of the cells from the layer below. Cancers that originate in this lining are therefore known as "transitional cell carcinomas."

There exists a spectrum of abnormal tissue formation in the bladder that ranges from benign to highly invasive. There is some disagreement over exactly where along this continuum one should make the demarcation between cancerous and noncancerous tumors, the major point of contention being the classification of growths known as "papillary tumors." Some argue that some of these tumors should be excluded from the category of cancer and referred to as "papillomas," while the majority classify these tumors as papillary carcinomas and consider them to be cancer.

The most frequent first sign of a malignancy in the bladder is blood in the urine. Since this sign often appears early in the progression of the tumor, bladder cancer is most often diagnosed in its early stages. The disease progresses by spreading along the lining of the bladder and eventually penetrating into and through the muscle of the organ. It is unclear how important the extent of lateral spread is, but it is widely acknowledged that the depth of penetration is the critical prognostic factor. It is also clear that some tumors invade the muscle rather quickly while others, the papillary carcinomas, may never penetrate.

One somewhat unique characteristic of bladder cancer is its tendency to appear in a number of different locations in the organ. The "multifocal" nature of the disease is not well understood but is an important aspect of diagnosis and treatment in that, when biopsies are performed, tissue samples have to be randomly selected from a number of locations in the organ.[1]

Surgery, radiation therapy, and chemotherapy all have roles in the treatment of bladder cancer Surgical options range from excision of superficial tumors to removal of the entire organ ("cystectomy"). Radiation therapy is now often used in combination with surgery and is useful for treating any undetected disease outside the bladder. Chemotherapy is the only treatment available for advanced disease, although rarely achieving cure, it does have some moderate success in extending survival.

The sensitivity of the bladder to carcinogens has been known for some time. As far back as 1895, it was demonstrated that aromatic amines, a class of chemicals, were potent bladder carcinogens. These chemicals, used principally in the dye and rubber industries, increase the risks of bladder cancer in exposed workers anywhere from 10 to 50 times that of the general public. It has been determined that cigarette smoking increases the risk of getting the disease. Finally, coffee and cyclamates have been implicated as risk factors, although no clear-cut relationship between them and bladder cancer has been established.

Disease Trends

The incidence of bladder cancer increased from 1950 to 1982 In the data, no distinction is made between papillary and other transitional cell

[1]The three theories that explain this phenomenon are (1) these growths spring up independently of one other in response to carcinogens, (2) malignant cells from an original growth float through the urine and are implanted elsewhere, and (3) during urination, when the bladder deflates, the cells spread from the original site by actual contact caused by the bladder's collapsing

carcinomas, so that it is unclear whether the increase was uniform for both tumor types. Mortality rates, in contrast, declined. Consistent with these divergent trends, survival rates improved. Whereas only about 50 percent of the bladder cancer patients lived for 5 years following diagnosis in 1950, by 1982 almost 3 of every 4 bladder cancer patients did so.

Changes in Disease Management

We summarize our findings on the major changes in the management of bladder cancer in table 3.1. The changes fall into the three broad areas of disease detection, pretreatment evaluation, and treatment. For each change, we indicate the panels' impressions as to whether the change had a real effect on survival as well as other consequences the change has had on disease management.

Table 3.1: Changes in the Management of Bladder Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Earlier detection of the disease	Other A variety of reasons were cited, including greater patient and physician awareness, but these were not thought to be sufficient to explain all of the trend	Real Since the disease is more treatable in its early stages, earlier detection leads to increased survival rate, lead-time bias was discounted as a factor because of the decreasing mortality rate	None mentioned
Pretreatment evaluation	Greater effort being made at determining depth of tumor penetration	Other Recognition that depth of penetration into bladder muscle is the key prognostic variable needed to select appropriate treatment	Real Identifying the group of patients at high risk allows the adoption of more aggressive therapies that cure some of these patients, most of whom would die without such therapies	Identifying patients who have tumors with little chance of progression allows them to be treated more conservatively, thereby reducing the morbidity associated with more-aggressive therapies
Treatment	Use of combined treatment for advanced disease, involving preoperative radiation followed by surgery	Other Recognition that radiation has beneficial effects by treating undetected disease outside the bladder	Real If disease is confined to the bladder, the combined treatment will not have a major effect, since surgical removal will achieve a cure, however, radiation can destroy the metastases that would become fatal if left alone	None mentioned
	More frequent use of total cystectomy for invasive early disease	Technological Improvements in surgical techniques, support, and training make total cystectomy a more viable procedure than it used to be	Real Cystectomy is known to cure specific patients and its expanded use has improved survival	None mentioned
	Cytoscopic exams done on regular basis for patients following treatment for limited disease	Other Awareness that cancer patients who have had any growth are at greater risk of developing subsequent tumors	Real Tracking a group that is at high risk of recurrent disease detects recurrences earlier, when they are more treatable	None mentioned
	Chemotherapy performed for advanced disease	Technological Development of a variety of tumoricidal drugs	None At least one drug regimen has been shown to be effective, but it is relatively new and has not affected published rates, in addition, this regimen extends survival from a few months to 2-3 years, which would not effect 5-year survival	None mentioned

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

The two panels that discussed bladder cancer agreed that there were real improvements in patient survival from 1950 to 1982. Despite this consensus, the panel members expressed considerably varying opinions on the reason for the improvements. The panels cited the advent of combined modality therapy for advanced disease, earlier detection, and the increased use of total cystectomies as contributing factors. The actual contribution of these changes is difficult to evaluate, since the relevance

of combined therapy is unclear (the disease is detected sufficiently early in 80 percent of the patients that this treatment is not used), there was no sense as to why the disease was being detected earlier, and the extent of increase in cystectomies is not known.

The major problem in reaching judgments concerning survival trends for bladder cancer, however, is the inclusion of papillary carcinomas in the data. As long as these relatively benign tumors are enumerated as bladder cancer, almost all of which could always be cured, changes in their relative frequency will greatly influence survival rates If more and more of these tumors are discovered, survival rates will improve, even without changes in the management of the disease. One of the panelists indicated that the inclusion of greater numbers of papillary carcinomas was the major contributor to the reported survival rate improvement.

Nonetheless, in light of the divergent trends in incidence and mortality, as well as the changes in the management of the disease, we conclude that

- there was a real improvement in bladder cancer patient survival from 1950 to 1982 and
- both the magnitude of and the reasons for this improvement are not well understood

Breast Cancer

Overview

Breast cancer is the most prevalent form of cancer among women in the United States. Estimates are that approximately 119,000 women develop the disease annually and that this form of cancer killed almost 40,000 women in 1985. Although almost all cancers of the breast are carcinomas, the category includes a rather heterogeneous mix of disease types. Some breast cancers grow slowly and others grow very rapidly Some spread primarily by invading adjacent tissue, while others frequently metastasize. Some tumors seem dependent on the hormone estrogen for growth, while others do not seem to need estrogen.

In the early stages, breast cancers typically manifest themselves as painless, movable lumps that a patient can feel by self-examination Most breast cancers are first discovered in this way. Even before the

tumor is palpable, however, its presence can be detected by "mammography," a procedure involving x-ray examination of the breast. As with many other cancers, the earlier the disease is detected the better the prognosis is for the patient. Therefore, it stands to reason that mammographic screening should lead to earlier disease detection, in turn decreasing the number of deaths from breast cancer. That breast cancer screening efforts using mammography can save lives was first shown by a study conducted in the 1960's in New York; it was confirmed by a recently completed controlled experiment conducted in Sweden.[2]

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. Many breast cancers are thought to grow at a relatively slow rate, moving from the breast to the axillary lymph nodes (under the arm) and eventually spreading to distant organs, the liver, lung, and bone being the most likely locales for metastatic activity. The traditional principles of patient management were constructed on this assumption of an orderly disease progression. However, it is now believed that the progression is not always orderly and that breast cancer should really be considered a "systemic" disease. That is, whenever a malignancy is detected in the breast, the treatment plan should account for the possibility that cancer may exist throughout the body and not just in the area where the tumor is located.

One of the risk factors for breast cancer is age, incidence rates in Western countries starting to climb at age 30 and increasing to approximately the age of 70, when they level off. Other risk factors have been identified, including heredity, diet, reproductive factors, and ionizing radiation, although no causal agent has been determined.

Disease Trends

Despite variations among subgroups, mortality rates for breast cancer remained relatively stable from 1950 to 1982, while incidence rates increased Published survival rates show considerable improvement between 1950 and 1982, increasing from less than 60 percent to 75 percent. The improvement in survival is consistent with the divergent trends for incidence and mortality. It should be noted, however, that incidence trends are considered unreliable because of a dramatic

[2] S Shapiro, P Strax, and L Venet, "Periodic Breast Cancer Screening In Reducing Mortality from Breast Cancer," Journal of the American Medical Association, 215 (1971), 1777-85, and L Tabar et al , "Reduction in Mortality From Breast Cancer After Screening With Mammography Randomised Trial From the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare," Lancet, 1 (1985), 829-32

increase in the number of cases detected in 1974, which some have attributed to publicity surrounding the celebrated cases of Betty Ford and Happy Rockefeller

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of breast cancer in table 3.2.

Table 3.2: Changes in the Management of Breast Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Earlier detection of the disease	Other Greater awareness on the part of women and physicians, promotion of breast self-examination	Mixed Since it is commonly accepted that the earlier the disease is detected, the more curable it is, earlier detection should result in real improvement in survival rates, the other consequence of earlier detection is to artificially inflate survival rates as a result of lead-time bias	None mentioned
	Different types of tumors being detected	Other Detection of increasing numbers of noninvasive breast cancers	Artifactual Since many of the new tumors being detected, or being detected at a greater rate, are relatively indolent and have excellent prognoses, their addition leads to improved survival rates as a result of length-time bias	None mentioned
Pretreatment evaluation	Improved assays for determining whether or not tumors are estrogen receptive (ER)	Other Recognition that ER status was an important prognostic factor to be considered in treatment planning	Unclear With different treatments for estrogen-receptive and nonestrogen-receptive patients, the ability to determine ER status should improve survival, it is questionable, however, whether these tests were pervasive enough in the 1970's to have affected the latest published rates	More appropriate administration of effective therapies in specific classes of patients improved their quality of life
	Redefining some tumors as stage 2 rather than stage 1	Not mentioned	Artifactual Artificially inflates improvements in survival for stages 1 and 2 as a result of stage-migration bias, this form of bias is not relevant when examining survival for all patients combined	None mentioned

Area	Change	Reason for change	Consequences for survival	Other consequences
Treatment	Decline in the number of radical mastectomies being performed	Other. Realization that the treatment was considered excessive by patients and studies that showed equivalent survival benefits with less-disfiguring procedures	None. The argument is that less-radical procedures provide equivalent survival, there is no contention that they improve survival	Should eliminate administration of excessively drastic therapies in specific classes of patients, thereby improving their quality of life
	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	Other. Recognition that radiation therapy was not particularly effective for advanced disease and often not necessary for early breast cancer	None. The treatment is used less	Reduced morbidity and consequently improved quality of life
	Advent of multimodal chemotherapy as adjuvant to surgery for stage 1 patients with poor prognoses and for stage 2 patients	Technological. Results of randomized clinical trials showed survival and disease remission improvements when adjuvant chemotherapy was administered	None. Potentially real effect is considered significant, however, this regimen has only recently been widely used, so it has not had a significant effect on the latest published survival rates	None mentioned
	Development of synthetic "anti-estrogen" drugs	Technological. The hope of providing an alternative to adrenalectomy and other surgical procedures for blocking estrogen	None. Latest trial results show improved survival for postmenopausal, estrogen-receptive women receiving tamoxifen, this therapy is too new in the United States to have influenced 1982 survival rates	Reduced morbidity and improved quality of life for patients receiving hormonal therapy, since hormone drugs have low morbidity relative to other forms of hormonal therapy

[a]An explanation of the terms used in this table appears in apendix IV

Survival Discussion

Table 3.2 shows that the management of breast cancer has changed considerably. Some changes, notably the advent of chemotherapy, seem to hold promise for improving patient survival but are too recent to have significantly affected the latest published rates. Other changes—for example, the more aggressive therapeutic approach for some patients—are thought to have improved survival for discrete subpopulations. However, these groups are so small that the effect on the overall survival rate is probably minimal. The expert panels expressed the belief that the disease is managed in a more humane manner now than in 1950. This is most strongly reflected in more conservative surgical interventions for the early stages of the disease. In addition, the improved ability to detect advanced disease, for which curative therapy may increase pain but offer no real hope of cure, has allowed the selection of more appropriate treatments. Neither of these changes has extended patient survival, but both have considerably improved the quality of survival.

Where, then, did the reported improvements in survival come from? One possible factor is the increasing number of patients with slowly developing tumors, thereby creating length-time bias and an artifactual increase in survival. The most widely held opinion of our panels, however, was that the earlier detection of the disease was the major factor in its improvement.

As indicated before, however, earlier detection has two consequences: one results in real improvement because of the greater curability of the disease in its early stages, and one results in artifactual improvement because of lead-time bias. Although all our panels believed that lead-

time bias was a factor, opinions ranged from the belief that it was the only contributor to the improvement to the position that it was impossible to determine its contribution relative to greater curability. From these findings we conclude the following:

- There was some real improvement in breast cancer patient survival from 1950 to 1982
- The improvements in survival were the most relevant for certain classes of breast cancer patients.
- Earlier disease detection was the major contributor to the improvement in survival.
- A large percentage, if not most, of the reported improvement in survival resulted from either length-time or lead-time bias.
- Changes in the management of breast cancer have resulted in improved quality of life for victims of the disease.

Cervical Cancer

Overview

The uterus, a pear-shaped organ in the pelvis, consists of two parts: the body ("uterine corpus") and the neck ("uterine cervix").[3] Cancers of the corpus and cervix, because of the involvement of different cells and different courses of progression, are considered to be different disease types. In this section, we discuss cervical cancer, which accounted for approximately 15,000 cases of cancer and 6,800 deaths in the United States in 1985. Our findings on cancer of the uterine corpus are presented in the section on endometrial cancer.

Running through the cervix, which is cylindrical in shape, is a hollow space referred to as the "endocervical canal." Cervical cancer originates in the lining of this canal. However, the cellular composition of the lining is not uniform throughout the length of the cervix and, consequently, the precise site of origin for a tumor determines the type of cancer. The upper part of the endocervix (closest to the uterine corpus) is lined with tall, columnar epithelial cells, the lower part (closest to the vagina) with squamous cells. The area where the two parts of the endocervix meet is referred to as the "squamocolumnar junction." All cervical cancers, with rare exception, are carcinomas, since they originate in the cells that line the organ. If the site of origin is in the part of the cervix lined with

[3]For simplicity, we use the term "cervix" to indicate the uterine cervix

columnar cells, the cancers are classified as "adenocarcinomas," and if the cancers originate in the squamous-cell-lined part, they are known as "squamous-cell carcinomas." Of the two, squamous-cell carcinomas are much more prevalent, accounting for approximately 85 percent of all cervical cancers.

In the 1940's, George Papanicolaou developed a way to detect cervical cancer that involved taking a sample of cells from the vagina, cervical surfaces, and endocervical canal. This procedure, known as the "Pap smear," is easily performed and is fairly accurate in detecting abnormalities in the cellular lining of the cervix.[4] The implications of the Pap smear for the management of cervical cancer are considerable. To understand why, it is important to review the way in which this disease forms and progresses.

It is commonly believed that cervical cells undergo a series of changes resulting in invasive cancer. The first stage is "dysplasia" (abnormal tissue development), this is followed by "carcinoma in situ" (CIS, literally, "cancer in place," a noninvasive cancer) and, eventually, invasive cancer. The progression is not inevitable, since dysplasia frequently regresses to normal tissue, and no conclusive empirical evidence exists that all carcinoma in situ becomes invasive. Nonetheless, the evidence is sufficient to warrant removal of both dysplastic and CIS tissue in order to prevent the onset of invasive cancer.

The Pap smear's contribution is that it can identify all three forms of abnormal cervical tissue, thereby allowing for their excision. The benefits of excising them seem obvious. By removing cervical cancers early in their progression, when they are highly curable, the patient's survival should be extended. In addition, the excision of precancerous lesions identified by Pap smears should prevent the onset of cancer, resulting in a reduced incidence of disease.

Once invasive cancer begins, it can spread, along a variety of routes, to the vagina or the uterine corpus, through the wall of the cervix, and to other pelvic organs. Eventually, the disease metastasizes through the lymphatic and venous systems to distant organs.

[4]The accuracy of Pap smears is dependent on the site of the abnormality, lesions higher up in the cervix being more difficult to detect The skills of the physician taking the cell sample and the pathologist interpreting the results also influence accuracy

Risk factors for cervical cancer revolve primarily around sexual activity. The behaviors shown to elevate risk include first coitus at an early age and having multiple sex partners, although no cause-and-effect relationship has been demonstrated for either. Until recently, it was thought that the presence of the herpes virus was also a risk factor. This is no longer believed, but there is evidence that specific members of a class of viruses collectively called "human papilloma viruses" do indeed increase the chances of developing cervical cancer.

Disease Trends

In describing trends for cervical cancer, one major problem is that CIS was included in early data collection efforts but is dealt with separately in SEER. Another problem is that the data on incidence are questionable in that all women, the denominator used in calculations, are not at risk of developing this cancer, since women who have had hysterectomies are not at risk. The more appropriate denominator would be the total number of women who have retained their uteruses. In not accounting for the true population at risk, incidence and mortality rates would be biased if there were changes over time in the percentage of the population who have had hysterectomies. These problems, as well as the considerable increase in screening for the disease and changing precision in distinguishing between uterine and cervical cancer on death certificates, make definitive statements concerning trends extremely difficult. Nonetheless, what is reported is a major decline in both incidence and mortality for the disease from 1950 to 1982. Survival rates improved somewhat, going from high-50-percent to high-60-percent figures.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of cervical cancer in table 3.3.

Table 3.3: Changes in the Management of Cervical Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Cervical cancer is being detected earlier in its progression	Other Widespread application of the Pap smear	Mixed Since the earlier the disease is detected the more curable it is, earlier detection should result in real improvements in survival rates, the other consequence of earlier detection is lead-time bias	Detection and treatment of precancerous conditions and carcinoma in situ should decrease incidence and mortality
Pretreatment evaluation	Carcinoma in situ no longer enumerated as cervical cancer	Other Decision based on the invariable cure achieved by removing these lesions	Artifactual Not all cases become invasive and even when they do the process is thought to take a long time, therefore, inclusion of carcinoma in situ in cancer registries would result in misleadingly high survival rates, excluding it at the later time and then comparing rates means the results could be misleading, by artifactually dampening the magnitude of improvement	None mentioned
Treatment	Improved methods for performing pelvic exenteration, a surgical procedure for patients for whom primary therapy that involves the removal of all or most of the pelvic viscera has failed	Technological General improvements in surgical procedures, training, and support mechanisms	Real The procedure, by offering some hope of cure to a class of patients who would inevitably have died of the disease, should improve survival rates, it is unclear how large this group is	This surgery was performed in 1950 as well, but it had a high mortality and morbidity rate, improvements in the procedure have reduced the morbidity and, consequently, improved quality of life for patients undergoing this type of surgery

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

Radiation therapy is an important form of therapy for all stages of cervical cancer. It is used as an alternative to surgery for early disease and is the primary therapy for patients with advanced disease. Because of this reliance on radiation therapy, changes in radiation technology noted earlier in this chapter have considerable significance for cervical cancer The expert panels believed that the increased ability to target tumoricidal doses of radiation at the cancers has improved survival. The newer generation of radiation devices has also eliminated many of the complications associated with earlier forms of radiation therapy, thus improving the quality of patient survival

Another development in the management of cervical cancer is the increasing use of the Pap smear.[5] In its earliest stage, cervical cancer is a highly curable disease. The earlier detection brought about by the Pap smear should have contributed to improved survival, and there was consensus among the experts that it did. Furthermore, our panels believed that failure to achieve truly impressive gains in survival rates can be attributed to the significant proportion of women who do not have themselves tested. One institution we visited reported that approximately 50 percent of its cervical cancer patients had not had a Pap smear in the last 4 or 5 years. This reinforces the explanation for less-than-optimal survival rates, since the disease is highly curable when it is in the cervix, somewhat curable when restricted to the pelvis, and usually fatal once it has advanced beyond the pelvis. From these findings we conclude the following.

- The increase in survival rate in cervical cancer is real and results primarily from earlier detection, which, in turn, derives from the widespread application of the Pap smear
- The advances in therapeutic approaches, primarily in radiation, and to some extent in surgery, have contributed somewhat to improved survival rates in certain groups of patients.
- Therapeutic advances have resulted in significant improvements in the quality of survival of cervical cancer patients.

Colorectal Cancer

Introduction

The large intestine is the part of our digestive tract that includes the colon and the rectum. Cancer can and does occur in all parts of the organ, although not with uniform frequency In 1985, an estimated 96,000 new cases of colon cancer and 42,000 cases of rectum cancer occurred in the United States. The two diseases are strongly related in that they share a common set of risk factors, have similar symptoms, are treated by the same medical specialties, and are classified by a single staging system. However, significant differences exist between colon and rectum cancer, especially in terms of their responsiveness to different therapies and, consequently, their prognoses

[5]Although the precise date was not mentioned, one expert believed that the use of the Pap smear reached a plateau during the 1960's

Taking these differences into account, we considered colon cancer and rectum cancer as distinct disease types. Therefore, we provide separate tables on changes that have taken place in the management of colon and rectum cancer and also separate discussions on the implications of these changes for survival rates. However, in light of the similarities between these two diseases, we discuss them together in the overview and disease trends sections.

Overview

The colon and rectum constitute the lower end of the gastrointestinal tract, leading from where the small intestine ends at the cecum to the anus, where the tract exits from the body. The primary functions of the organ are to remove liquid from the waste products of digestion and to expel solid waste from the body. The entire length of the organ is lined by a mucous membrane, the topmost layer of which is made up of epithelial cells. It is in this layer that the most prevalent form of colorectal cancer, adenocarcinoma, begins.[6]

Current thought is that the normal epithelial cells undergo a series of changes that eventually transform them into malignant cells. The intermediary points in this progression are manifested as growths that are abnormal in cellular composition but not truly malignant These growths, usually in the form of polyps, are often referred to as "precancerous" or "premalignant " Although there is still not conclusive evidence that all polyps will inevitably become cancerous, they are generally removed when found. With the current technology, this procedure is relatively simple and is therefore considered justifiable, even if only a small percentage of the growths become malignant.

Once malignant cells appear in the lining of the large intestine, they usually begin their invasion in what is thought to be an orderly fashion, progressing into and through the layers of muscle tissue to the lymph nodes that drain the organ and, eventually, through metastases, to distant organs.

The earliest symptoms of colorectal carcinoma include blood in the stool and changes in bowel habits. Unfortunately, not all tumors in this region bleed, tumors that do so may bleed only intermittently, and blood is usually present in such small amounts that it is difficult to detect. In addition, noticeable changes in bowel habits may occur only after the growth is large enough to cause obstruction. Finally, colorectal tumors are not

[6]Adenocarcinomas account for well over 90 percent of all colorectal tumors.

palpable to the individual patient. For these reasons, the initial detection of this disease is invariably made by a physician, and a considerable number of patients (approximately 50 percent) have tumors that when first detected have advanced beyond the localized stage.

Risk factors for colorectal cancer include a history of polyps, ulcerative colitis, some other digestive disorders, and increasing age. In addition, a high-fat, low-fiber diet is thought to increase risk, although the exact nature of the relationship between diet and colorectal cancer has not been determined.

Disease Trends

The incidence of colon cancer has risen since 1950, and mortality has remained relatively stable. Consistent with the divergence in these two trends, survival rates have improved, rising from approximately 40 percent to a little over 50 percent. Survival rates for cancer of the rectum, although slightly below those for colon cancer, showed similar improvements between 1950 and 1982. As with colon cancer, this improvement was consistent with divergent incidence and mortality trends. Unlike colon cancer, however, the incidence of rectum cancer remained relatively stable while mortality declined.

The different incidence trends for the two diseases, increasing for colon cancer and stable for rectum cancer, is puzzling, since they originate in the same tissue and share a common set of risk factors. One explanation is that the locations of large-bowel cancers have shifted in response to changes in the prevalence of risk factors. This hypothesis is based on the observation that cancers are concentrated closer to the beginning of the organ (in the cecum and ascending colon) in low-risk populations and, as risk factors become more prevalent, there is an increase in cancers of the lower end of the bowel (the rectum and sigmoid colon).

Another explanation offered for the difference in incidence trends in colon and rectum cancer is that they result from inconsistencies over time in the way that tumors at the juncture of the colon and rectum (the "rectosigmoid junction") are classified. If tumors in this area were predominantly called rectum cancer in 1950 and are now classified as colon cancer, this would explain a sharper increase in incidence rates for colon cancer. Because of the potential problem with classification, some analysts suggest that colon cancer and rectum cancer be combined when examining incidence and mortality trends for the two diseases.

Changes in Disease Management

We summarize our findings on the major changes in the management of colon cancer in table 3.4. Table 3.5 provides similar information for cancer of the rectum.

Table 3.4: Changes in the Management of Colon Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Development of tests to detect occult (hidden) blood in the feces	Technological Recognized need for a way of detecting colon cancer early	None In general, there is no earlier detection of the disease now than there was, one reason for this may be, as one study demonstrated, that there is not much awareness of these tests among the general public, in addition,some experts believe that the most commonly available test does not work very well	The efficacy of these tests is debated, some experts arguing that the high rate of false negatives (erroneous indication that there is no disease) with the most commonly available test leads to more harm than good, detection and consequent excision of precancerous growths, if done with any frequency, should result in lower incidence and mortality rates
Pretreatment evaluation	Development of fiberoptic endoscope, a flexible instrument that allows visualization of the entire colon	Technological The need to examine the entire colonic tract visually in order to detect precancerous growth and to more accurately diagnose cancers, previous instruments allowed visualization of only the rectum and last few inches of the colon	Unclear Although the fiberoptic endoscope was developed in the early 1970's, it was not until the latter part of that decade that large numbers of physicians became skilled in its use, the ability of the fiberoptic endoscope to detect and allow for excision of precancerous lesions should have little effect on survival, however, its use to track previously treated patients for signs of recurrent disease has considerable potential for improving survival	None mentioned
	Identification of carcinoembryonic antigen (CEA), a potential colorectal cancer marker	Technological. The hope of an easily performed diagnostic procedure to establish disease and prognosis	Disputed The experts we talked with thought that CEA has little or no utility, it was mentioned, however, that others believe that CEA levels are good for monitoring treated patients, since there is some evidence that levels rise shortly before the recurrence of the disease	Extensive use of CEA tests may add unnecessary costs to patient care

[a]An explanation of the terms used in this table appears in appendix IV

Table 3.5: Changes in the Management of Rectum Cancer[a]

Area	Change[b]	Reason for change	Consequences for survival	Other consequences
Treatment	Use of radiation therapy and chemotherapy in combination as adjuvants to surgery	Other. Recognition, based on recently completed studies, that multimodality therapy is more effective than surgery alone	None With increased use of this therapeutic approach, survival should improve, however, it is too recent to have had any significant effect on the latest published rates	None mentioned
	Development of new suturing devices allows for surgery alternative to traditional anterior-posterior resection, which required removal of the anal sphincter	Technological The hope of allowing surgical patients to retain the use of the sphincter	None New surgery is hoped to have equivalent prognosis for patients with rectal cancer	If the new surgical procedure provides equivalent prognosis for patients with rectal cancer, it will greatly improve their quality of life in that they can retain sphincter function

[a]An explanation of the terms used in this table appears in appendix IV

[b]Changes listed for colon cancer in table 3 4 apply to rectum cancer as well; this table includes changes relevant only for cancer of the rectum

Survival Discussion

Colon Cancer

Surgery remains the cornerstone of colon cancer management; it is the only treatment that has proven effective. To understand if and why survival has improved, therefore, we need to look at changes in surgical procedures. At first glance, there seem to have been few modifications in the surgical management of this disease. After all, as one panelist indicated, the basic surgery for colon cancer has remained unchanged for the past 80 years. But changes have occurred in the support mechanisms for colonic surgery. That is, with generally improved medical care, patients who would not have been candidates for surgery in previous times can now be operated on; included in this category are patients with heart and respiratory problems. To the extent that the number of patients eligible for curative surgery expands, we should see improvements in survival rates.

Another change that has implications for survival improvements is the advent of new technologies, such as the CAT scan, for detecting metastatic activity. When such activity could not be detected, curative surgery failed, as the metastases inevitably resulted in death. In certain cases in which isolated metastases are now detected, however, their surgical excision may cure some patients, leading to improved survival.

The last change mentioned in our discussions that may account for some of the reported improvement in survival is the ability of the fiberoptic endoscope to detect recurrent disease early in its progression. The development of this instrument was considered by many panelists to be the most significant change in colon cancer management from 1950 to 1982. Its effect on the latest published survival rates is unclear, however, since some panelists thought that it was not until late in the period that a large number of physicians became skilled in its use From these findings we conclude the following:

- The divergent trends in incidence and mortality, combined with the changes in the management of the disease, suggest that there has been a real improvement in colon cancer survival rates.
- The absence of a therapeutic "breakthrough," the failure to detect disease earlier in its progression, and the continuingly significant number of patients for whom primary therapy fails suggest that the improvement is small.

Rectum Cancer

The changes in disease management for colon cancer and their implications for survival, as well as the conclusions arrived at for colon cancer, also apply to cancer of the rectum. The two changes noted for cancer of the rectum, however, suggest two additional conclusions for this disease.

- The advent and demonstrated effect of combined therapy, such as surgery with radiation and chemotherapy, are expected to improve the survival of some small, but significant, group of patients with cancer of the rectum. However, this therapeutic approach is too recent to have implications for the latest published survival rates.
- The new surgical procedures that allow some patients to retain their anal sphincters result in a considerable improvement in the quality of survival for these patients.

Endometrial Cancer

Overview

As described in the previous section on cervical cancer, the uterus consists of both the cervix and the uterine corpus. The uterine corpus is covered with a lining referred to as the "endometrium," where the vast majority of uterine tumors originate. To avoid confusion deriving from

the ambiguous term "uterine cancer," we employ the more specific term, "endometrial cancer."

Most endometrial cancers are carcinomas, and the overwhelming majority are adenocarcinomas. Other carcinomas that occur are adenosquamous and squamous. Less common are endometrial cancers showing characteristics of both sarcomas and carcinomas ("mesodermal mixed tumors"). Pure sarcomas may also occur in the endometrium.

Endometrial carcinomas are one of the most prevalent forms of cancer in the female reproductive organs. Two characteristics of the disease explain why approximately 90 percent of these tumors are diagnosed while still in stage 1: (1) Even early endometrial cancer often results in vaginal bleeding and (2) women are predominantly at risk following menopause, when bleeding would otherwise serve as a clear danger signal.

When the tumor is detected as early as stage 1, endometrial cancer is a highly curable disease, the percentage of survivors exceeding 90 percent Despite this good news, initial therapy fails for a small percentage of women (one estimate is 6 to 7 percent) and their diseases progress. This progression occurs with the invasion of surrounding tissues and organs and, eventually, metastasis to distant organs

The risk factors for endometrial cancer include obesity, hypertension, diabetes, and a history of menstrual irregularity. One other risk factor, estrogen, has been so strongly associated with elevated risk that the hormone, used as a treatment for hormonal imbalance, is now given with a progestational agent to reduce its carcinogenic potential.

Disease Trends

The incidence of endometrial carcinoma, using the broader category of cancer of the uterine corpus as an indicator, declined slightly between 1950 and 1982. Mortality rates also declined, but more sharply. Survival rates, consistent with the greater decline in mortality than in incidence, rose from approximately 72 to 87 percent.

The data on incidence, however, are questionable, for the reason mentioned in our discussion of disease trends for cervical cancer: women who have had hysterectomies are not at risk of developing this cancer. In light of this problem, the more appropriate denominator would be the total number of women who have retained their uteruses. In not accounting for the true population at risk, incidence rates would be

biased if there were changes over time in the percentage of women who had hysterectomies.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of endometrial cancer in table 3.6.

Table 3.6: Changes in the Management of Endometrial Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Earlier detection of the disease	Other Recognition of estrogen as a risk factor has led to closer monitoring of women who received estrogen therapy, which in turn has resulted in earlier disease detection	Real Since some of the women might have had their cancers diagnosed at a later stage had they not been monitored, survival might increase from these monitoring efforts, however, since 90 percent of women with disease are diagnosed early anyway, it is unlikely that the monitoring has led to dramatic survival rate improvement	None mentioned
Pretreatment evaluation	Improved ability to identify women who are at high risk for the failure of initial therapy	Other Recognition that a small percentage of women for whom initial therapy continually fails led to research that identified their characteristics	None One panelist stated that "We can now pretty well predict who will fail but we don't know what to do about it"	None mentioned
Treatment	Elimination of the radical hysterectomy as a surgical procedure for endometrial cancer	Other Realization that survival rates were equivalent with standard hysterectomy	None There is no assumption that the more-conservative procedure results in better survival rates	Reduced morbidity as a consequence of more-conservative surgery
	Adoption of combined modality therapy (surgery and radiation) as standard for treating early disease	Other Recognition that surgery and radiation improved survival over surgery or radiation alone	Unclear If widely adopted, this therapy would lead to real survival improvements, but the extent to which it has been adopted is unclear	None mentioned

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

There was sharp disagreement between the two panels that discussed endometrial cancer on the issue of whether survival rates have actually improved One group believed that there has been a real improvement and that is has resulted primarily from the combined use of surgery and radiation therapy to treat early disease. The other panel agreed that the combined use of surgery and radiation is the optimal treatment for early disease (although whether radiation should be administered prior to or following surgery remains in question) and should achieve impressive survival rates. They did not, however, believe that the potential of this therapeutic approach had been realized.

The general position the panelists took was that although most, if not all, patients with stage 1 endometrial cancer can be cured, treatment practice is highly varied and many patients continue to receive suboptimal therapies. The group members supporting the contention that survival has improved based this view on data collected at their own institution, which has uniformly adopted combined surgery and radiation treatment, and did not address the question of how widely this therapy is applied at other institutions. From these findings we conclude the following:

- A treatment regimen is available that has the ability to yield survival rates higher than those provided by the treatments used in 1950.
- The extent to which this treatment is applied has been questioned and, consequently, so has the improvement in survival rates. If the use of the treatment is widespread, the improvement is real; if only limited use of the treatment has been made, the improvement is artifactual.
- Improvements in the technology of radiation therapy have led to reductions in side effects associated with such therapy and, consequently, have led to improved quality of survival.

Head and Neck Cancers

Overview

The oral cavity is the point of entry into the body of all our food. It is also a point of contact for many carcinogens and, consequently, cancers arise in this region with some frequency. It is estimated that approximately 29,000 persons in the United States were diagnosed as having cancers of the oral cavity and pharynx in 1985.

These cancers are difficult to discuss for a number of reasons. One problem is that the terminology used to describe this class of diseases varies considerably. Besides "oral cavity," the terms "head and neck" and "buccal cavity" are also used to refer to the region. Each term refers to slightly different specific sites (for example, cancer of the eye is included in head and neck cancer but not in cancer of the oral or buccal cavity, whereas cancer of the tongue is included in all three terms), which makes comparisons of data series and research findings problematic. In our discussion, we use the term "head and neck cancer," a term more expansive than our focus, which is on cancer of the upper aerodigestive tract. The specific diseases we include are cancers of the

lip, tongue, cheek, roof of the mouth, floor of the mouth, nasopharynx, hypopharynx, and oropharynx.

Another problem in discussing these cancers is the diversity resulting from the abundance of specific primary sites. Although the overwhelming majority (approximately 90 percent) of cancers found in the head and neck are squamous-cell carcinomas, the natural histories, routes through which they spread, responsiveness to treatment, and prognoses vary considerably from one site to the next. For example, a tumor on the front part of the tongue differs considerably, because of a different pattern of invasion and operability, from a similar tumor on the back part of the tongue. Because of these differences, the statements that follow provide a general description of head and neck cancer rather than specific details applicable equally to all tumors of this region.

In theory, head and neck cancers should be relatively easy to detect, since much of the region is readily visible. The reality, however, is that many patients continue to be diagnosed only after the disease is advanced. The information we gathered suggests that unlike many other cancers, these tumors did not exhibit a general trend toward earlier detection from 1950 to 1982. This lack of earlier detection is partly accounted for by the relatively unique composition of the population that falls victim to these diseases

Two of the risk factors identified for head and neck cancer are tobacco and alcohol, which are thought to have a synergistic effect. It is not surprising that a significant number of head-and-neck cancer patients are individuals who consume both alcohol and tobacco at higher rates than the general public. According to our panels, the general disregard that these people display for their health serves as a major obstacle to earlier detection of head and neck tumors

Cancers of the head and neck generally progress by invading surrounding tissue and then metastasizing to the lymph nodes in the neck. The route through which they spread is varied, because of the bones in the area, which are typically circumvented by the tumors. From the "cervical," or neck, lymph nodes, the metastases eventually spread to distant organs. Therefore, the objectives of treatment for head and neck cancer are to achieve local control and to prevent them from spreading to the cervical lymph nodes. Unlike many other tumor types, for which preventing metastatic activity may be the primary goal, the local control of head and neck tumors is also critical, since the region plays an important role in many functions. That is, since eating and breathing are

essential for life, advanced cancers of this region that interfere with these activities can be lethal, even when there is no metastatic activity.

One additional aspect of these cancers deserves mention. Whereas the effects of treatment for many cancers, such as breast, lung, colon, and prostate cancers, can be "covered up," this is not true for head and neck cancers. The face, unlike other areas of the body, is clearly visible to everyone we meet and is generally not covered with clothing. This places an additional burden on the treating physicians to adopt therapies that will not disfigure their patients beyond a point that they are willing to accept.

Disease Trends

Because of the problems in terminology and the diversity of specific disease types in the category "head and neck cancer," providing accurate and specific information on trends for this disease is difficult. In general, incidence and mortality rates for head and neck cancers remained relatively stable from 1950 to 1982. Reported survival rates improved somewhat, moving from approximately 45 to 55 percent.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of head and neck cancer in table 3.7.

Table 3.7: Changes in the Management of Head and Neck Cancers[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Treatment	Increasing use of radiation therapy in combination with surgery for patients with locally advanced disease	Technological Improved radiation techniques and the recognition that adding radiation therapy to surgery improves local tumor control and lowers recurrence rates	Unclear The thought was that this new therapeutic approach was beneficial in that it reduced mortality from locally advanced disease, but at the same time the experts were not sure that it "cured" patients, and the extent to which this therapy was being used was also questioned	None mentioned
	Development of improved techniques for reconstructing and rehabilitating patients who have undergone surgery	Technological Development of improved techniques for the administration of therapy	Real These techniques allow surgery, which has curative potential, to be performed on patients who previously would not have been candidates because of the extreme disfigurement and disability caused by surgery	Significant improvement in the quality of life for patients undergoing surgery

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

According to our expert panels, important advances have been made in the management of head and neck cancers since 1950. Perhaps most

prominent among these advances has been the developments in radiation therapy that have contributed to both extended survival and an improved quality of life for patients. Advances in surgery have also been made. In addition, the use of prosthetics to reconstruct the facial area and the ability to maintain the vocal and swallowing functions following surgery have greatly improved the quality of survival. Despite these advances, however, the general sense of our panels was that there have been only marginal improvements in survival rates for patients with head and neck cancers.

A number of factors were cited as possible explanations for why, in light of the advances, there has been so little improvement in survival rates. One major obstacle was thought to be the fact that so many of the victims of these tumors do not seek medical attention early in the progression of the disease. Another problem mentioned was the relative lack of expertise of many physicians in dealing with head and neck cancer, which may be a consequence of the infrequency with which these tumors are encountered. For evidence of this problem, one panelist provided data showing that at major cancer centers, survival rates did in fact improve considerably between 1950 and 1986. Finally, the number of deaths caused by other diseases among head and neck cancer patients (including new cancer developing at other sites) was considered to be an important factor limiting the effect of the therapeutic advances. From these findings we conclude the following:

- There was, at best, only small improvement in patient survival for head and neck cancers from 1950 to 1982.
- Improved surgical and radiation techniques have resulted in considerable improvements in the quality of life for head and neck cancer patients.

The Leukemias

Overview

The word "leukemia" is derived from the Greek words for white ("leukeos") and blood ("haima") and is used to describe a disease first discovered in 1845 in which the victims had such high levels of white blood cells ("leukocytes") that their blood actually appeared white upon autopsy. Since that time, we have learned a great deal about this cancer of the blood, including the fact that the singular, "leukemia," is probably inappropriate, because many diseases are characterized by the

unrestricted proliferation of abnormal blood cells. Although these diseases share the characteristic of interfering with the critical functions performed by the blood, they differ in such important characteristics as rate of progression, types of blood cells affected, and responsiveness to treatment and prognosis.

The primary distinction between the leukemias is based on the rates at which they progress. The acute leukemias, if untreated, are rapidly and invariably fatal, causing death in a matter of months from their diagnosis. In contrast, the chronic leukemia victim can often live for a number of years before the disease results in death

Chronic and acute leukemias differ in other ways, such as in the age groups affected by the diseases. Whereas acute leukemia strikes at almost any age, including small children, the chronic disorders tend to be concentrated among the elderly (the average age of victims is about 60). Another important difference between the two diseases is that acute leukemias tend to be composed of poorly differentiated, immature cells, while chronic leukemias usually have cells that are fairly well differentiated and mature

The leukemias are further categorized by the type of cells displaying abnormalities. Employing this criterion, along with that of the rate of progression, yields the following disease types:

Acute leukemias

- Acute lymphocytic leukemia (ALL)
- Acute undifferentiated leukemia
- Acute differentiated myelogeneous leukemia
- Acute promyelocytic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia (AML)
- Acute erythroleukemia
- Acute megakaryoblastic leukemia

Chronic leukemias

- Chronic myelocytic or granulocytic leukemia (CML)
- Chronic lymphocytic leukemia

The complexity of the leukemias does not end (indeed, it only begins) here. Recent advances in histochemistry and cytogenetics demonstrate

that the surface chemistry and genetic composition of leukemic cells vary even within a single disease type. For example, current belief is that there are at least five different forms of ALL, each of which might merit consideration as a distinct disease type. Our intent, however, is to provide not a comprehensive review of everything that is currently known about the leukemias but, rather, a general overview. Toward this end, we focus our attention on the three general types of leukemia that occur with the greatest frequency: ALL, AML, and CML. Chronic lymphocytic leukemia is omitted from the discussion because evidence suggests that it is more accurately classified as a form of lymphoma.

ALL is the most common form of cancer among children, with a concentration of cases among children younger than 10 and a peak in incidence in children 2 to 4 years of age It is a rapidly progressing cancer; if untreated, it typically causes death by interfering with the body's ability to deal with infection and bleeding. The symptoms include pallor, fatigue, bone pain, bruising, and an inordinate number of infections or prolonged duration of infection. An initial diagnosis of leukemia can be rendered by the examination of a blood sample, a definitive diagnosis by a bone-marrow aspirate.

Treatment of childhood ALL is generally provided in two stages The induction stage involves high-dose combination chemotherapy, in which the goal is to achieve complete remission of the disease. This is followed by maintenance chemotherapy, the second stage, which is given on an outpatient basis over a number of years. In addition, since the involvement of the central nervous system is a danger in children suffering from ALL, the cranium is often irradiated to prevent such involvement. Complete remission can now be achieved through induction therapy in about 90 percent of cases. The problem that remains with the disease is in treating relapses effectively.

The most common form of leukemia among adults is AML. Similar to ALL, it is a rapidly progressing disease that inhibits the body's ability to fight infection. Because it strikes the cells that assist in the clotting of blood, it frequently results in bleeding and internal hemorrhages Treatment is generally similar to ALL, although it adds a consolidation phase involving moderate doses of chemotherapy following the high-dose induction phase. The complete remission rate for adults with AML is lower than that for adults with ALL and, consequently, the prognosis for the disease is poorer.

Approximately 1 of every 5 leukemia patients is afflicted with CML. The disease strikes ages 40 to 55 with the greatest frequency. Symptoms of CML, like the disease itself, develop slowly and include weight loss, fever, and fatigue. The danger from CML occurs during the transition from its chronic phase to an acute "blast crisis"—that is, bone-marrow failure. During the blast crisis, symptoms include increased frequency of infection and abnormal levels of bruising and bleeding. Treatment of CML includes maintenance therapy, usually in the form of chemotherapy or radiation, and bone marrow transplants. The transplants are the most effective if carried out while the patient is in the chronic phase of the disease. This procedure involves identification of a suitable donor, radiation to kill the bone marrow of the recipient, and the actual transplantation. It is dangerous, and not all patients are eligible, for reasons that are described in the survival discussion.

Risk factors for the leukemias have been studied extensively. Among the factors implicated most strongly as increasing an individual's risk are radiation, benzene, and certain chemotherapeutic agents used in the treatment of other cancers. Although certain viruses have been shown to cause leukemia in some animals, no causal link between viruses and the vast majority of human leukemias has been established.

Disease Trends

The incidence of leukemias increased slightly for males from 1950 to 1970 and remained stable for females. From 1974 to 1983, however, there was a decrease in incidence in all categories (white males, white females, black males, and black females). Consistent with a decreasing mortality rate between 1950 and 1982, survival rates improved. Whereas a little less than 10 percent of leukemia patients lived for 5 years in 1950, by 1982 this figure had climbed to close to 30 percent.

Caution should be exercised in interpreting these numbers, because they combine diseases with different patterns. For example, despite the overall decrease in leukemias recently, some of the experts who participated in the study believed that incidence data may be biased because of changes in detection practices for the chronic leukemias.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of the leukemias in table 3.8.

Table 3.8: Changes in the Management of the Leukemias[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Chronic leukemias are being detected earlier	Other Increased frequency with which blood tests are performed has led to more coincidental diagnoses	None The one therapy with curative potential for chronic leukemia, bone-marrow transplantation, is more effective the earlier it is performed, but this therapy is too recent to have affected the latest published rates	None mentioned
Pretreatment evaluation	Improved categorization of diseases under the term "leukemia"	Technological Advances in histochemistry and cytogenetics have allowed for a more precise distinction between disease types and subtypes	Real Improved ability to categorize diseases has led to better targeting of therapeutic interventions	Improved understanding of the differences between leukemias promises a better understanding of disease etiology
	Greater understanding of prognostic factors	Other Findings from the numerous clinical trials and research protocols have provided insight into which patients are likely to respond or not respond to therapies	None Although patients who will not respond to available therapies can now be identified, little can be done to help them	None mentioned
Treatment	Development of chemotherapeutic regimens	Technological Identification of a variety of cytotoxic agents that are effective in achieving remission of disease	Real The multiphase regimens have been proven effective in the treatment of acute leukemias and have actually achieved cures in many cases	None mentioned
	Development of allogeneic bone transplantation	Technological Improved radiation technology, blood support, and understanding of immunological processes have made the procedure possible	None The procedure has been proven effective in the treatment of chronic leukemias and acute leukemias that fail initial therapy, however, transplantation is suitable for only a very small percentage of leukemia patients and is performed too infrequently to have affected the latest published survival rates	None mentioned

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

All the participants in the leukemia discussions believed that there was a real improvement in patient survival from 1950 to 1982. This improvement, though, was not considered to be uniform for all diseases included in the category "leukemia." Survival rates increased most dramatically for childhood ALL, which was transformed from an invariably fatal disease to one in which cures can be achieved in a majority of cases. Although precise figures were not cited, the panels believed that the overall 5-year survival rate of 40 percent cited for acute leukemias was probably too low for children with ALL but overestimated the survival of adults suffering from the acute leukemias. Nonetheless, even for adults, the improvement in survival was considered to be real.

These survival improvements in the acute leukemias came primarily as a result of the introduction of chemotherapeutic regimens. The gains have been greater for childhood diseases for two reasons: the complete remission rates from the induction phase of therapy are considerably greater for children than for adults, and adults tend to relapse at higher rates than children.

With respect to the chronic leukemias, it is unclear whether there has been any real increase in survival rates. The one curative therapy for these diseases, bone-marrow transplantation, was not considered to have had a major effect because the procedure is suitable for only a small segment of the population of chronic leukemia patients—those under the age of 50 who have suitable donors. From these findings, we conclude the following:

- There was a real improvement in survival rates for the leukemias from 1950 to 1982.
- The improvement was greatest and the most dramatic for childhood victims with ALL.
- There was improvement, although more modest, for adults suffering from acute leukemias.
- The improvements in survival came primarily as a result of the advent of effective chemotherapy.
- It is unclear whether any survival gains occurred for the chronic forms of leukemia.

Lung Cancer

Overview

Of all cancers, those of the lung are by far the most prevalent. In 1985, approximately 144,000 new cases of lung cancer were diagnosed in the United States, and roughly 126,000 deaths were caused by the disease. Similar to cancers that strike many other organs, tumors of the lung are not homogeneous; there are a dozen or more variants. Many are relatively rare, more than 90 percent of all cases accounted for by the four most prevalent diseases:

- adenocarcinoma (ADC),
- large-cell carcinoma (LCC),
- small-cell (or "oat-cell") carcinoma (SCC), and
- squamous-cell carcinoma (SQC)

We restrict the discussion to these four types of lung cancer.

Although the exact developmental path taken by lung cancers is not well understood, we do know some things about the progression of these diseases. Both squamous-cell and small-cell cancers tend to arise in central locations, while adenocarcinomas and large-cell carcinomas usually occur in peripheral regions of the lungs Squamous-cell carcinoma is thought to be preceded by many years of premalignant changes in the lining of the lungs; small-cell carcinoma grows so rapidly that few patients are discovered before symptoms develop. All four cancers can metastasize, although they do so at seemingly different rates and to different locations. Squamous-cell tumors display the least metastatic activity of the four cancers and, when metastases occur, frequent locations of such activity are the regional lymph nodes and bone. Adenocarcinomas and large-cell cancers metastasize regularly and attack the brain, liver, and bone marrow, among other sites. Small-cell cancers seem the most virulent of all lung tumors in terms of metastatic potential.

The early symptoms of lung cancers may include persistent cough, blood in the sputum, and chronic chest pain. Unfortunately, most tumors remain asymptomatic throughout their developmental stages, so that by the time symptoms appear, the patients are often found to have advanced, incurable disease. Less than half the patients with lung cancer are diagnosed sufficiently early to allow for surgery.

The initial detection of lung cancer most often occurs by a chest x-ray Other diagnostic procedures include the examination of the sputum to see if malignant cells are present (sputum cytology) and visual inspection through bronchoscopy or thoracoscopy. The objectives of these procedures are to determine (1) the type of tumor present, (2) the exact location of the tumor, and (3) the extent and location of metastatic activity. These pieces of information are critical in formulating a treatment plan. The tumor type has to be known, since small-cell carcinoma is the only one for which chemotherapy has been shown to have curative potential. For the three other cancers, surgery is the only treatment that offers any real hope of cure, and information is required on the extent of the tumor to determine if surgery is possible.

Exposure to a number of environmental factors such as air pollutants, radiation, radon, and asbestos increases an individual's risk of getting lung cancer However, all identified risk factors pale by comparison with the dangers posed by cigarette smoking. Although debate still goes

on, the surgeon general of the United States has stated that cigarette smoking causes lung cancer.

Disease Trends

In the twentieth century, the United States has experienced what can be best described as an epidemic of lung cancer. Until very recently, the incidence and mortality rates have risen steadily every year. The magnitude of this increase is apparent when one considers that in 1912, only 374 cases of lung cancer were identified through a review of the world literature, whereas now more than 100,000 deaths result from the disease annually in the United States. In the 1970's, the death rate rose by 50 percent for men and 260 percent for women. The only hopeful sign for the incidence of lung cancer has come recently, with the first decrease in the number of men getting the disease. For women, however, the incidence continues to increase steadily. These divergent trends have been explained by differences in smoking habits, men cutting back and women continuing to smoke. Reported survival rates improved between 1950 and 1982, but even by 1982, only about 1 of every 9 lung cancer patients was expected to survive for 5 years.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of lung cancer in table 3.9.

Table 3.9: Changes in the Management of Lung Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Earlier detection of tumors, especially for ADC, LCC, and SQC	Other More people having more frequent contact with physicians	Unclear Earlier detection should have improved survival for surgically curable cancers, but experts are not sure that this trend is strong enough to have significantly affected survival rates	None mentioned
Pretreatment evaluation	More accurate classification of patients into stages	Technological and attitudinal New technologies have improved the ability to detect distant metastases, physicians have also become increasingly aware of the importance of identifying the correct stages of patients	Artifactual More precision in classifying patients results in survival improvements stage by stage as a result of stage-migration bias, this form of bias does not affect survival rates for all patients combined	Improved ability to accurately identify patients with metastases, for whom surgery cannot be effective, should improve their quality of survival by avoiding morbid and inevitably futile treatments
Treatment	More-aggressive radiation therapy for ADC, LCC, and SQC patients	Other Results of clinical trials have shown radiation therapy effective in extending survival for some patients	Real Since radiation can cure a small group of patients who would have died without such therapy, overall survival rates should have improved slightly	None mentioned
	Surgery performed on patients who were formerly considered ineligible for surgery	Technological Improvements in surgical techniques and support mechanisms	Real Survival should have improved as a result of curing some patients with surgery, primarily those with stage 3 nonsmall-cell cancers	None mentioned
	The availability of chemotherapeutic treatment regimens for SCC patients	Other Clinical trial results have shown that chemotherapy has curative potential for SCC	Real By achieving 5-year survival for approximately 10 percent of SCC patients, all of whom would have probably died of their disease, overall survival should have increased	None mentioned

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

Both groups with whom we discussed lung cancer believed that there was a real improvement in patient survival between 1950 and 1982. The major advances contributing to this improvement, however, came for specific subsets of lung cancer patients. Perhaps the most dramatic was the advent of chemotherapeutic regimens for victims of small-cell carcinoma. Whereas this disease was invariably fatal in 1950, by 1982, about 8 to 10 percent of small-cell cancer patients lived for 5 years. Improvements in surgical techniques also occurred, expanding the pool of patients whose tumors are considered operable. These improvements have had the greatest relevance for patients with the three nonsmall-cell cancer types, primarily those with extensive, nonmetastatic, stage 3 disease. Other changes in disease management include a trend toward earlier detection and more aggressive and effective radiation therapy.

In evaluating these changes, it must be remembered that the overwhelming majority of lung cancer patients die of their diseases within a relatively short time. This is because the improvements have been relevant for only small subsets of the total lung cancer population. For example, the chemotherapy cures for small-cell cancer affect only about one and a half percent of the total lung cancer population (that is, 15 percent of all lung cancer patients have small-cell cancer, and within this group, only 10 percent are cured by chemotherapy). It should be mentioned that given the large number of people with lung cancer, these small percentages can translate into significant numbers in absolute terms: 1.5 percent of 125,000 means that more than 1,800 lung cancer patients live 5 years after diagnosis. Finally, some of the experts expressed the belief that current care is not optimal in that, even with the available treatment technologies, survival rates could be higher if these treatments were applied more appropriately. From these findings we conclude the following:

- There has been a real improvement in survival for selected groups of lung cancer patients.
- Even within the groups that have benefited from changes in the management of lung cancer, the majority of patients die of their diseases.
- Improved procedures for classifying patients in stages have allowed us to avoid inevitably futile surgery for specific patients, thereby improving their quality of survival.

We would be remiss if we did not add a postscript to this review of lung cancer. Both the panels on lung cancer and those discussing other cancer types strongly urged that some action be taken to curtail cigarette smoking. As one panelist stated,

"Until we start to do something about [smoking] in this perhaps most preventable of all malignancies, [we] will have to chip away a percentage point at a time But it is something that could be done better by a comprehensive anti-smoking policy."

Non-Hodgkin's Lymphoma

Overview

The lymphatic system is an integral component of the body's ability to identify and destroy infectious and other foreign agents. It does so by producing special cells that attack intruders. These cells circulate

around the body in a clear fluid ("lymph"), which travels in specially designated vessels. Interspersed along the path of these vessels, which are to lymph what veins and arteries are to blood, lie small glands ("lymph nodes") that serve as filters to remove impurities from the lymph. One manifestation of the lymphatic system at work that we are all familiar with is the feeling of "swollen glands" (which are actually lymph nodes) that we may have in our necks during illness.

Cancers of the lymphatic system are known as "lymphomas" and they constitute a heterogeneous group of diseases. One form of lymphoma, Hodgkin's disease, is considered sufficiently different to be dealt with separately in the presentation of incidence, mortality, and survival statistics, and it is excluded from the discussion that follows The remaining lymphomas are referred to by the somewhat clumsy term "non-Hodgkin's lymphomas" (NHL).

The categorization of non-Hodgkin's lymphomas has changed considerably in recent decades. The traditional categories of lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma have been generally abandoned The most widely used taxonomy, proposed in 1956 and modified in 1966, is known as the "Rappaport classification." Although this schema is widely accepted, it is already somewhat outdated and is increasingly being replaced by a taxonomy known as the "working formulation." The Rappaport classification does serve, however, to show how varied the class "NHL" really is.

Rappaport classification of NHL

- Nodular lymphocytic well-differentiated lymphoma
- Nodular lymphocytic poorly differentiated lymphoma
- Nodular histiocytic lymphoma
- Nodular mixed histiocytic-lymphocytic lymphoma
- Diffuse lymphocytic well-differentiated lymphoma
- Diffuse lymphocytic poorly differentiated lymphoma
- Diffuse histiocytic lymphoma
- Diffuse undifferentiated (non-Burkitt) lymphoma

As can be seen, the lymphomas are classified by employing three dimensions: pattern of involvement (nodular or diffuse), cellular type (lymphocyte, histiocyte, or mixed), and cell grade (well, poorly, or undifferentiated). The differences between the various NHLs are significant in that they have implications for disease progression, responsiveness to treatment, and, consequently, for both prognosis and survival.

Unlike Hodgkin's disease, which usually involves an orderly disease progression, NHL does not spread in a regular pattern. NHL tumors, composed of congregations of malignant lymphatic cells, can appear initially almost anywhere in the body. Furthermore, the irregular disease progression (or, more to the point, the current lack of understanding of its progression) presents problems for diagnosticians, who often disagree in distinguishing one type of NHL from another, in determining whether a tumor is an NHL or a carcinoma, and even in classifying cells as malignant or benign.

NHL patients usually have advanced disease at the time of diagnosis This does not present the problem that it does with the carcinomas in that, unlike carcinomas, NHL is often curable at an advanced stage. However, as with carcinomas, the prognosis is better for patients in the earlier stages of the disease.

Both radiation and chemotherapy demonstrate potential for curing NHL Their effectiveness varies, depending upon the disease type and stage, and, in light of the differences within NHL, considerable expertise is required to determine the most effective treatment. Surgery plays a relatively minor role in the management of NHL compared to carcinomas.

A number of factors, including occupational exposures, radiation, diet, and infectious agents, have been explored as potential risk factors for NHL, but no definitive causal relationship has been established. Problems with the immune system, either congenital or drug- or disease-induced, do increase the risks for getting some forms of NHL. In addition, age is associated with NHL in that a considerable number of patients are children and young adults, although the relationship is not as clear as it is with most of the carcinomas.

Disease Trends

The incidence of NHL increased in the United States from 1950 to 1982, the greatest increases occurring among black females, among whom the incidence rate almost doubled from 1974 to 1983. Mortality rates also increased, although the rise was less than for incidence rates. Consistent with the different rates of increase in incidence and mortality, survival rates improved. Whereas less than one third of NHL patients in 1950 lived for 5 years, by 1982, nearly half lived that long from the time of diagnosis.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of non-Hodgkin's lymphoma in table 3.10.

Table 3.10: Changes in the Management of Non-Hodgkin's Lymphoma[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Pretreatment evaluation	More precise classification	Other Better understanding of cellular basis of disease origin	Real With an understanding of which disease types within specific patient types have poor prognoses, physicians can adopt aggressive therapies with curative potential, thereby extending survival	Knowledge of prognostic factors has allowed identification of the patients requiring less-aggressive therapies in order to survive, more conservative methods (for example, simply monitoring disease progression in some instances), improve the quality of survival by reducing morbidity associated with treatment
	Delineation of more prognostic factors	Other With more-precise classification, data more clearly indicate the notable prognostic factors	Real Same as above	Same as above
Treatment	The availability of combined radiation and chemotherapy	Technological Better radiation devices and the recognition that the two treatment modalities are more effective together than either is alone for some patients	Real Combined therapy has been demonstrated to improve survival in some patients	None mentioned
	Increasing use of chemotherapy in treatment	Technological Development of a set of chemotherapeutic agents with proven effectiveness	Real The new drugs have been demonstrated to have curative potential and their application should have extended the survival of patients	None mentioned

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

Both of our panels on NHL believed that there was a real and significant improvement in patient survival from 1950 to 1982 The changes listed in table 3.10 show that our understanding of these diseases has increased and that effective therapies were developed during this period. This is not to say that NHL has been conquered; it should be recognized that approximately half of NHL patients die of their disease. However, this is a considerable improvement over the time when many forms of NHL were invariably and rapidly fatal. From these findings we conclude the following:

- There was a real improvement in NHL patient survival from 1950 to 1982
- This improvement resulted from the combination of a better understanding of the diseases and the development of effective therapies

- Increased understanding has led to more appropriate treatment planning, which, in turn, has improved the quality of survival for some NHL patients.

Prostate Cancer

Overview

The prostate is the gland that produces the milky fluid that is part of semen. It is subject to a variety of conditions, including enlargement and both benign and malignant tumors. Prostatic cancer, typically adenocarcinoma, caused the deaths of approximately 26,000 men in the United States in 1985.

Because the prostate surrounds the urethra, the tube that carries urine from the bladder to the opening of the penis, the earliest symptoms of prostate cancer are often problems with urination, such as obstructed flow or frequency When such symptoms appear, physicians perform a digital rectal examination. In addition, when an obstruction of the urethra exists, either as a result of an obstructing cancer or because of other conditions, a "transurethral resection" is performed. This involves the insertion of an instrument into the urethra in order to remove enlarged prostate tissue, some of which may contain cancer, thus allowing an easier flow of urine. In the transurethral resection, a sample of cells is examined by a pathologist to determine whether malignant cells are present.

A study of 114 cases of prostate cancer conducted in 1888 revealed that the disease is rapidly fatal, survival from the time of diagnosis ranging from 3 months to a maximum of 5 years. Beginning in the early 1960's, however, one cancer center studied a group of prostate cancer patients for intervals ranging from 2 to 20 years and found that two thirds of them did not exhibit any signs of disease progression.

These seemingly contradictory data suggest that prostate cancer has two rather distinct manifestations. One form of the disease is fairly typical of most carcinomas in that malignant cells invade surrounding tissue, metastasize to regional lymph nodes, and eventually spread to distant organs, causing death. It is also clear that in other cases, the malignancy remains in a preclinical phase for such a lengthy time that the patient dies of other causes before a tumor becomes apparent

The existence of tumors that progress at different rates is certainly not unique to prostate cancer, nor are malignancies unique that can be characterized as essentially indolent. What is unique about prostate cancer is the prevalence of the indolent manifestation of the disease. It is estimated that the 26,000 men who die of the disease annually represent less than 1 percent of the population who have malignant cells in the gland. That large numbers of men who have prostate cancer may never show any symptoms of the disease has important implications for understanding survival rate trends. These implications are presented in the survival discussion for prostate cancer.

The primary risk factor for prostate cancer is age, the disease almost invariably occurring in males past the age of 60 and increasing in incidence steadily from that point. Race is also a risk factor, black Americans having the highest incidence rate of prostate cancer in the world.

Disease Trends

The incidence of prostate cancer increased steadily from 1950 to 1982 Overall mortality rates, despite an increase among blacks, have remained relatively stable. Consistent with these trends, survival rates have improved. The magnitude of the improvement, increasing from 43 to 71 percent, was the largest for all the carcinomas included in our review.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of prostate cancer in table 3.11.

Table 3.11: Changes in the Management of Prostate Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Disease detection	Earlier detection of the disease	Other A general increase in public contact with the health care system	Unclear Earlier detection should improve survival rates, since disease is more treatable in earlier stages, the trend toward earlier detection, however, also can result in artifactual increase through lead-time bias	None mentioned
Pretreatment evaluation	More precise classification of patients into stages[b]	Other Recognition that some patients in the early stages of cancer have excellent prognoses whereas others have poorer prognoses	Real Identifying patients with early disease who have poorer prognoses allows the adoption of more-aggressive therapies, improving the survival rates	Identifying patients with excellent prognoses, many of whom do not require treatment, avoids unnecessary treatment
	Better understanding of prognostic factors	Other Research findings demonstrated the utility of prostatic acid phosphatase and other factors for determining prognosis	Real Identifying patients with poorer prognoses allows the adoption of more-aggressive therapies, thereby improving the survival rates	Identifying patients who do not require treatment avoids unnecessary treatment
	Decreasing use of diethylstilbestrol (DES) as a form of hormonal therapy	Other Recognition that DES leads to cardiovascular complications	Real The lessened use of DES should have improved survival by decreasing the number of deaths caused by the treatment itself	None mentioned
	Increasing use of interstitial radiation therapy	Technological Development of improved techniques for the administration of this therapy	Real Since radiation has been shown to cure some patients, better delivery mechanisms that allow for greater employment of this therapy should have improved the survival rates of some patients	None mentioned
	Ability to retain potency for patients undergoing prostatectomy	Technological Development of a new surgical procedure	None The procedure is not assumed to improve survival over standard prostatectomy	By allowing surgical patients to remain potent, the procedure will improve the quality of their survival

[a]An explanation of the terms used in this table appears in appendix IV

[b]Stages for prostate cancer are A, B, C, and D

Survival Discussion

As one author states, "the problem of distinguishing facts from artifacts of data collection is constantly with us. This problem appears to be greater [for prostate cancer] than for most cancers."[7] A number of factors make the interpretation of survival rate trends especially difficult for this disease.

[7]P Greenwald, "Prostate," in D Schottenfeld and J F Fraumeni, Jr (eds), Cancer Epidemiology and Prevention (Philadelphia W. B Saunders Co , 1982), p 939

One problem is the inappropriateness of the most commonly reported interval for survival rates, 5 years. A study by the Veterans Administration showed that untreated stage B prostate cancer patients had a median survival of 7.7 years. This and the even longer survival for untreated stage A patients make the utility of a 5-year interval for detecting changes in survival questionable. Another study of patients with cancerous lymph nodes who had survived for 5 years showed that it is impossible to determine whether survival is a benefit of treatment or a consequence of slow tumor progression.

The major problem with determining how "real" the reported improvements in survival rates for this disease are is the prevalence of an indolent form of prostate cancer. If estimates of the prevalence of this disease come even close to being accurate, reported survival rate improvements are misleading. This is because in 1950, a large number of patients were diagnosed, from their symptoms, as having prostate cancer. Since many of these symptoms (for example, back pain, enlargement of the gland, and bleeding from the penis) occur when the cancer is relatively advanced, we could reasonably conclude that these patients had the more aggressive form of prostate cancer Since then, the contact of the general public with the health care community has increased, and many men are now diagnosed as having prostate cancer coincidentally (for example, during transurethral resections to widen the urethra, which gets narrower as a natural consequence of aging). Furthermore, given the prevalence of the indolent form of the disease, it is justifiable to conclude that a large percentage of these coincidentally diagnosed cases would have excellent 5-year prognoses, even if left untreated. Following this line of reasoning, the increasing number of cases of presymptomatic disease would improve 5-year survival rates, even without improvements in treatment. That this has, in fact, occurred is attested to by the steadily increasing incidence rates and the relatively stable mortality rates.

Nonetheless, as table 3.11 indicates, some changes were thought by our panels to have led to actual improvements in survival rates. From these findings, we conclude the following:

- There was real improvement in prostate cancer patient survival from 1950 to 1982.
- The improvement was primarily because of an increased understanding of which patients would benefit from more aggressive therapies.
- A large percentage, if not most, of the reported improvement resulted from length-time bias.

- The ability to identify patients who have excellent prognoses with greater certainty has allowed for a more conservative therapeutic approach, thereby reducing the side effects associated with treatment.

Stomach Cancer

Overview

The stomach is the organ that lies between the esophagus and the small intestine and is the first stop for food as it moves through the digestive system. Stomach, or "gastric," cancers usually arise in its lining and are therefore classified as carcinomas. As in carcinomas that affect other organs, it is believed that the normal epithelial cells constituting the stomach lining undergo a series of changes in their progression to malignant cells; some believe that this progression may take as long as 20 years. The intermediary points in this movement from normal to malignant cells manifest themselves as cells of varying degrees of dysplasia, or abnormality. Relatively little is known of the natural history of stomach dysplasia and, consequently, no consensus exists on how to manage this condition.

A major problem with gastric carcinoma is that the disease may remain asymptomatic until it is advanced. In addition, many of the early symptoms—indigestion, belching, and loss of appetite—are also symptoms of minor digestive problems and so are easily overlooked. Because of this, the disease is rarely detected in its earliest stages and almost two thirds of the diagnosed cases have advanced beyond the point at which curative surgery can be performed

Gastric carcinoma progresses by moving into and through the stomach wall to adjacent organs and eventually metastasizes to distant organs. As with other cancers, the further the tumor is along in the progression, the poorer the prognosis is for the patient However, unlike some cancers (for example, breast and bladder cancers) even localized gastric cancer may be too far advanced to be successfully treated by surgery.

Risk factors for the disease include digestive disorders, heredity, sex (males are twice as likely to develop gastric cancer), and dietary habits. The latter category is not well understood, but studies suggest that high intake of salt and complex carbohydrates may contribute to the development of the disease.

Disease Trends

In 1930, gastric cancer was the leading cause of cancer deaths among men in the United States and ranked third as a cause of cancer mortality for women. Since then, both incidence and mortality rates have dropped precipitously and in parallel. Survival rates have improved only slightly, increasing from approximately 12 percent to a little more than 15 percent. This improvement, although small, is inconsistent with the parallel incidence and mortality trends.

Changes in Disease Management

We summarize our findings on the major changes that have occurred in the management of stomach cancer in table 3.12.

Table 3.12: Changes in the Management of Stomach Cancer[a]

Area	Change	Reason for change	Consequences for survival	Other consequences
Treatment	Less aggressive surgery for patients with advanced disease	Attitudinal Recognition that aggressive surgery did not improve survival but was associated with considerable morbidity	None Less-aggressive surgery will not improve survival but will simply reduce morbidity	Improved quality of survival for patients as a result of reduced morbidity
	Advent of chemotherapeutic regimens	Technological Studies demonstrated that chemotherapy has benefits as palliative treatment	None In latest studies, the survival increment associated with chemotherapy was minimal (6-8 week improvement, on the average)	Improved ability to relieve patients with advanced, incurable disease has improved the quality of their survival

[a]An explanation of the terms used in this table appears in appendix IV

Survival Discussion

As table 3.12 shows, none of the advances have been effective in extending gastric cancer patient survival; they have only improved the quality of survival for victims of the disease In addition, the parallel decline of incidence and mortality rates and the small change in patient survival rates from 1950 to 1982 leads us to conclude the following:

- There was no improvement in gastric cancer patient survival rates from 1950 to 1982
- Changes have taken place in the management of this disease that have improved the quality of patient survival.

Has Progress Been Made?

Introduction

To determine whether progress has been made in extending cancer patient survival, we focused on a statistic often used as an indicator of progress, the survival rate, and addressed a number of specific questions:

- How accurate are the survival rates published by NCI?
- What do survival rates actually measure? (That is, How meaningful are survival rates?)
- What measurement problems limit our ability to interpret changes in survival rates over time?
- Did survival rates improve from 1950 to 1982 for specific types of cancer?
- Where improvements in survival rates occurred, what factors can best account for them?

In this chapter, we review our principal findings for the 5 questions before turning our attention to the issue of progress.

Summary of Findings

The first 3 questions explore various aspects of cancer survival rates—accuracy, meaningfulness, and interpretability— that speak to their utility as indicators of progress. With respect to accuracy, we determined that survival rates generated since the introduction of the SEER program in 1972 seem more accurate than rates derived from previous data collection efforts. However, apart from this seeming improvement in accuracy, survival rates provide only limited information on progress These rates measure a relatively narrow aspect of survival, the percentage of cancer patients living for a specified interval, and provide little insight into how long, or how well, they survive.

The more significant limitation on survival rates as measures of progress is that changes in rates over time are extremely difficult to interpret because of several forms of bias. These biases, discussed in the concluding section of chapter 2, result from changes in how and when cancers are detected and make it difficult to determine whether a reported improvement is real or illusionary.

In light of the various forms of bias, determining whether survival rates have actually improved cannot be accomplished by simply comparing the published rates for two different times. Rather, this requires a detailed examination of changes in detection, pretreatment evaluation, and treatment practices; potential sources of measurement bias; and incidence and mortality trends. We conducted such an examination for

12 types of cancer and a summary of our findings is displayed in table 4.1. In presenting these findings we use four different terms to characterize the extent of progress: (1) "dramatic" is used to refer to improvements that have transformed invariably fatal cancers to cancers that in a significant percentage of patients can be cured; (2) "moderate" is used for cancers in which changes in disease management occurred that can extend survival and that are relevant to a significant number of patients; (3) "slight" improvement serves as our conclusion when either there were only modest changes in patient management or the changes were only relevant to discrete subpopulations of patients; (4) "no improvement" is used in the one case in which there were no changes in detection or treatment with the potential to extend survival and the reported improvement was inconsistent with parallel declines in incidence and mortality from 1950 to 1982.

Table 4.1: Survival Trends by Cancer Type

Cancer type	Reported 5-year survival rate[a] 1950	1982	Factors for consideration: Survival	Bias	Treatment	GAO conclusions
Bladder	53%	77 3%	Improvements consistent with increasing incidence and decreasing mortality rates	Length-time bias resulting from inclusion of papillary carcinomas	Increasing use of cystectomy, tracking of high-risk patients, improved staging, use of combined modality therapy for advanced disease, and earlier disease detection considered to have improved patient survival	There was moderate improvement in patient survival
Breast	60	74 6	Improvements consistent with increasing incidence and stable mortality, although incidence rates unreliable	Both lead-time and length-time bias	Therapeutic breakthroughs too recent to have significantly affected survival	There was slight improvement in survival, the improvement is considerably less than that reported
Cervical	59	67 4	Problems with incidence and mortality data make it difficult to determine whether data are consistent with reported improvement	With earlier detection, lead-time bias possible	Earlier disease detection credited with improving patient survival, treatment improvement considered relevant for only small segment of patient population	There was slight improvement in survival
Colorectal colon	41	52 8	Improvements consistent with rising incidence and stable mortality rates	None	None, although improvements in support mechanisms for surgery occurred	There was slight improvement in survival
Colorectal rectum	40	49 7	Improvements consistent with stable incidence and decreasing mortality	None	Increasing use of radiation and chemotherapy in combination as adjuvants for surgery too recent to have improved survival	There was slight improvement in survival
Endometrial	72	87 1	Improvements consistent with sharper decline in mortality than in incidence rates, although incidence data are biased	None	Extent to which combined modality therapy adopted and its contribution to extending survival are unknown, earlier detection has benefitted a small segment of the patient population	If the new therapy was widely adopted, there was moderate improvement in survival, if not adopted, there was no improvement

Cancer type	Reported 5-year survival rate[a]		Factors for consideration			GAO conclusions
	1950	1982	Survival	Bias	Treatment	
Head and neck	45	54 3[b]	Improvements inconsistent with stable incidence and mortality rates	None	Improvements in surgical procedures have expanded pool of patients eligible for surgery	There was slight improvement in survival
The leukemias	10	33	Improvements consistent with decreasing mortality rate, incidence slightly increased early in period and showed decline following 1974	None	Advent of chemotherapy for acute leukemias improved patient survival	There was dramatic improvement in survival for the acute leukemias, for the chronic leukemias, there was only slight, or no, improvement
Lung	6	11 6	Survival rate improvement inconsistent with approximately equivalent increases in incidence and mortality rates	Stage-migration bias shown to exist but is not relevant for examining survival trends for all patients combined	Development of chemotherapy for small-cell lung cancer patients has improved survival	There was slight improvement in survival for small-cell carcinoma patients but no change for other patients
Non Hodgkin's lymphoma	31[c]	48 1	Improvements consistent with slower increases in mortality rates in incidence rates	None	Better understanding of NHL, the advent of effective chemotherapy, and the use of radiation in combination with chemotherapy have improved patient survival	There was dramatic improvement in patient survival
Prostate	43	71 1	Improvements consistent with increasing incidence rate and stable mortality rate	Length-time bias exists	A better understanding of risk factors has allowed for improved targeting of therapies, increased use of interstitial radiation has also led to survival gains	There was moderate improvement in survival, however, the improvement is considerably less than that reported
Stomach	12	15 7	Improvements inconsistent with equivalently sharp decrease in incidence and mortality rates	None	None	There was no improvement in patient survival

[a]To allow appropriate comparisons, we have presented rates for whites only since other reporting categories changed over time

[b]1960 rates are used because those for 1950 are provided only on a site-specific basis (lip, tongue, floor of mouth)

[c]Rates used are those for 1960 because the 1950 rates are in categories no longer used to classify NHL

As can be seen from table 4.1, our findings concerning survival rate improvement vary considerably by cancer type. Despite this variation, some general conclusions can be drawn:

- Of the 12 cancers examined, a conclusive statement that survival has not improved can be made only for stomach cancer.

- For the majority of the cancers we examined, the actual improvements have been small or have been overestimated by the published rates.
- In cancers where survival improvements have taken place, there remain distinct groups of patients who have not benefited from those improvements.

With respect to the factors that are the most responsible for the survival gains, we conclude the following:

- Advances in radiation technology and refinements in surgical techniques contributed significantly to the improvement in survival. Surgery and radiation both existed in 1950.
- The advent of chemotherapy, which was not widely used in 1950, has also contributed to survival rate improvements for some cancers, primarily leukemia and non-Hodgkin's lymphoma.
- The newer therapeutic approaches, primarily immunotherapy, had not by 1982 made any significant contribution to extending survival.
- A host of factors, including more precise categorization of patients, greater understanding of disease progression, improved radiation technologies, and more appropriate surgery, have led to improvements in the quality of survival for cancer patients.

Three additional findings should be mentioned, given the evidence presented by the expert panels. It appears that survival rates could be significantly improved if available diagnostic and treatment procedures were applied more appropriately by a larger number of physicians, and survival rates could be improved, and mortality reduced, if more cancers were detected earlier. Although earlier disease detection did occur for many of the cancers we examined, for some cancers (for example, cervical cancer), relatively easy detection procedures are not universally applied. Finally, many experts emphasized that some way of reducing cigarette consumption must be found if cancer's effect on society is to be reduced in the near future.

Cancer Progress: Two Perspectives

The answer to the question of whether real progress has been made in extending patient survival depends almost entirely on how the term "progress" is defined. Two different definitions are offered below.

1. Absolute. One way to define the question of whether progress has been made is to ask whether more lives were saved or extended in 1982 than in 1950. Using this perspective, we must unequivocally conclude that progress has been made. Evidence is provided by the examples of

the acute leukemias and many non-Hodgkin's lymphomas. For both diseases, which were almost invariably fatal in 1950, cures are now possible for many patients. Since there are no cancer types for which anyone believes fewer people are surviving for 5 years, the improvements in leukemia and non-Hodgkins lymphoma necessarily result in more lives being extended for cancer as a whole.

2. Relative. The absolute perspective suffers from its failure to provide us with any real-world context. In other words, if the increment in survival resulted in 10,000 additional lives being extended, our belief about the merits of this accomplishment would be strongly influenced by how many people had the disease—saving 10,000 of 20,000 victims is clearly more remarkable than saving 10,000 of 1 million victims.

This difficulty could be overcome by constructing a ratio of percentage survival in 1982 to percentage survival in 1950. Unfortunately, in light of the methodological problems with the reported survival rates, it is not possible to construct this ratio so that it is empirically valid. Alternatively, we can use the findings from our review of specific cancer types to approximate the ratio. Reviewing the relevant conclusions from chapter 3, we see that major survival gains have been accomplished for only 2 of the 12 cancer types, leukemia and non-Hodgkin's lymphoma, which constitute only a small percentage of all cancer cases. For lung, colon, rectum, and breast cancer (the most prevalent malignancies), gains in survival have been only modest. The result is that the dramatic improvements in leukemia and NHL are muted by the overwhelming prevalence of the other cancers. From this perspective, it is difficult to find that there has been much progress, but it is also impossible to say that there has been none.

Because of these differing perspectives, we cannot provide a single, definitive answer to the question of whether progress has been made against cancer. Doing so would require us to say that one perspective was more legitimate than the others, a judgment that is necessarily subjective. What we have done, instead, is to provide comprehensive descriptions of the advances in extending patient survival for the most prevalent forms of cancer and to indicate the methodological pitfalls in interpreting changes in survival rates. Armed with this information, readers must select the perspective that they view as most appropriate and reach their own conclusions. Whichever perspective one adopts, it is clear that progress has been made in extending patient survival. However, it is also clear that the extent of progress appears greater from an absolute perspective.

Recommendation to the Secretary of Health and Human Services

Because of the methodological problems discussed in this report, the survival rates reported by NCI should not be used as the sole indicators of progress in extending patient survival. We recommend that the secretary of the Department of Health and Human Services include a description of the biases that can lead to misinterpretation of survival rate changes in all future publications on patient survival. In this way, misinterpretation of changes in survival rates can be minimized.

Agency Comments and Our Response

The Department of Health and Human Services concurred with our recommendation and will implement it in calendar year 1987. HHS also agreed with many of our conclusions, including that

- survival rates should not be used as sole indicators of progress in extending patient survival;
- earlier detection, improved case management, refinements in surgical procedures, new radiation therapy devices, and the advent of chemotherapy are the factors that most often account for the improvements noted;
- the quality of life for cancer patients has improved; and
- patient survival could be improved through better application of existing treatments.

However, HHS did express a number of general concerns with the report HHS believes that the absence of quantitative estimates could result in a biased reading of the report, our methodology has some weaknesses, and the tone of the report is unduly negative In addition, many of the comments HHS provided are critical of the scope of the study and imply that the focus on survival is overly narrow. After careful review of these four issues, we do not consider HHS's criticisms to be valid for the following reasons.

It is true that quantitative estimates of the magnitude of survival gains from 1950 to 1982 were not provided, and we agree that it would have been beneficial had we possessed the resources to provide them. Indeed, it is clear that, in some cases, the quantification of the effect of specific forms of bias for specific types of cancer (for example, of lead-time bias in breast cancer) is possible. However, this would not have been possible for all forms of bias, for many different forms of cancer, in the context of any single study. As HHS notes, even a study to determine the magnitude of improvement noted for one type of cancer (where all patients were enrolled in carefully controlled experimental situations) was very costly in agency resources.

During the planning phase of the project, when we realized that any attempt to provide quantitative estimates of the extent of bias or improvement in survival rates for a large number of cancer types was beyond the resources of any single effort, we explored a number of options. One was to restrict the focus of the project to a single type of cancer. This option was rejected because it would have done little to answer the congressional questions that sought to resolve a controversy that is general in nature. That is, by concluding that the actual improvement in breast cancer, for example, was 13 percent, we would not address the committee's concern about whether progress had been made in extending the survival of cancer patients in general.

Another option, also rejected, was to abandon the project. Had we believed that no useful information could be provided to illuminate the controversy, we would have stopped right there. However, we believed that a qualitative treatment of the issue was both feasible and worthwhile. That we were correct in this assessment is attested to by the comments of many of our independent reviewers, who think that the report will make a significant contribution by increasing the public's awareness of the issues in the controversy and will provide the committee with the most currently available answers to the questions that it posed in its request.

It is true that the lack of quantitative estimates may allow readers to make their own inferences about the extent of progress in survival. However, since readers of publications on cancer patient survival will now be alerted to the methodological problems presented in this report, these inferences can be made with the knowledge that the published rates often overestimate the extent of true progress. We believe that this situation is preferable to the one that existed prior to this report.

HHS's concerns with our methodology are perhaps best reflected in the agency's characterization of our report as "opinion, not fact." To characterize the report in this way is inappropriate. Most of the information provided in the report is factual. The overviews of each of the 12 cancers, the discussions of incidence, mortality, and survival trends, and the potential of the various forms of measurement bias to cloud interpretation of changes in survival rates are only some of the types of factual information we have presented.

We used opinions to help in reaching our conclusions, but the opinions were not ours but, rather, those of leading experts in the fields of cancer research and treatment. More importantly, we did not simply translate

the opinions into conclusions. Rather, they were synthesized with the documentary evidence and empirical data according to an established set of decision rules.

Recognizing that tone is an important consideration in controversial areas, we asked each of the independent reviewers to specifically address the issue of whether the tone that we adopted in this report is both fair and objective. From their responses, the majority of which indicated that the tone is, in their estimation, appropriate, we must disagree with HHS on this issue. Evidence that our tone is fair is that, of the small number of reviewers who did not think so, some felt the tone to be too positive while others thought it was overly negative. (See page 20 for a description of our review process.)

Beyond this issue of fairness in tone, HHS is also concerned that the tone of the report may be "counterproductive, in that it can lead physicians and the public to feel that appropriate treatment is not important—that it does not make a difference in patient outcomes." We are not sure how the agency reached this conclusion. We have cited numerous instances of treatment advances that have led to real improvements in extending patient survival. We have also concluded that for most of the cancers we examined, improvements have taken place in the quality of life for patients as a result of advances that have been made since 1950. Most importantly, perhaps, is the recognition that the failure to make even greater gains in patient survival for many cancers can be attributed to the latest in detection and treatment technologies not having been widely adopted. Given our inclusion of these points in the discussions of specific diseases, the executive summary, and this chapter, we not only disagree with the agency's contention that our report could dissuade people from seeking or adopting appropriate treatment but also believe that it will have the opposite effect.

Finally, we do not disagree with HHS's contention that the report's focus on cancer patient survival ignores important advances in the area of cancer control. However, an evaluation of the extent of progress in all aspects of cancer—basic research, reducing incidence and mortality, and improving survival—is an undertaking beyond the resources of any single study. In addition, it is important to remember that of the three major empirical indicators of progress—incidence, mortality, and survival rates—the only indicator that improved since 1950 was the survival rate. Any implication that the focus of the report is somehow biased is, therefore, inappropriate.

In addition to these general comments, HHS had many technical comments that were extremely helpful in our revising the report. The full text of the agency's review is provided in appendix V along with our responses to each point raised in that review.

Survival Rate Computation

Survival rates are computed by using the "life table," or "actuarial," method. For each group of patients in each year of follow-up, a record is kept on the number of patients alive at the beginning of the interval, the number who died during the interval, the number alive at the close of the follow-up period, and the number lost to reporting during the interval. Groups are then combined by number of years of follow-up, and survival is calculated on accumulated cases over several follow-up periods. Table I.1 presents hypothetical data for 1,000 patients diagnosed between 1976 and 1981 and tracked until the end of 1981.

Table I.1: Hypothetical Survival Data for Cancer Patients Diagnosed From 1976 Through 1981 and Followed Up Through 1981

		Number of participants			
Year of diagnosis	Years after diagnosis	Alive at beginning of interval	Who died during interval	Lost to follow-up during interval	Withdrawn alive during inverval
1976	0-1	175	70	20	•
	1-2	85	5	•	•
	2-3	80	•	1	•
	3-4	79	1	•	•
	4-5	78	•	•	•
	5-6	78	•	•	78
1977	0-1	150	75	•	•
	1-2	75	10	5	•
	2-3	60	5	•	•
	3-4	55	5	•	•
	4-5	50	•	•	50
1978	0-1	150	65	•	•
	1-2	85	25	5	•
	2-3	55	5	•	•
	3-4	50	•	•	50
1979	0-1	175	75	•	•
	1-2	100	20	•	•
	2-3	80	•	2	78
1980	0-1	200	80	•	•
	1-2	120	4	•	116
1981	0-1	150	55	5	90

As can be seen from table I 1, not all the cases diagnosed in this interval were followed up for 5 years. One option for dealing with the data is to include in the calculation only cases that have been followed up a full 5 years; this is called the "direct" method The direct method has the drawback of excluding information that could be gained from cases with

partial follow-up data. Therefore, the actuarial, or life-table, method is generally used.

The actuarial method is considered more reliable than the direct method because all available information is used. The cases observed for fewer than 5 years are entered into the calculations as "withdrawn alive." The survival rate on withdrawn cases and cases lost to follow-up are assumed to be similar to the data on cases followed for the full observation period. Evidence of the superiority of the actuarial method can be demonstrated by the decreased standard error of the survival rates when computed by the actuarial, compared to the direct, method.[1]

In table I.2, we present the steps necessary for the computation of an observed 5-year survival rate that uses the hypothetical data in table I.1.

Table I.2: Hypothetical Survival Rate Computation for 1,000 Patients Diagnosed From 1976 to 1981 and Followed Up Through 1981

Years after diagnosis (1	Alive at beginning of interval (2)	Died during interval (3)	Lost to follow-up during interval (4)	Withdrawn alive during interval (5)	Exposed to the risk of dying[a] (6)	Proportion dying[b] (7)	Proportion surviving[c] (8)	Cumulative proportion surviving from diagnosis through end of interval[d] (9)
0-	1,000	420	25	90	942 5	0 45	0 55	0 55 (1-year survival)
1 2	465	64	10	116	402 0	0 16	0 84	0 46 (2-year survival)
2 3	275	10	3	78	234 5	0 04	0 96	0 44 (3-year survival)
3-4	184	6	0	50	159 0	0 04	0 96	0 43 (4-year survival)
4-5	128	0	0	50	103 0	0	1 00	0 43 (5-year survival)

[a]The values in this column are computed by subtracting from column 2 one half the sum of columns 4 and 5

[b]The values in this column are computed by dividing column 3 by column 6

[c]The values in this column are computed by subtracting column 7 from 1 0

[d]The values in this column are computed by multiplying the progressing values for survival by years in column 8 (for example, 0 55 x 0 84 = 0 46, 0 46 X 0 96 = 0 44, and so on)

[1]A standard error is a measure of confidence used to interpret statistical results The standard error indicates the extent to which a statistic can be influenced by data variation. When the standard error is added to and subtracted from the computed value, the resultant numbers provide a range within which the true value lies for a given probability level.

The "crude," or "observed," survival rate can be misleading because persons who died from causes other than cancer are included One way to compensate for this is to compute an adjusted survival rate that takes into account the specific cause of death for each case.

The calculation of an adjusted rate is not always possible, because information on the cause of death is not always available or is unreliable. Therefore, adjustments for other causes of death are usually made indirectly by computing a relative survival rate.

The relative survival rate is the ratio of the observed survival rate to the survival rate expected for a population similar to the patient group in terms of age, sex, and race but without the disease. The difference between the observed and relative survival rates can be substantial. For example, the observed 5-year survival rate for bladder cancer patients 75 years old or older is 32 percent, but the relative rate for the same group is 58 percent.[2]

In order to calculate expected survival, life tables published by the National Center for Health Statistics used to estimate the probability of survival for a person similar to each of the patients in the group in terms of age, sex, and race. The individual probabilities are then summed and an average for the group is computed.

It should be noted that although age is a variable in computing expected survival, additional age adjustments may be necessary when comparing the relative survival rates of groups with different age compositions. This is because some cancer prognoses are associated with the age of the patient, which would not be reflected in the expected rate.

[2]Adjustments can also be made for geographical area and other common characteristics Here, for simplification, only age, sex, and race are discussed

The Surveillance, Epidemiology, and End Results (SEER) Program

Twice a year, SEER receives information on incidence and follow-up for cancer patients from population-based cancer registries in the United States and Puerto Rico. Together, these registries cover 12 percent of the total population. Table II.1 shows the registries participating in the SEER program.

Table II.1: Seer Participants

Registry	Area covered	Year of entry	1980 area population
Connecticut	State	1973	3,108,800
Detroit, Michigan	3 counties	1973	4,039,374
Hawaii	State	1973	969,077
New Mexico	State	1973	1,307,273
Puerto Rico	Commonwealth	1973	3,196,520
San Francisco and Oakland, California	5 counties	1973	3,275,702
Utah	State	1973	1,473,083
Atlanta, Georgia	5 counties	1974	1,694,781
Iowa	State	1974	2,915,561
Seattle and Puget Sound, Washington	13 counties	1974	2,769,406

NCI maintains contracts with nonprofit, medically oriented organizations to consolidate and maintain a record on every cancer patient diagnosed in their areas. The data are submitted to NCI on computer tape, using a standardized format with all identifying information removed to insure confidentiality.

Cases are identified for SEER registries in a variety of ways. Death certificates are searched by all registries. In some states, the reporting of cancer cases is mandatory. Some of the larger hospitals maintain their own registries and submit the information to the SEER contractors. Alternatively, or in addition to these methods of identifying cases, registry field staff abstract cases from records at hospitals, private laboratories, nursing homes, and other sources.

Procedures used to ascertain patient survival also vary among the registries. Contractors are required to actively follow up all living patients. All registries review death certificates and hospital readmissions. Supplemental techniques for patient follow-up include written contact with the attending physician or the diagnostic related group records and Medicaid records. In addition, some registries have tried matching voter

registration or motor vehicle registration files. The registry in Puerto Rico goes so far as to conduct house-to-house interviews.

The selection of SEER participants was based in part on the desire to cover particular population subgroups. Table II.2 breaks down the SEER population by race. While the SEER population is not a probability sample of the country, some argue that the sample is representative of overall cancer patterns because of the wide geographical coverage and the proportion of ethnic minorities.

Table II.2: SEER Population by Race in 1980

Race	U.S. total	SEER total[a]	SEER percentage of U.S. total
White	195,170,670	24,307,769	12 4%
Black	26,897,581	3,166,427	11 7
American Indian	1,364,033	365,914	26 8
Chinese	812,769	261,086	32 1
Japanese	706,503	322,438	47 0
Filipino	781,063	298,253	38 1
Hispanic	14,608,673	1,749,485	11 9

[a]Excludes 3,196,520 people in Puerto Rico

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LUNG CANCER

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STOMACH CANCER

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Cancer Management Table Terms

1. Area. This column identifies the area in which the change occurred and uses the following terms:

- Disease detection describes tests or procedures relating to the detection of cancer.
- Pretreatment evaluation describes tests or procedures used to determine tumor histology, stage, grade, or patient prognosis.
- Treatment describes how patients are treated following diagnosis.

2. Change. The actual change is described in this column; no categories are used.

3. Reason for change. This column identifies the factors that allowed the change to occur: technological, attitudinal, and other.[1]

4. Consequences for survival. This column indicates whether the changes noted affected patient survival and categorized them as being

- real when the change actually extended survival,
- artifactual when the change improved survival rates simply by introducing of measurement bias,
- mixed when the change both improved actual survival and introduced bias, and
- unclear when the panels disagreed on the implications of the change for survival.

This column also uses the term none.

5. Other consequences. This column describes the effect of the change on other dimensions of interest (for example, improved quality of survival). The term none mentioned is used when the panelists did not indicate any other consequences.

[1]In one case, the term not determined is used in this column to indicate that a reason for the change was not discussed in the panel sessions

Comments From the Department of Health and Human Services

Note GAO comments supplementing those in the report text appear at the end of this appendix

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington D.C. 20201

DEC 1 1986

Mr. Richard L. Fogel
Assistant Comptroller General
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Fogel:

The Secretary asked that I respond to your request for the Department's comments on your draft report, "Cancer Patient Survival: What Progress Has Been Made?" The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of the report is received.

Thank you for the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT, "CANCER PATIENT SURVIVAL: WHAT PROGRESS HAS BEEN MADE?"

We appreciate the opportunity to comment on the draft report. Our response contains both general comments with respect to the conclusions reached, the methodology used, the report recommendation, and technical comments on specific points raised in the report. Also included, as Attachment 1, is a revised version of Table 1.1 "Survival Trends By Cancer Type" from the report.

GENERAL COMMENTS

A. Background: Cancer Statistics Published by the National Cancer Institute

The National Cancer Institute (NCI) conducts an extensive data collection program to track the incidence of cancer and the prognosis for cancer patients. The NCI data collection program has been underway for the past 30 years, and led in 1972 to the establishment of the Surveillance, Epidemiology, and End Results Program (SEER), which has allowed a continuous cycle of data collection and analysis and is providing the consistency and data collection methods to enable trends to be assessed. The data is collected from 11 population-based registries throughout the United States and Puerto Rico and includes data on all residents of these areas diagnosed with cancer including annual follow-up information on their overall health status. The total population under surveillance amounts to about 12 percent of the United States population.

The purpose of this data collection is to enable the NCI--and researchers worldwide--to track both progress and problems in cancer. The data is constantly explored for cancer sites in which progress is evident, or sites showing changes in incidence, mortality or survival without concomitant indications from research that such changes are likely. These analyses give leads to the Nation's cancer researchers toward a more thorough understanding of the causes of cancer, the processes of cancer detection and treatment, and extent to which state-of-art treatments are being applied.

B. Report Methodology and Summary Conclusions

Some of the information in the Report was taken from NCI reports. The bulk of the information, however, consists of experts' opinions gathered in group interviews held at a number of cancer centers. The experts were asked their opinions on changes in disease management and whether reported differences in survival were real or "artifactual." They were also asked to identify the specific factors contributing to any reported improvements. The Report's authors realize the limitation in such subjective data noting that,

> "It should be emphasized that our design included elements of subjectivity (e.g., selection of participating centers and expert opinion) and is heavily dependent on qualitative data. As such, our findings do not have the same conclusivity as that of studies which rely on objective, empirically validated data. However, since a major rationale for conducting this

study is that such data do not exist, we believe our results constitute the strongest comprehensive evidence, to date, on what has actually occurred in the area of cancer patient survival for the period 1950-1982."

See comment 1

We believe that the following major conclusive statement (as written in the Executive Summary) does not reflect the subjectivity inherent in the methodology, nor does it reflect the past accomplishments in cancer research, and the present state of the art in treatment:

"Finally, with regard to the question of whether progress has been made against cancer, GAO concludes that the answer is yes, but the amount of progress is as much a function of the particular definition of the term 'progress' being used, as it is a reflection of what has actually occurred in the field."

The tone of this statement will reflect a view that progress has been relatively modest, yet this is in stark contrast with statements made in Chapter 4, such as

". . . whichever perspective one adopts, it is impossible to say that there has been no progress made in extending patient survival."

The Report goes on to say that the survival rates should not be used as the

"sole indicators of progress made in extending patient survival."

Indeed, we agree with this point and so state when we release the cancer statistics. Tables 1 and 2 from the NCI 1985 Annual Cancer Statistics Review present information on numbers of new cases, numbers of deaths, changes in incidence and mortality, changes in the level of survival, and changes in the number of deaths between 1970 and 1984. We believe that incidence, mortality and survival must all be brought together in analyzing trends in cancer. Morever, this information must be coupled with the results of clinical research to judge the extent to which proven treatments have been, and are being, applied.

This analysis must be done with the knowledge and judgement that because of the nature of the disease, the benefits of new treatments are not necessarily reflected immediately as changes in the measures of cancer. Indeed, an analysis reported in the 1985 Annual Cancer Statistics Review showed about 20 percent of the breast cancer patients who died during 1983 had been diagnosed more than ten years before, at a time when detection and treatment methods differed from those available today.

See comment 2

The Report itself must be considered opinion, not fact. In general, we believe that the conclusions that cancer patient survival has increased are appropriate, but that the tone of the Report is negative in terms of the real progress in cancer. Indeed, the tone is counterproductive, in that it

See comment 3

can lead physicians and the public to feel that appropriate treatment is not important--that it does not make a difference in patient outcomes. The statistical evidence from clinical studies, and from the SEER program points to the contrary.

C. Progress in Controlling Cancer

See comment 4

In the Executive Summary to the Report, GAO states that the "only hopeful sign" that we are making progress against cancer has been a steady increase in reported survival rates. Indeed, there are a number of hopeful signs, including: falling mortality rates among those less than 65 years of age; a steady decrease in the percentage of the population who smoke and a slow-down in lung cancer incidence in white males--although smoking still accounts for some 30 percent of all cancer deaths; a decline in overall mortality for a number of cancers that is directly connected with changes in treatment for those cancers including Hodgkins Disease, the childhood cancers, ovarian cancer and testicular cancer among others. We also see declines in stomach cancer mortality and cervical cancer. We also have results of the major clinical trials concerning screening for breast cancer; one in the United States and another from Sweden, which found that at least 30 percent of breast cancer mortality in women over age 50 can be eliminated through breast cancer screening.

In addition, over the past decade, the strides in basic research have been enormous. We now understand many of the cellular level events which cause a cell to be transformed into a cancer cell. We also understand the number of the factors related to the promotion of the cancer, once this initiation takes place. There is literally an explosion of information concerning the mechanisms of cancer growth as well as cancer metastasis. To say that there is only one hopeful sign is at once naive and shortsighted.

See comment 5

In concentrating on survival as an indicator of improved prognosis for cancer patients, the Report notes that

> ". . . it becomes clear that improvements in survival have taken place for almost all cancer types, although the actual improvements are typically less than those reported."

The reason the improvement is not as great as reported is, according to the Report, that a number of "forms of measurement bias exists." As far as is known, this bias is of almost academic interest and is not a practical limitation to the interpretation of the data. Indeed, the Report does not outline the impact of these measurement biases on the survival rates.

The Report also notes there are trends toward early detection of many cancer types, improved case management, refinements in surgical procedures, new radiation therapy devices, and the advent of chemotherapy and that these are the factors which most often account for the improvements noted.

We agree with these conclusions, but, regret the tone of the statement:

> ". . . these improvements in survival are nontheless limited, because they have occurred primarily for the rarer forms of cancer; and that the improvements in survival have been greatest for those cancers which strike the young."

See comment 6

It should be noted that young not only includes those under 15 but those under age 65 as well. The latest ten-year national mortality statistics for the period 1975 through 1984 show a decline in mortality in whites from

all cancer except lung cancer up to age 65, and a decline in all cancers including lung cancer up to age 55. This group makes up some 42 percent of all cancers.

The Report also notes that the quality of life has improved for cancer patients; this is a strong, positive conclusion, and we concur.

D. The Challenge to Improve Cancer Survival

It is a particularly important conclusion that survival could be improved through better application of existing treatments. We believe strongly that this is true and have taken a number of steps to reduce the gap between state-of-the-art and practice. NCI has developed an extensive network of cancer research centers across the country and a clinical research program that enables community physicians to participate in multi-center clinical trials of cancer treatment. This program has recently been expanded to include cancer control research as well as clinical research.

NCI has also developed an information system that includes the state-of-the art cancer treatments as defined on a continuous basis through an editorial board of cancer researchers. The computer-based information system, known as PDQ (Physician Data Query), is available through the National Library of Medicine and through a number of commercial information services. PDQ also lists all clinical treatment protocols underway under the auspices of, or approved by, NCI and where these clinical treatment protocols are being conducted across the United States.

In addition, NCI has put in place a network of information services (The Cancer Information Service) available through a nationwide phone number--1-800-4-CANCER. Both physicians and the public are encouraged to use this number for treatment information as well as information on cancer detection and cancer prevention.

All of these efforts are part of the nationwide cancer control effort to apply optimal treatment to the cancer patient.

E. Conclusions

See comment 7

1. The specific findings point out that progress has occurred but not to the extent shown in the survival statistics. Unfortunately, no percentages or other quantitative estimates are given to indicate to what degree the survival has improved, nor is the potential impact of the "measurement biases" outlined, leading the reader to infer what he will.

See comment 8

2. The methodology used--an analysis of the subjective opinion of experts--is only a first step, the next steps would involve detailed reviews of research reports for a number of cancer sites. This would be extremely time-consuming and in turn would need to be addressed by experts working from a body of data. Recent experience with the Concensus Conference on Breast Cancer in which the data from the breast trials were pooled and analyzed, testifies to the fact that it can be done and that it is useful, but that it is costly in terms of analysis resources. The method used here is a

step toward an answer but is not sufficiently quantified to allow the reader to draw his own conclusions.

See comment 7

3. The report discusses a number of "measurement biases" that may be present and if present must be considered in the interpretation of the survival statistics, as well as incidence and mortality trends; however, the potential impact of the biases is not quantified and the reader is left to infer a large magnitude when the measurement bias or factor may be a purely hypothetical concept.

See comment 9

4. We agree with the conclusion that in 11 of 12 cancers addressed survival has increased, although the increase in stomach cancer survival is not explained. This increase, albeit small may reflect improved technique, or earlier detection, and concomitantly better treatment results.

See comment 10

5. The tone of the Report seems to contradict the conclusion that survival has increased, and could make the Report counterproductive in perpetuating the notion that treatment is ineffective. The following examples are quoted from the Executive Summary:

> "When additional evidence is examined for specific forms of cancer, it becomes clear that improvements have taken place for almost all cancer types, although the actual improvements are typically less than those reported."
>
> "The GAO review shows that more cancer patient lives are being saved or extended than in 1950, these improvements are nonetheless limited because they have occurred primarily for the rarer forms of cancer."
>
> ". . . interpretation of survival trends remains difficult primarily because of changes in detection practices and what is, or is not, called cancer. These changes introduce a number of biases which artificially inflate the actual improvement in patient survival."

See comment 11

6. Use of the term "the war on cancer" is inappropriate. The NCI does not use this term which connotes that all of the Nation's cancer resources are devoted to clinical treatment research. Basic and applied research on prevention are important components of the program, as is research on screening, cancer etiology, and cancer biology.

Now on p. 80.

7. We fully concur with the Report (for example, on page 4-2) that (five-year) survival rates provide only limited information on the full extent of patient survival and do reflect cancer morbidity.

See comment 12

8. Progress in terms of the potential to extend the life of cancer patients is not measured through the survival statistics, but instead through the results of carefully controlled clinical studies. The experts were asked their opinions on research advances, but data from clinical studies exist to document the potential gains in survival. The comparison of SEER rates over time reflects

actual survival in the general population and does not measure the potential for survival, i.e., that which can be achieved through state-of-the-art cancer treatment.

9. We are pleased that the Report concludes that the survival rates as measured by the SEER Program are more accurate than the rates derived from earlier studies.

GAO RECOMMENDATION

GAO recommends that the NCI include a description of the bias that can lead to misinterpretation of survival rate changes in all future publications on patient survival. In this way, misinterpretation of changes in survival rates can be minimized.

HHS COMMENT

We concur. Beginning in calendar year 1987, the NCI will include a description of the potential sources of bias likely to cloud the interpretation of survival rates in its annual presentation and publication of cancer survival rates.

TECHNICAL COMMENTS

The following comments or corrections are directed at specific statements made in the GAO report and are listed below in order of their appearance in the text of the original document.

1. INTRODUCTION

. Comments regarding the methodology are included in the cover memo accompanying this statement.

2. CANCER SURVIVAL RATES AS MEASURES OF PROGRESS MADE

See comment 13

. (Page 2-19) The statement implying that criteria for the diagnosis of cancer have changed over time is incorrect and misleading. This comment permeates the discussions of prostate cancer, bladder cancer and breast cancer. Histologic definitions have not changed since 1950.

3. CHANGES IN CANCER MANAGEMENT, 1950-1982

See comment 14

. (Page 3-3, 1st par) In addition to innovations in imaging techniques and improvements in radiation therapy delivery, a wide array of changes have also occurred in the practice of medicine over the past two decades. Major advances in supportive care (antibiotics, blood product availability), cancer treatment (e.g., surgery and chemotherapy in addition to radiotherapy) all have had an impact on cancer treatment.

See comment 15

. (Page 3-4) The statement, "The ability to detect micrometastases . . ." is not strictly correct. Chemotherapy is the treatment of choice for most cases of metastatic disease. Excision of metastases for cure is possible only in selected cases.

See comment 16

. On the same page, the Report states that most patients with metastatic disease still die, but it should point out that advanced disease is curable in the majority of patients with childhood ALL, aggressive lymphoma, Hodgkin's disease, and testicular cancer. In addition, many patients with metastases to lymph nodes in breast and other cancers can be successfully treated with adjuvant therapy to improve their survival.

BLADDER·CANCER

See comment 17

. (Page 3-14) The conclusion in this section could state that there are a number of changes in the management of bladder cancer that might explain the improvement in survival. Such a statement would be consistent with Table 3.1 which reports real improvements in disease detection pretreatment evaluation, and treatment.

. Available data show a five year survival of 53 percent in 1950 and 77 percent in 1982 (Table 4.1). Reasons for this improvement such as early detection and better follow-up (cystoscopy) as well as improved treatment (surgery, radiation and chemotherapy) are cited. Other advances, such

See comment 18

as the use of intravesical chemotherapy and biological therapy (BCG) to avoid cystectomy and retain bladder function are not mentioned.

See comment 19

. This section focuses on the divergent opinions offered by the experts and concludes that the gain is not well understood. This seems unreasonable, since it is not clear that the experts polled are in a position to assess the reasons behind a 30-year trend. Nor are they in a position, based only on patients seen in their practices, to assess the magnitude of a national trend.

See comment 20

. (Page 3-9) Coffee and cyclamates have not been clearly linked to bladder cancer, while cigarette smoking is a definite risk factor.

See comment 21

. (Page 3-13) The possibility that the inclusion of greater numbers of patients with papillary carcinoma as a major contribution to the reported improvement in survival rate is an appropriate statement. But by affixing no magnitude or range of effect to the statement, the entire change in survival is called into doubt.

This may reflect the opinion of one of the experts, but it should not be construed as explaining all the gain in survival. The Report agrees by noting that there has been a gain in survival, but the conclusion is muted.

BREAST CANCER

See comment 22

. (Page 3-15) Breast cancer rates continue to increase after age 70. Ionizing radiation might be mentioned as a causal agent for some cases.

Now on p. 41

Now on p 41

. (Page 3-16) The statement that "most breast neoplasms . . . eventually spread to pelvis, liver and lung" is incomplete and slightly incorrect. Breast cancer commonly spreads to liver, lung, bone, lymph nodes and skin. Pelvis may be affected only as bony or nodal involvement.

Now on p. 41

. (Page 3-16) The statement dealing with the rise in incidence vs. survival rates (1st paragraph) begs the question as to what extent the mortality rates should reflect the increase in survival from 60 to 74.6 percent over the 30-year period in question. Are there changes in the age distribution or in other possible causes of mortality that could affect these rates? The answer is not known, and is under study, but the unequivocal conclusion that real improvement is not present is not justified. In fact, it might be said that earlier detection could play a role in survival: early detection that affords improved prognosis because the cancer is treated earlier may be one of the reasons for the improvement in survival in these patients.

Now on p 41

. (Page 3-16) The last sentence probably should read "The sharper rise in survival rates than in incidence rates . . . ."

Now on p. 43

. (Page 3-17) Bottom right: "ineffective" should be "effective".

See comment 23

. (Page 3-19, #2) The NCI disagrees with the statement that there is a possiblity of improving survival by using "curative" surgery in Stage III breast cancer patients. Surgical inoperability on advanced disease patients has been defined since the mid 1940's.

See comment 24

. (Page 3-19, #4) Adjuvant chemotherapy has been used since 1975. Bonodonna reported the use of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) at ASCO in 1975 (published in the NEJM 294:76). A National Surgical Adjuvant Breast Project study had been reported earlier. The September 1985 NIH consensus conference confirmed 25 percent improved survival for Stage II premenopausal women treated with adjuvant chemotherapy and 20 percent improved survival for post-menopausal women treated with adjuvant tamoxifen.

It is indeed unlikely that the effects of treatment in the early 1980's would be reflected in the 1982 survival figure for breast cancer. However, earlier application could have an impact, but we do not know the extent to which the treatment was applied. Moreover, note that the longevity of patients with breast cancer is such that the mortality rate at any time reflects patients diagnosed many years before.

See comment 25

. (Page 3-20) We do not know of any data to support the statement that the "more aggressive therapeutic approach to selected Stage III patients" has had an impact on survival.

See comment 26

. (Page 3-21) The concluding statement "there are too many potential sources of bias . . ." is not supported by identifiable data in the body of the report. Quantification of the potential bias should be presented, or this statement should be eliminated.

The importance of the decline in the mortality rate for women under 50 years of age between 1975 and 1984 is not discussed.

COLORECTAL CANCER

See comment 27

. (Page 3-30) The comments regarding lack of distinction between colon and rectum cancer in early NCI surveys are incorrect. Very early data

did not fail to separate cancers of small and large intestines, but data for colon and rectum separately have been available for the entire period under question.

See comment 28

. (Page 3-33) In discussing the relationship of diet to colon and rectal cancer, the Report states that there is no definitive relationship. In fact, there clearly is a definitive relationship between diet and colon cancer, but what is not known is what that relationship is due to. Fat, fiber, chemicals, and micronutrients have all been hypothesized to play an important role, with no unanimity as to which is or is not the most important.

See comment 29

. (Page 3-33) The statement that trends in colorectal cancer cannot be meaningfully discussed because of mis-diagnosis of metastatic lesions as separate primary sites is not supported by data. Hepatocellular carcinoma is easily distinguished from adenocarcinoma metastatic to the liver.

See comment 30

. (Page 3-34) The Report notes that "the ability ot detect and allow for excision of precancerous lesions (with endoscopy) should have little effect on mortality." The data and reasoning behind this statement is not clear. In fact, the opposite conclusion may indeed be true.

See comment 31

. (Page 3-36) Survival figures on Table 4.1 indicate a five-year survival for colon cancer improving from 41 to 52.8 percent between 1950 and 1982, a striking change. Comparable figures for rectal cancer are 40 and 49.7 percent. In each case, the conclusion is that a "slight" improvement in survival has occurred. The important point is that the improvement is real, and given the rising incidence and decreasing mortality this is most likely a significant effect. In a disease which affects nearly 150,000 patients per year in the U.S. (colon 96,000/rectal 42,000) even small improvements in survival are highly significant.

See comment 32

. (Page 3-38) It is important to note that a recent meta-analysis by Chalmers and Buyse indicates that treatment with 5-FU leads to significant improvement in disease-free survival when used postoperatively. In confirmation of this observation, recently completed cooperative group trials of colon and rectal cancer confirm 20 percent improved disease-free five-year survival using FU-based treatments in colon cancer and 24 percent improved five year disease-free survival in rectal cancer using FU and radiotherapy.

Indeed, the best explanation for improved survival in colorectal cancer between 1950 and 1982 is improved surgical techniques and supportive care as well as widespread empiric use of 5-FU chemotherapy. Thus, the

See comment 33

conclusion that therapeutic approaches are "too recent to have implications for the latest published survival rates" is likely to be incorrect.

HEAD AND NECK CANCER

See comment 34

. One of the reasons why methods for the early detection of head and neck cancers has not improved is probably because they have always been very visible and easily detectable cancers.

See comment 35

. (Page 3-45) From an epidemiologic standpoint, we recommend using the term oral cavity and pharynx cancers instead of head and neck cancers.

LEUKEMIA

See comment 36

- (Page 3-55) The therapeutic approach discussed in this section confuses adult and childhood ALL. The incidence of complete response rates in adult ALL is actually greater than complete responses in adult AML.

See comment 37

- The statement that patients with CML in blast crisis can be treated with bone marrow transplant is wrong. Bone marrow transplantation is still a highly experimental approach to therapy in CML patients, but if used is recommended for patients in the chronic phase of the disease rather than for those in blast crisis.

See comment 38

- To state that chronic leukemias are being detected earlier because of Medicare-supported blood testing (Table 3.8) seems unjustified unless supportive data can be referenced.

See comment 39

- (Page 3-61) The statement that "the improvement [in leukemia survival] has been greatest for childhood victims with ALL" is significantly understated and does not express the magnitude of this contribution over the period of interest. In 1955, a study done by the Cancer and Leukemia Group B (CALGB) identified only 103 children worldwide who were five-year survivors of leukemia. All of these children had received some form of then highly-experimental chemotherapy. Today, as the report notes, half of all children with ALL can be cured. This is an extrememly significant gain.

LUNG CANCER

See comment 40

- (Page 3-62) The ACS national estimates for 1985 are 144,000 rather than 125,000 new cases of lung cancer and 126,000 rather than 100,000 deaths.

- (Page 3-63) The most common site of metastases from squamous cell cancer of the lung is bone rather than GI tract.

See comment 41

- (Page 3-69) Clearly, there is room for improved treatment options for lung cancer patients, but it must be agreed that real advances have been made in this disease, particularly small cell lung cancer. This is inconsistent with the study's conclusion that treatment advances have only occurred in uncommon malignancies. Small cell lung cancer was diagnosed in over 25,000 Americans last year, and small advances in this area can yield large benefits in lives saved.

See comment 42

- The statement in Table 4.1 for lung cancer that "stage migration" has been shown to exist can be deleted as stage migration will not affect changes in overall survival.

NON-HODGKIN'S LYMPHOMA

See comment 43

- It was unclear why Hodgkin's disease was omitted from any discussion of the lymphomas. Hodgkin's was uniformly fatal in 1950, and overall cure rate exceeds 75 percent today. This study ignores this important treatment accomplishment.

See comment 44

. (Page 3-71) This notwithstanding, it is an exaggeration to state that there is "no consensus on a uniform terminology to discuss the non-Hodgkin's lymphomas". The implication is that the field, in which there has been great treatment success, is in chaos: "discussing non-Hodgkin's lymphomas is a little like shooting at a moving target." This is likely a reflection of lack of familiarity or inexperience with the terminology used for histopathologic diagnosis of lymphomas.

The working formulation (not discussed here) is the accepted framework for diagnosis. On page 3-76, it is claimed that combined radiation and chemotherapy is more effective than either alone for certain patients. This is obsolete; there is no non-Hodgkin's lymphoma for which the statement is true.

See comment 45

. Any discussion of treatment advances must separate out treatment of common high grade lymphomas, where success has been most outstanding. For example, in 1973, only 10 percent of patients with diffuse histiocytic lymphomas survived five years; today's cure rate is 65 percent. In fact, Table 3.10 (Changes in the Management of Non-Hodgkin's Lymphoma) should distinguish between patients with aggressive and more indolent disease.

See comment 46

. (Page 3-74) The report states that the major risk factors associated with NHL are any problems in the immune system. This is not true for the great majority of lymphomas.

See comment 47

. (Page 3-75) The statement is made that survival rates have improved but a decrease in mortality has not been observed in the non-Hodgkin's lymphomas. Since it is quite certain about one-third of the non-Hodgkin's lymphomas (the diffuse large cell lymphomas) can be cured, the disease likely represents an example of where either mortality rates lag behind improvements in relative survival rates or physicians have not been using state-of-the-art therapy widely, or they have not been using it well.

The situation is even more dramatic than with breast cancer because in the lymphoma cases, patients have widespread disease and if they fail, they die shortly after diagnosis; while in breast cancer, patients treated with adjuvant therapy who recur, live a long time. The best explanation is that physicians have not been quick to accept and use the more effective therapies.

PROSTATE CANCER

See comment 48

. (Page 3-79) The statement beginning "lest we assume . . ." is a strong statement which should be qualified. This VA study was small (approximately 30 patients in each treatment group), and randomized patients with presumably localized prostate cancer to surgery or observation. However, the study was performed in an era (1960's) when bone or CT scans were unavailable to determine which of these patients already had metastatic disease beyond surgical cure at the time of prostatectomy.

Patients can now be appropriately selected for surgical cure of this disease, and it makes little sense to quote this small, and dated VA study out of context.

See comment 49

. In the next paragraph (Page 3-79), the statement is made that prostate cancer has two distinct manifestations, with an "indolent" form being more prevalent. The Report then concludes that much of the improvement seen in prostate cancer survival can be explained by the prevalence of the "less malignant" form of the disease.

Table 4.1 shows improved five year survival between 1950 and 1982 as 43 percent vs 71.1 percent, respectively. While some of this improvement may be due to increasing TURPs and diagnosis of A1 disease (for which survival is unimpaired), it is also true that during this interval improved surgical techniques, radiation therapy, and diagnostic imaging techniques became available.

See comment 50

. (Table 3.1) "Changes in the Management of Prostate Cancer Patients", "nuclear roundness" is not an important prognostic indicator. Does this mean grade?

See comment 51

. (Page 3-84) When discussing prostate cancer, it may be more precise to call "preinvasive" cancer as either presymptomatic or latent cancer.

STOMACH CANCER

See comment 52

. There is one important omission in the section on stomach cancer, which is later described as the only cancer about which "a conclusive statement that survival has not improved" (Page 4-10). Since the 1930's, the mortality rate of this disease has decreased dramatically. Between 1969 and 1980, age-adjusted mortality from gastric cancer fell 27.4 percent in men and 30.2 percent in women. Alhough the specific reason for this decline in mortality is uncertain, the decreased incidence of this tumor is most likely related to changing patterns in diet and nutrition, and reflects a capability of actually preventing cancer by manipulating diet. Certainly, this important observation should be mentioned in the report.

See comment 53

. (Page 3-87) Ulcers have not been confirmed as a risk factor for stomach cancer in U.S. studies.

4. HAS PROGRESS BEEN MADE?

See comment 54

. (Page 4-3) The biases noted may affect the observed survival rates but do not result from changes in the way survival rates are measured.

See comment 55

. (Page 4-6) Endometrial cancer: Although the potential influence of hysterectomy is acknowledged earlier, the incidence data were not called biased. To the extent that hysterectomies have increased, then corrected incidence rates would have increased more during recent years than in the past. This would increase further the divergence of incidence and mortality.

See comment 56

. (Page 4-8) Why are the incidence rates for lung cancer not reliable?

See comment 57

Is stage migration bias a valid explanation for improvements in overall survival for this cancer? For prostate cancer, how would "a better understanding" of risk factors improve the targeting of therapy?

See comment 58

- (Page 4-10) In the conclusions, rather than the statement "of the twelve cancers examined . . .), it would seem clearer to say that 11 of the 12 examined showed evidence improvements in survival.

See comment 59

- It would seem that both sides of the question of the extent of increase in survival should be presented. For instance, the statement

  "Even in cancers where survival improvements have taken place, there remain distinct groups of patients who have not benefited from these improvements."

  has an obverse, that there are distinct groups of patients for all these diseases where the gains have been impressive. Still another point to be made is that the report concludes that advances have been made only in cancers which afflict small numbers of young patients. Hodgkin's disease and testicular cancer, for which treatment gains have also been particularly notable are not mentioned.

See comment 9

Now on p 83.

- (Page 4-9) What is the explanation for the observed (small) increase in survival for stomach cancer? The reported survival increased from 12 to 15.7 percent, and it is not clear why the authors conclude that no improvement in survival rates has occurred.

See comment 60

- "For lung, colon, rectum, and breast cancer, on the other hand, there have been only modest gains in survival rates."

  An important point is that this improvement is real, and since these diseases affect over 400,000 Americans annually, even modest gains are important in terms of public health.

See comment 61

ATTACHMENT 1. TABLE 4.1: SURVIVAL TRENDS BY CANCER TYPE (REVISED)

Cancer Type	Reported 5-Year Survival Rate[a] 1950	1982	Factors for Consideration	Conclusions
Bladder	53%	77.3%	. Survival improvements consistent with increasing incidence and decreasing mortality . Increased use of cystectomy, tracking of high risk patients, improved staging, use of combined modality therapy for advanced disease and earlier disease detection were all considered to have improved survival	Real improvement
Breast	60%	74.6%	. Improved early diagnosis, allowing curative surgery . Positive adjuvant trials in pre- and postmenopausal Stage II recently confirmed . Therapeutic breakthroughs expected to have significantly impacted on survival	Real improvement
Colon	41%	52.8%	. Survival improvements consistent with rising incidence and falling mortality rates . No indication that measurement biases exist . Widespread empiric use of 5-FU based chemotherapy, recently shown to be effective in randomized studies	Improvement in survival has occurred

[a]In order to make appropriate comparisons the rates presented are for whites only since other reporting categories changed over time.

Cancer Type	Reported 5-Year Survival Rate[a] 1950	1982	Factors for Consideration	Conclusions
Rectum	40%	49.7%	. Survival improvement consistent with increasing incidence and decreasing mortality . No indication that measurement biases exist . Increasing use of radiation and chemotherapy in combination as adjuvants to surgery have helped extend survival	Improvement in survival has occurred
Cervix	59%	67.4%	. There was no indication given by expert panels that any measurement biases exist . Earlier disease detection is credited with improving patient survival; greater emphasis on screening could have a still greater impact	Improvement in patient survival and mortality rates
Endometrial	72%	87.1%	. Survival improvement consistent with sharper decline in mortality than in incidence rates . No indication that measurement biases exist in survival rates	Improvement in patient survival

Cancer Type	Reported 5-Year Survival Rate[a] 1950	1982	Factors for Consideration	Conclusions
Head and Neck[b]	45% in 1960	54.3%	. Survival improvements inconsistent with stable incidence and mortality rates . No indication that measurement biases exist . Improvements in surgical procedures have expanded pool of patients eligible for surgery . Improved radiotherapy options . Availability of effective chemotherapy	Improvement in survival rates
Leukemia	10%	33%	. Survival improvements consistent with a decreasing mortality rate; incidence increased slightly early in period and showed a decline following 1974 . No measurement biases exist . Advent of chemotherapy for acute leukemias has dramatically improved patient survival	Real improvement in survival rates for patients with acute leukemias No improvement for chronic leukemias
Lung	6%	11.6%	. Survival rate improvement is inconsistent with approximately equivalent increases in incidence and mortality rates. incidence rates, however, are not reliable . Development of chemotherapy for small cell lung patients has improved their survival	Real improvement in survival rates for patients with small cell carcinoma (affects 25,000 patients annually) No change for other patients

[b] Rates for 1950 are provided only on a site specific basis (lip, tongue, floor of mouth, etc.)

Cancer Type	Reported 5-Year Survival Rate[a] 1950	1982	Factors for Consideration	Conclusions
Prostate	43%	71.1%	. Survival rate improvement consistent with increasing incidence rate and stable mortality rate . Improved detection and diagnosis; improved surgical options . Length time bias may exist . A better understanding of risk factors has allowed targeting of therapies; increased use of interstitial radiation has also led to survival gains	Real improvement in survival has occurred
Non-Hodgkin's Lymphoma[c]	31% in 1960	48.1.%	. Survival rate improvement is consistent with slower increases in mortality rates than in incidence rates . No indication that measurement biases exist . Better understanding of NHL; the advent of effective chemotherapy and the use of radiation in combination with chemotherapy have all improved patient survival	Real improvement in patient survival
Stomach	12%	15.7%	. Survival improvements inconsistent with equivalently sharp decrease in incidence and mortality rates	No improvement in survival rates; however, overall mortality has decreased because of decreasing incidence of the disease

[c] Rates provided for 1950 are by categories no longer used to classify NHL.

GAO Comments

1. The statement in the executive summary, on page 2, has been modified to clarify that our conclusion relates to progress in extending patient survival. The other points HHS made in this section of its review were addressed in the concluding section of chapter 4. We state in chapter 4 that the inclusion of subjective opinions as one source of information does not mean our conclusions are subjective, that advances in cancer research are beyond the scope of this report, and that the tone of the report was considered fair by the majority of independent reviewers.

2. The question of whether the report is "opinion" or fact is addressed in chapter 4.

3. The tone of the report, as we state in chapter 4, was considered appropriate by the majority of independent reviewers These reviewers were drawn from the 11 comprehensive cancer centers that did not participate in the data collection for the project.

4. The phrase "only hopeful sign" has been changed to read "one hopeful sign" (see page 2). The other "hopeful signs" mentioned by HHS fall outside the defined scope of the report.

5. This criticism by HHS is not well understood. We believe that we have conclusively shown that the biases can and do lead to distorted estimates of the magnitude of true improvement in cancer patient survival. In addition, the criticism is particularly puzzling given HHS's concurrence with our recommendation. HHS's quotation from the report has been deleted.

6. The information provided by the agency as evidence that advances have been made in age groups other than the young concerns mortality and incidence rates, neither of which was the focus of the project

7. Our failure to provide quantitative estimates of the degree to which survival rates have actually improved is discussed in chapter 4.

8. The agency's characterization of the methodology as a "first step" is somewhat incorrect. The actual first step in this area was the initiation of data collection efforts by NCI to track survival trends. Our study is therefore more appropriately thought of as a second step That is, having evaluated the strengths and weaknesses of the published rates, we expect that our study will both inform current users of survival rate data in public debates and stimulate more extensive quantitative

studies, by NCI or others concerned with the issue of progress against cancer. In addition, the characterization of the methodology as "an analysis of the subjective opinions of experts" is incorrect in that these opinions were only one of many sources of data used to reach our conclusions.

9. Our conclusion that there has been no improvement in patient survival for stomach cancer is based on 3 factors: (1) the parallel declines in incidence and mortality rates, (2) the lack of advances in treatment for this disease that demonstrate the ability to extend survival, and, finally, (3) the experts' opinion that no improvement in extending patient survival occurred from 1950 to 1982. Each of these factors, although not conclusive evidence by itself, supports the conclusion that survival has not improved.

10. The issue of tone is addressed in chapter 4. As to the specific statements HHS cites, HHS has presented no evidence to contradict them. The statement on the interpretation of survival trends now appears on page 3. The two other statements were deleted from the report.

11. The term "war on cancer" is widely used in discussions of progress against the disease. However, since our focus in the report is only on patient survival, we have deleted the term.

12. The report is concerned with actual and not potential improvements in cancer patient survival. The results of clinical trials only tell us of the potential of therapies to extend survival and are therefore not relevant.

13. The statement, now on page 32, has been amended to indicate that the types of cancer being detected have changed.

14. As can be seen from our discussions of the specific cancers in chapter 3, we concur with this view. However, it is our impression that many of these changes (for example, advances in surgery, chemotherapy, supportive care) are better understood at the disease-specific, rather than at the general, level. This accounts for our decision to discuss these changes in the context of the individual cancers. The reference is to pages 35-36.

15. The statement, now on page 35, has been changed to read "distant metastases." The point regarding chemotherapy is not relevant to the discussion of imaging devices because it relates to treatment and not to diagnosis or patient evaluation.

16. We agree that cure can be achieved for childhood ALL and the aggressive forms of lymphoma and so state in our discussions of them in chapter 3. We did not make any statement regarding their curability at this point in the text simply because it was not relevant to the benefits of the new imaging technologies. With respect to Hodgkin's disease and testicular cancer, we can make no comment because neither was one of the 12 cancers we examined. The reference is to page 35.

17. The conclusion could be stated in a number of ways. We see no evidence that makes us believe that our wording is either incorrect or inappropriate. The reference is to page 40.

18. The expert panels did indicate that these therapies, especially BCG, were promising for the treatment of bladder cancer. However, the panels also believed that the extent to which they had affected patient survival by 1982 was unclear. Therefore, the treatments were not considered relevant for reaching conclusions on changes in survival from 1950 to 1982.

19. Since each of our panels on bladder cancer included physicians who have been practicing for the last 30 years, we consider them to be capable of addressing developments during that period. In addition, the panel discussions were held at the nation's leading cancer institutions, where the magnitude of improvement in patient survival is, arguably, as great as if not greater than that nationally. If there is any bias in the perspectives of our panels, we believe it is one that would exaggerate, rather than minimize, the extent of progress.

20. The text, now on page 37, has been changed to reflect this point

21. As we state in our first conclusion for bladder cancer, there was a real improvement in patient survival from 1950 to 1982. Had our intention been to question all of the reported improvement, this conclusion would have been omitted. The reference is to page 40.

22. The changes indicated here and in the next four paragraphs have been made in the report. The references are to pages 41-43.

23. The statement, on page 43, has been deleted.

24. The agency's comment is not well understood. Our report indicates that adjuvant chemotherapy has the potential to extend survival for breast cancer patients, but this therapy is too recent to have affected

the 1982 rates. The agency makes the same points in its comments. The reference is to page 44.

25. The statement, now on page 44, has been changed.

26. The falling mortality rate is not mentioned since mortality for specific age groups is outside the scope of the report. The reference is to page 45.

27. The text, now on page 51, has been changed.

28. The statement, now on page 51, has been changed.

29. The statement, now on page 51, has been changed.

30. The statement, now on page 52, has been changed to read "little effect on survival."

31. In light of the differences of opinion between HHS and GAO on two issues—that is, contributions made by 5-FU and the recency of combined modality therapy—it is understandable that we reach different conclusions as to the magnitude of the improvement in survival. Since our position on both issues remains unchanged, we retain our conclusion that the improvement in colorectal cancer patient survival should be characterized as "slight." HHS, however, does make an important point with respect to the use of this term. Since colorectal cancer is such a pervasive disease, even small improvements in the survival rate affect large numbers of cancer patients. We concur with this position and at no time intended to imply by the use of the term "slight" that the improvements are trivial or of no consequence. The reference is to page 82.

32. We do not dispute the results of these trials, but their recent completion does not change our conclusions on either colon or rectal cancer. For colon cancer, our disagreement is based on the information provided to us by the expert panels. When asked about the contr butions made by the treatment advances, one panel indicated that "as far as colon carcinoma is concerned, adjuvant therapy of any kind has not materially altered survival or recurrence rates" (emphasis added). The second panel, well aware of the trials HHS refers to, stated that "in colon cancer, systemic chemotherapy in [its] view, has not been demonstrated to be effective." With respect to rectal cancer, we discussed the benefits provided by chemotherapy in the draft HHS reviewed, and our conclusions remain unchanged.

33. We believe that HHS's concern over whether advances were "too recent" to be incorporated into our findings results from a misreading of our discussion of colorectal cancers. We conclude that advances in surgery resulted in improved survival. Had we believed that all therapeutic advances were too recent, we would have concluded that no improvement in survival had occurred. In the one case in which we have considered a therapeutic advance too recent—that is, combined modality therapy for rectal cancer—our position is supported by the views expressed by both panels of experts

34. Despite the ease of detection, a considerable number of patients with head and neck cancers are diagnosed with advanced disease.

35. We do not contest the position that the term "oral cavity and pharynx" may have been preferable from an epidemiologic perspective. However, since our panels were heavily composed of clinicians rather than epidemiologists, we thought the phrase "head and neck" was preferable.

36. The discussion, now on page 62, has been clarified to account for HHS's comment.

37. The discussion, now on page 63, has been changed

38. The statement has been deleted.

39. This is once again an issue of tone, which is addressed in chapter 4. The reference is to page 65.

40. The changes have been made on pages 65 and 66.

41. Even for the one malignancy for which a treatment advance was noted, small-cell carcinoma, only 10 percent of patients survive for 5 years. Therefore, we continue to believe that the statement that advances are relevant for only small, discrete subpopulations of lung cancer patients remains accurate. The reference is to pages 68-69

42. The statement has been amended to reflect that stage migration is not relevant when examining overall survival. The reference is to page 68

43. Hodgkin's disease was omitted because it was not among the 10 cancers with highest incidence rates in 1950 or 1982. The implication that

cancers for which dramatic improvements have occurred were omitted from the study must be weighed against the omission of such diseases as cancer of the liver, esophagus, and pancreas, for which progress has been minimal at best.

44. The language in the text, now on page 70, has been modified to include the "working formulation." It should be noted, however, that acceptance of any framework for diagnosis is a process that can take many years.

45. We agree that progress against NHL has been most dramatic for the high-grade forms of the disease. We agree also that an examination of NHL would be more informative if it were more narrowly focused. This is true for most of, if not all, the cancers in our study. In almost every case, the advances in treatment that have been noted are relevant mostly for specific disease subtypes. However, our purpose was to determine whether progress has been made not only in extending patient survival for specific types of cancer but also in helping cancer patients generally. In light of this objective, we believed that a detailed review of 8 different categories of breast cancer, 12 varieties of leukemia, and so on, would be inappropriate.

46. We have changed the text, now on page 71, to reflect this point

47. One possible explanation for the discrepancy is that the advances in treatment are relatively recent, and the mortality rates are simply lagging behind. Given that so many NHL patients are diagnosed when they have advanced disease, which would be rapidly fatal should treatment fail, another explanation is more likely, according to HHS: "physicians have not been using state-of-the-art therapy widely, or they have not been using it well." We do not have any evidence to dispute or support this contention for NHL. However, we do conclude that suboptimal patient management was one reason that the potential inherent in a number of treatment advances has not been realized. The reference is to page 71.

48. The reference to this study, which would have been on page 73, has been deleted from this section.

49. All these points are made in the review of prostate cancer. The statement referred to is now on page 76.

50. The term has been deleted from the table.

51. The change in wording, now on page 76, has been made.

52. Our examination of progress made was primarily restricted to efforts relevant to extending patient survival, which explains why we did not emphasize the point suggested by HHS in the draft of the report. We agree, however, that any evidence that would aid in the prevention of cancer is noteworthy and do mention that both incidence and mortality have declined. The reference is to page 78.

53. Ulcers have been omitted as a risk factor for stomach cancer The reference is to page 77.

54. The language, now on page 80, has been clarified.

55. The report does indicate on page 55 the bias that might exist in incidence data as a result of the hysterectomy issue HHS's point that corrected incidence would increase as hysterectomies increase is correct However, if "corrected incidence" is used, it should not be compared to mortality, since the measures apply to different populations

56. The reference to incidence rates, which would have been on page 83, has been deleted. The statement regarding stage-migration bias has been amended on page 83 to clarify that it is relevant only when examining survival on a stage-by-stage basis.

57. The statement, now on page 83, has been changed to "prognostic" factors.

58. The language suggested by HHS is not as precise as that contained in the report because it ignores our conclusion that progress for endometrial cancer is dependent on the extent to which new therapies have been applied. As a result, we cannot conclude that survival has improved for 11 of the 12 cancers. The reference is to page 83.

59. HHS misstates our conclusion by substituting "only" for "primarily." We addressed the point concerning the exclusion of Hodgkin's disease and testicular cancer in comment 16. The criticism concerning the obverse is not understood, since we consistently mention groups of patients who have benefited from the advances that have been made

60. Survival rates are proportions and, therefore, we focus on percentage improvement throughout the report. HHS's point—that small percentage gains in prevalent types of cancer will benefit many

people—is made by us in the presentation of the "absolute" perspective in chapter 4.

61. Representatives from NCI indicated that the revised version of table 4.1 should be viewed as suggesting changes that they would like to see in the report but that actual revisions were expected only for points made in the narrative section of HHS's review.

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