Cancer of the Breast:

Its Outcome as Measured by the Rate of Dying and Causes of Death

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Mortality forces in women with cancer of the breast were measured by calculating the rate of dying and determining the cause of death in women who develop breast cancer. In the Syracuse-Upstate Medical Center Cancer Registry, 1,513 patients were followed for 15 years. The death curve of this group assumed a major slope characteristic of a single exponential curve, with a half life of 5.9 years. The cause of death was examined in a randomly selected group of patients from the Ontario Cancer Foundation, Hamilton, Ontario, and a group from the Syracuse Registry dying after 10 years. In these 136 patients, 130 died of breast cancer. From the National Cancer Institute Cooperative Studies of 3,225 women undergoing treatment for primary breast cancer, 914 died during the study—705 of cancer of the breast and 209 of competing risks. These data suggest that 80-85% of all women who die after developing cancer of the breast die of their breast cancer. Modification of the time of dying (rate of dying) or cause of death should be used as objectives of management rather than 5-year survival figures.

WITH 90,000 newly diagnosed cases annually, carcinoma of the breast is the single largest cause of death from cancer among women in the United States and Canada.[15] Halstead's initial use of radical mastectomy as the preferred treatment for breast cancer emphasized management of the local tumor.[9] Subsequently, the concept has emerged that adequate management of the local tumor could possibly result in a "cure" or otherwise favorably influence the ultimate outcome of patients who have a predicted certainty of death due to the cancer.[1] Despite all therapeutic efforts, this disease's death rate has remained fairly constant over the past several decades.[11] However, reported 5-year survival rates during the past 50 years have gradually improved because of earlier case selection, revised staging, or more aggressive therapy.[10]

In this report, three data sources describe two outcomes of patients with cancer of the breast: 1) The rates of dying in an unselected group of women with carcinoma of the breast are calculated from information generated from the Upstate Medical Center (Syracuse) Cancer Registry; 2) The causes of death of individuals who develop breast cancer are examined using data from the Syracuse Cancer Registry, the Ontario Cancer Foundation Clinic in Hamilton, and the National Cancer Institute Studies (known as Breast I, Breast II).

This study attempts to answer the following questions: 1) What is the RATE OF DYING in a group of women who develop cancer of the breast? 2) Does this rate change with time? 3) What are the CAUSES OF DEATH of those women who have died following the development of cancer of the breast? 4) Is death caused by competing risks a significant factor?

The use of fixed-time survivorship generally deals with survivors. This report deals only with those who have died. Therapy is discarded here as an effective modifier of either the rate of dying or the cause of death, and we assume that therapeutic modalities employed in the various groups studied herein are reasonable samples of the surgical and radiologic efforts generally available in the United States and Canada. Therapy is thus considered an integral part of the disease course. We do not attempt to answer any of the questions regarding efficacy of one procedure vis-a-vis another, nor do we discuss whether therapy has any effect on either the rate of dying or cause of death.

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Materials

Data used as the basis for this report are derived from the following sources and for the following purposes:

1) *The Upstate Medical Center Cancer Registry, Syracuse, N.Y.* (a) To analyze the rate of dying by the life table (actuarial) method—1,513 cases. (b) To examine registry records of the causes of death of all women dying between the 10th and 15th year after diagnosis. 2) *The Hamilton Tumour Registry, Hamilton, Ontario.* (a) To examine the causes of death in a random sample of 51 women who died between 1 and 2 years after the diagnosis of breast cancer. (b) To examine the causes of death in a random sample of 41 women who died between 4 and 5 years after the diagnosis of breast cancer. (c) To compare the two groups at time of diagnosis. 3) *The National Cancer Institute Cooperative Studies–Breast I, II.* (a) To examine the cause of death of 914 women who died following enrollment in a cooperative study of the treatment of "curable" breast cancer according to studies known as Breast I and Breast II. (b) To compare the causes of death of those 914 women when divided into 3 age groups at time of diagnosis—Breast I and II. (c) To determine if competing risks have a continuous operative influence during 90 months following diagnosis—Breast I.

Description of Data Sources

The Syracuse Cancer Registry

Basic information was obtained from the 1967 Annual Report of the Upstate Medical Center Cancer Registry (Syracuse, N.Y.).[17] Additional data acquired during 1973 as a supplement to the 1967 report provide information about the rates of dying in a group at risk for 15 years. The Upstate Medical Center Cancer Registry accesses all cases of carcinoma of the breast identified within the Syracuse catchment area, and patients are automatically registered from all hospitals and pathology laboratories as well as the Bureau of Cancer Control, New York State Department of Health. Admission to the registry occurs upon diagnosis of cancer of the breast, and physicians responsible for these patients are contacted yearly regarding each patient's progress and annual status. Records are updated by information generated from the annual contact and a 99.7% completed followup is reported. Upon death of any registrant, the date and cause of death are entered in the file. The annual contact reports each registrant as follows:

1. Alive
2. Alive with disease

1-2. Status unknown

3. Lost to followup
4. Deceased with disease
5. Deceased—other cause of death
6. Deceased—cause of death unknown.

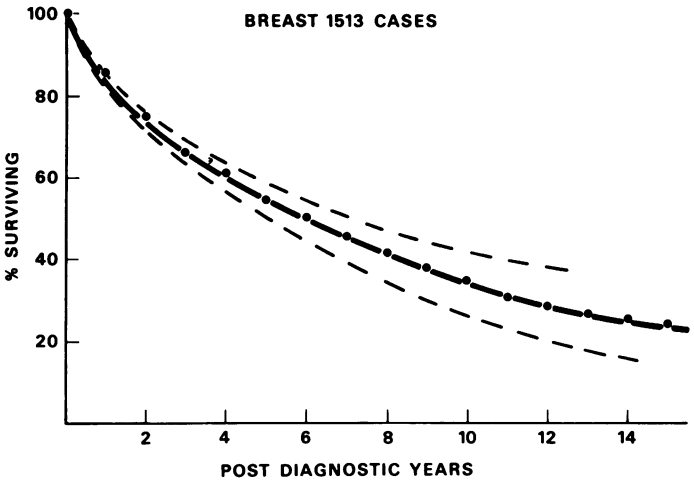

FIG. 1. A curve computed by life table analysis showing survivors in an unselected group of 1,513 women who develop carcinoma of the breast.

Considerable effort is made to determine the cause of death, and the doctor who signs the death certificate is contacted for precise information. When the cause of death is difficult to determine and the patient has had recent trouble related to her carcinoma, the cause of death is considered to be breast cancer.[2]

Ontario Cancer Treatment Research Foundation

The Ontario Cancer Treatment and Research Foundation in Hamilton maintains a registry for patients referred for treatment of breast cancer. This registry does not collect every patient in the Hamilton catchment area and is, therefore, less complete than the Syracuse Registry. Examination of the Hamilton data was carried out with a random sample of 51 women who died between 12 and 24 months, and 41 women who died between 48 and 60 months, following diagnosis. Registry records, doctors' office records, hospital records and pathology reports were reviewed to determine the status at time of diagnosis as well as the cause of death.

National Cancer Institute, Breast I–II Studies

In 1957 a collaborative study sponsored by the National Cancer Institute was initiated to determine whether improvement in the survival rate of cancer of the breast could be achieved with the use of adjuvant chemotherapy at the time of mastectomy.[8] The studies concluded that although time of first recurrence and postop morbidity were influenced to a measurable degree, the ultimate time of death was not altered and the fixed period survival was not significantly different between the two groups. Admission to this study was controlled by a protocol designed to identify curable cases and automatically excluded all women whose breast carcinomas had extended to a point which precluded a curative effort

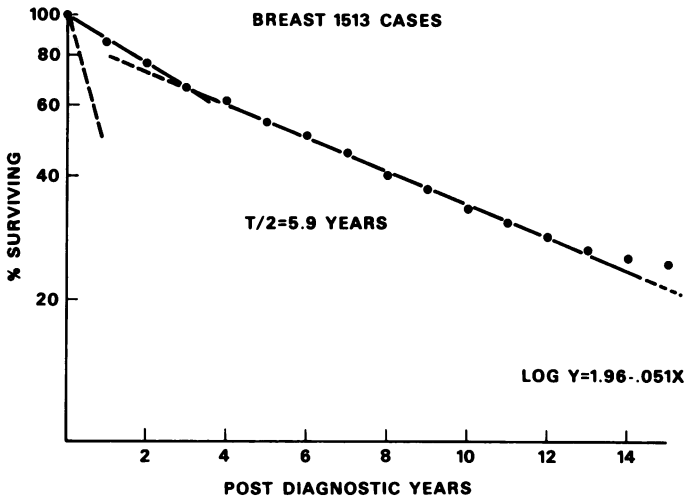

FIG. 2. A semi-log plot of the information presented in Fig. 1 showing that from the 3rd to the 15th year there is a steady rate of decay in the group of women with carcinoma of the breast.

through the surgical procedure and adjuvant chemotherapy. Thus, an unknown number of "incurables" was excluded, leaving only the most favorable cases in the study. Records were maintained of the causes of death of those women who died during the years of these two studies. Three age categories were used and deaths were classified as due to cancer or to competing risks. These studies which deal only with patients considered to have curable carcinoma of the breast are in some contrast to the lists of registrants obtained from Syracuse and Hamilton, which were not so restricted.

A general outline of the N.C.I. study is presented in Fig. 4, and shows the universal set of women (U) with a subset who develop carcinoma of the breast. A portion of the subset, 3,225 women, was then subjected to excisional surgery and adjuvant chemotherapy according to protocol. Admission to the study continued until a few months before the study was terminated, so that all women in the study were not at risk for the same period of time.

Results

A. *The Rate of Dying*

With the use of the annual information from the Syracuse Registry, a 15-year (actuarial) life table analysis of 1,513 patients was developed (Fig. 1). The date of accession is the time of diagnosis and the annual contact determines status in each subsequent year. The number of patients available as the study approaches the 15th year falls below 100. Confidence limits of the curve at the .95 level are presented.[4]

When presented on a semi-log plot, the death curve demonstrated in Fig. 1 suggests a single exponential function (Fig. 2) with the exception of a small component who

TABLE 1. *A Comparison of the Characteristics at Time of Diagnosis of Two Groups of Women Who Died 1-2 Years and 4-5 Years Following Diagnosis of Carcinoma of the Breast.*

	Death After Diagnosis	
At Diagnosis	1-2 Years	4-5 Years
Average Age	59	49
% Under 60	45%	80%
Nodes Involved at Time of Diagnosis	68%	37%
Average Size of Tumor	>2 cm	<2 cm
Clinical Stage	II	50% I 50% II
Carcinoma as Cause of Death	48/51	39/41

died at a more rapid rate in the initial three-year period.[14,20] If the method of least squares with data from the 3rd to 10th years is used, the bulk (88%) of this group demonstrates a half-life (50% mortality rate—T/2) of 5.9 years. A small portion (12%) appears to constitute a group which dies with a T/2 of .84 years.[18]

B. *The Cause of Death*

Examination of the cause of death was initially carried out to determine whether the rapidly-dying group could be distinguished from the slower-dying group at the time of diagnosis. Subsequently, the study was concerned with the influence of competing risks which might be operative simultaneously with influences produced by cancer of the breast.

Causes of Death–Hamilton Data. An examination of the records of these 92 women showed that only 5 died of causes other than breast cancer: 3 women in the 1-2 year group (ages at diagnosis were 71, 75 and 75), and 2

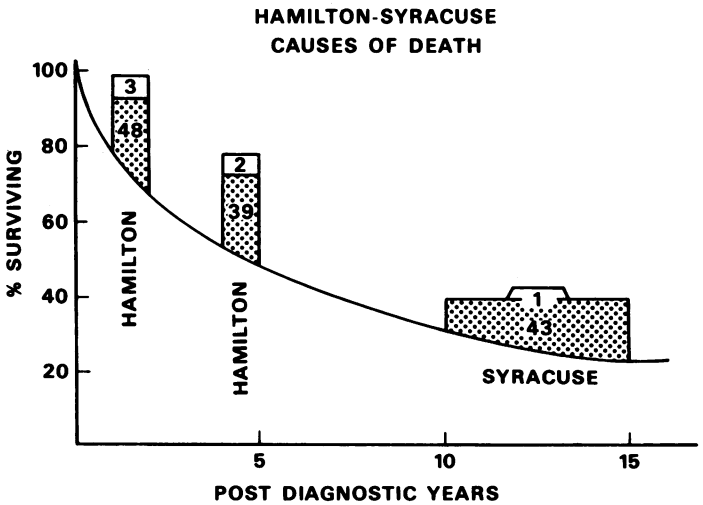

FIG. 3. A composite presentation of the causes of death due to breast cancer in 3 groups of women who died at 1-2, 4-5 and 10-15 years following diagnosis of carcinoma of the breast.

women in the 4-5 year group (ages at diagnosis were 71 and 59) died of cardiovascular diseases (Fig. 3).

Comparison Between the Two Groups. Those who died 1-2 years after diagnosis were approximately 10 years older at the time of diagnosis than those who died later (4-5 year group). Twice as many patients in the group who died shortly after diagnosis had axillary nodal involvement. The tumor sizes were measurably larger, the women were mainly Stage 2, and their course from diagnosis to death contained less adjuvant treatment such as chemotherapy or x-ray therapy. Data were not adequate for staging the Hamilton women, and no details emerged at time of diagnosis to be predictive in terms of time of dying (Table 1).

Causes of Death–Syracuse Data. The Upstate Medical Center Cancer Registry identified 139 women who survived at least 10 years post diagnosis. Of this group, 44 died in the interval between the 10th and the 15th year. Causes of death for these 44 women were obtained from the information present on the registry card regarding patient status. Of the 44 patients dying between the 10th and the 15th year, 43 died with cause of death recorded as carcinoma of the breast (Fig. 3).

Causes of Death–N.C.I. Data. During the course of the N.C.I. study, 914 women died, 705 because of carcinoma of the breast and 209 because of competing risks. The N.C.I. report shows the age at time of diagnosis and the outcome in terms of cause of death, without reference to time of dying. When divided into three age categories, it is apparent that incidence of death due to cancer of the breast is highest in the youngest group at risk and least in the oldest group. In women over 70 at diagnosis, causes of death due to competing risks exceeded the deaths due to breast cancer.

Continuous Influence of Competing Risks–N.C.I. Study. An analysis of the cause of death of patients dying during the first 90 months of the Breast I Study is presented in Fig. 5. Of 826 women admitted to the study, 337 died during the study period. The reported death information showed that approximately 8% per year died during the study, a figure compatible with the T/2 determined from the Syracuse data. In each of the observed periods, a small proportion died of competing risks. This fact suggests that the force of mortality due to competing risks continues to operate at a fairly steady rate throughout the subsequent life experience of women with breast cancer.

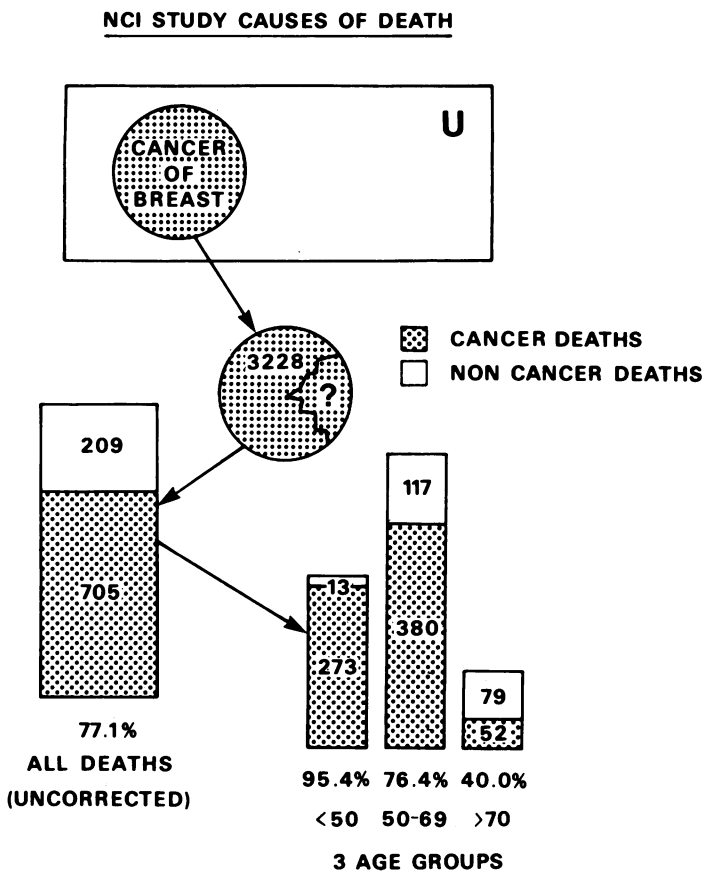

FIG. 4. A presentation of the Breast I-II Cooperative Studies which depicts that in the universal set of women (U) there is a subset who develop carcinoma of the breast. From this subset, 3,228 women were treated according to a fixed protocol while an unknown number were excluded from treatment. In the treated group, during the course of the study, 705 women died of breast cancer and 209 of competing risks. When divided into three age categories it is apparent that forces of mortality due to competing risks are greater in the older than the younger age group.

Discussion

Survival in groups of patients with breast cancer may be measured and reported by the use of several statistical methods. The most popular method is the 5- or 10-year survival in selected or staged groups of patients undergoing treatment. Staging invariably gives results which disregard the course or outcome of those patients excluded from the study by the process of staging (i.e., selection). Thus, the excluded group of patients, usually ill-defined and generally of unknown size, does not contribute to an overall view of end results. Outcome differences which may occur between supposedly comparable groups are generally attributed to influences of a diagnostic or therapeutic procedure, rather than subtle influences introduced by the timing of diagnosis, by the staging procedure[7] or by an unknown and unmeasured variability in the tumor-host relationship. Considerable uncertainty and fallibility are inherent in the process of clinical staging, despite the development of an improved and more rigorous classification system (TNM).[16]

In 1963, the American Joint Committee Task Force on End Results Reporting described the advantages of the actuarial method (life table analysis) for the measurement of survivorship as a preferred alternative to the direct

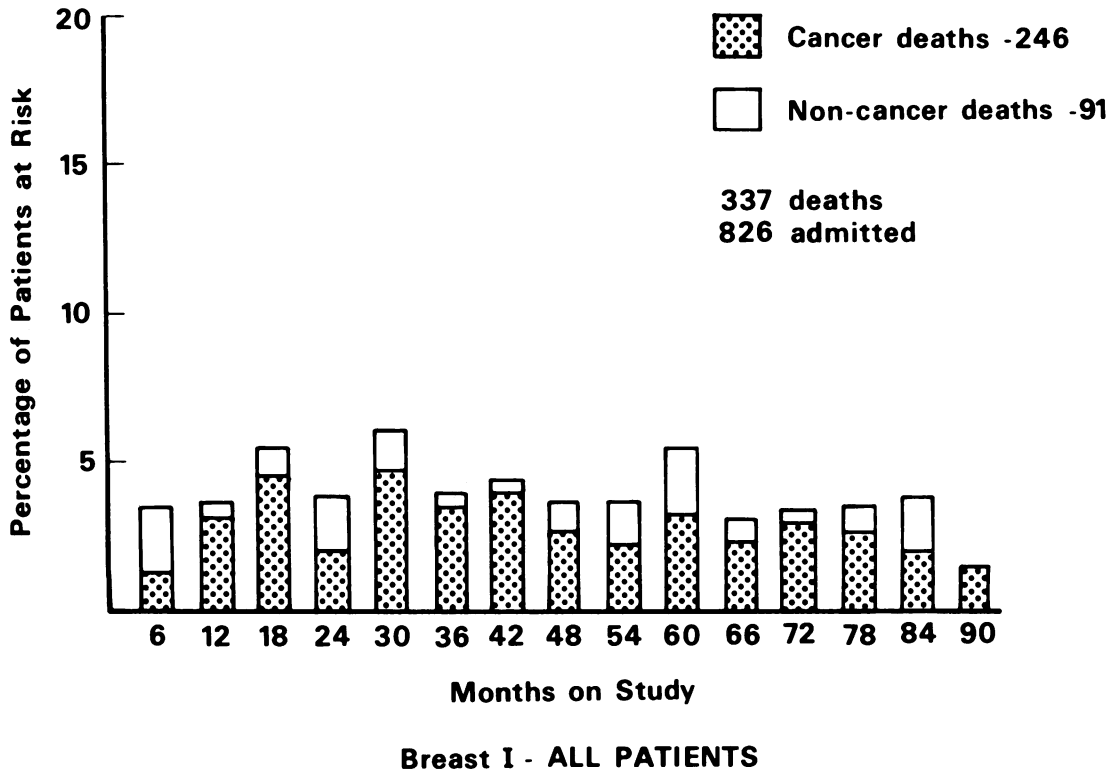

FIG. 5. A presentation of information gained during the NCI Breast I study showing the cause of death of 337 women who died during the course of the study. This demonstrates that competing risks operate continuously during the first 90 months after diagnosis.

method employed in the standard 5- or 10-year survivor analyses.[13] Life table analysis requires the determination of the annual status of all patients at risk and permits use of all data, including those data on patients who may subsequently be lost to followup. The actuarial or life-table method produces a curve which describes the rate of demise of the population at risk and gives a dynamic description of the death or decay rate, rather than a static description of survivorships at fixed time. This method is contrasted to methods such as "5-year survivals" which use terminal information about individuals who can be allocated as either "alive" or "dead" at the end of a fixed time. The major disadvantage of the life table method is the requirement of a large study sample in order to provide reasonable confidence limits as the analysis proceeds and the number of individuals at risk decreases.

The annual status "alive," "lost" or "dead" does not distinguish between death due to the primary disease or to competing risks, yet common clinical experience recognizes that individuals who develop cancer of the breast may die of diseases other than breast cancer. The causes of death have not been adequately reviewed in large series, perhaps because of difficulties in obtaining adequate records or because of less interest in the causes of death than in the time of death, with a general assumption that all deaths were due to cancer. When reviewed, death certificates in Connecticut proved sufficiently reliable in defining causes of death[5] for use in a study of death causes. The certificate study did suggest, however, that the diagnosis of non-cancer deaths in patients with breast cancer was slightly over-reported and, conversely, death due to breast cancer was under-reported.

In analyzing the rate of dying, the population at risk (i.e., the initial 1,513 in the Syracuse registry) includes every woman with the diagnosis of cancer of the breast and is not subdivided into age-related categories, types of lesion or method of treatment. No information is offered about the influence of treatment, early diagnosis, the effects of staging, the histologic character of the lesion, the extent of spread or the influence of age. The death curve represents the resultant of all mortality forces operating in this otherwise unselected population. The points on the curve following the 12-year period are generated by numbers too small to permit the conclusion that there has been a change in rate following the 12th year. This portion of the curve is similar to that presented in a Christie Hospital and Holt Radium Institute Report,[3] and studies to the 20th year are required to clarify this point.

Fig. 2 shows that the death curve appears to break into two rates at the third year, with a small initial group dying at a more rapid rate than the main group. Data referenced to other carcinomas, when presented in large enough groups to permit a similar analysis, suggest that other carcinomas studied seem to have a comparable, two-part death curve.[12,19]

The data presented here suggest that any woman who develops cancer of the breast has a high likelihood (probably 80-85%) of dying of her breast cancer. This likeli-

hood is higher in women who are younger at the time of diagnosis, whereas the competing causes of mortality are more apparent in the group in which the disease occurs at an older age. The forces of mortality due to cancer of the breast seem to be operative over a long period of time (at least 15 years). The percentage of women dying of their breast cancer seems to be a fixed proportion of those at risk in any year, unchanged throughout at least 15 years, except for the small group with early rapid mortality during the first 2 to 3 years after diagnosis. The women over 70 years of age experienced a higher proportion of death due to competing risks (79/52), presumably because the required exposure to their carcinoma was of insufficient duration and the mortality forces due to competing risks had increased sufficiently to overtake the shorter exposure to mortality forces of the carcinoma. Zumoff reports that the T/2 for competing risks doubles every 8.5 years, describing a downward exponential curve.[21] Therefore, competing risks ultimately achieve a rate equal to, or greater than, the T/2 which characterizes breast carcinoma. It has been customary to attribute a positive effect to any therapeutic modality used in cancer management when death curves due to the cancer approach the natural death curve of normal life expectancy.[6] This explanation is now open to reinterpretation, at least at that time when the competing risk rate exceeds the rate characteristic of cancer of the breast, as in the older-age group.

Since death for an overwhelming number of individuals was attributed to cancer of the breast, it appears that treatment may have little or nothing to do with the cause of death. No data are presented which answer whether a therapeutic influence may affect the rate of dying and justify the use of "delay of death" as an appropriate end point. All who treat patients with breast cancer have recognized clinical settings in which surgical, radiologic or chemotherapeutic procedures have evoked a feeling of wellbeing and a seeming delay in the initially anticipated time of death. Patients in whom this occurs appear to be relatively few in number, and perhaps their influence within the total group of breast cancer patients is so small that it is immeasureable.

Conclusions

The group of women with carcinoma of the breast have a measurable rate of dying: a) When the annual mortality is computed within the group at risk, the likelihood of dying is no different in the 15th year than in the 3rd year after diagnosis; b) The rate of dying is approximately 8% per year in the group at risk (T/2 = 6 years).

Of the women who die following a diagnosis of cancer of the breast, 80-85% do so because of their breast carcinoma.

The force of mortality due to competing risks a) operates continuously; b) increases with advancing age.

Fixed-time survivorship is a function of the four variables: 1) time of diagnosis; 2) stage of disease; 3) host-tumor relationship; 4) method of treatment; a) It cannot adequately express the force of mortality for at least 15 years after diagnosis; b) It cannot be related to a single variable without control of the other three.

Breast cancer treatment should: a) Treat the cancer only when and where it is known to exist; b) Not be proposed as a means of influencing either time of death or cause of death.

Measurements of quality of life should be established and should constitute the only realistic objectives of treatment.

Acknowledgment

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Discussion

Dr. Claude E. Welch (Boston): First, let me compliment Dr. Mueller upon his excellent study on cancrology, one of the first presented before this society.

I might say parenthetically of his last conclusion if it could be accepted it would remove many malpractice problems that are before the community, if we could say cancer of the breast has this fixed schedule of life and death, not influenced by treatment.

However, I believe that we have another point of view that should be presented. (Slide) This slide might be characterized as being the most ancient and venerable slide ever presented before this Association. It was made 40 years ago and has been shown only once before to any audience.

This represents a study made in 1937 by the late Dr. Ira Nathanson and myself on the life expectancy of cancer of the breast. This was done here with two curves. You can see that the lower curve here in the dotted line represented a hundred untreated cases of cancer of the breast, almost impossible to find these days. This was an extension of early work done by Dr. Ernest Deland.

The second curve, the solid line, represents the treatment of all patients who were seen in the Pontville and the Huntington Hospitals, the outstanding cancer hospitals of our community at that time.

You will note on this slide that the advantage of the treatment as seen there in 1937, almost 40 years ago, could be measured by the little space between those two lines.

You will also note that in Dr. Mueller's figures, that the half-life 50% death rate, decay rate, was 5.9 years. In other words, his curve would be at the 50% level way over here.

Now, I would submit to you that there is a definite difference then between what happened 40 years ago and what is happening now. I fully believe that we are erecting those little crosses a little less rapidly than indicated by the first picture.

Dr. Francis D. Moore (Boston): This is not a disease about which it's easy for someone to say something new and to think about it in a new way. Dr. Mueller is to be congratulated by looking at this with the kind of mathematical construct which permits new analyses.

He points out that 80–85% of women who die after getting this disease will die of the disease. Our data would certainly support that.

The slopes of the curve are indeed a single exponential. They are a straight line plotted on semi-log paper and that is something that always brings great joy to the heart of the statistician. Big changes in the slope can be made.

For example, in the treatment of the late disease, we found that the slopes were rather different and the half-times were very different according to the treatment.

We could change the half-times from 0.6 years to 3.0 years if the patient were a responder to the combination of oophorectomy, adrenalectomy and 5-FU, so that we were changing slopes in a way that was significant.

The quality of life is very important. It is evaluable by the patient (or her family if she has died) and it can certainly be graded by various methods. In our little study, we found a correlation between the half-time of the slope and the quality of life which was in a sense surprising until you stop to think that the quality of life has the dimension of time in it.

If a person feels well for one day, that's good quality of life, but if he feels like that for two years it's about 720 times as good a quality of life.

So on the basis of this type of statistical analysis, using the single exponential method, the half-time data exactly as Dr. Mueller did, we found that death delay was both possible and justified.

The trouble was that the delay was really much too short. Many years hence we will look back on this paper as being a tribute to our general ignorance in the field of neoplasia.

Dr. Benjamin F. Rush, Jr. (Newark, New Jersey): One can always rely on Dr. Mueller to bring before us exciting, stimulating and controversial new data and he certainly has done that this morning. I'd like to reflect a little on some of the questions he has raised.

First of all, the log normal plot is a new tool in the way we look at cancer of the breast or, for that matter, survival and end results in a number of other cancers.

If you apply it to untreated patients, then the half-life of that group is about 2.6 or 2.7 years, quite different from the half-life of the total group, containing I presume both treated and untreated patients, that Dr. Mueller presented to us.

So that would be our first question, how does one reconcile this difference?

Secondly, one of our major problems with all cancer data is that we are constantly looking back to examine what we have done rather than what we are currently doing.

With the enormous thrust currently in progress throughout the country to treat so-called minimal cancer, some of the very early data from that group is coming out. As you are aware, Urban, for instance, has reported that for lesions measuring 3–15 mm, he has had no deaths at five years in this selected group and at ten years only one death in 44 patients and no local recurrences. The age for that group is about the same as the average age for other patients being treated for cancer of the breast.

So, if the time of treatment alone is operative how do we explain this observation?

I would hope that what Dr. Mueller has brought us is the bad news from the past and that we can look forward to better news from the future.

Dr. Jonathan E. Rhoads (Philadelphia): The data which we have been shown seems to me to have an important corollary which has been referred to at various times in the past, but perhaps not adequately stressed. The surgical approach to cancer is to operate early enough to eradicate it and where metastasis has occurred in breast carcinoma—distant metastasis—the case is declared non-operable.

The data showing that the death rate in the second five years is essentially the same as it is in the first five years. It would seem to belie the idea that one very often gets around the whole cancer and gets it all out.

If one goes back in his thinking to the study that Warren Cole and several others did on cells circulating in the bloodstream, one also wonders whether cancers haven't disseminated. Perhaps they haven't taken root anywhere else but that there have been showers of cancer cells through the body long before the tumor really becomes palpable.

It's true most of the time that when you get, say, a tumor of a centimeter which is perhaps as small as you frequently feel them, why, you already have had so many multiplications of a cell—perhaps 50 times—that it's not biologically a small tumor, then what are we doing? I tend to accept Dr. Welch's view that we are doing some good.

I know it's possible to deposit, that you're simply moving the time before diagnosis to the time after diagnosis, but I find that hard to accept as a total explanation for the difference in the lines that he showed.