2 Cancer Survival Analysis

Analysis of cancer survival data and related outcomes is necessary to assess cancer treatment programs and to monitor the progress of regional and national cancer control programs. The appropriate use of data from cancer registries for outcomes analyses requires an understanding of the correct application of appropriate quantitative tools and the limitations of the analyses imposed by the source of data, the degree to which the available data represent the population, and the quality and completeness of registry data. In this chapter the most common survival analysis methodology is illustrated, basic terminology is defined, and the essential elements of data collection and reporting are described. Although the underlying principles are applicable to both, the focus of this discussion is on the use of survival analysis to describe data typically available in cancer registries rather than to analyze research data obtained from clinical trials or laboratory experimentation. Discussion of statistical principles and methodology will be limited. Persons interested in statistical underpinnings or research applications are referred to textbooks that explore these topics at length.

BASIC CONCEPTS

A *survival rate* is a statistical index that summarizes the probable frequency of specific outcomes for a group of patients at a particular point in time. A *survival curve* is a summary display of the pattern of survival rates over time. The basic concept is simple. For example, for a certain category of patient, one might ask what proportion is likely to be alive at the end of a specified interval, such as 5 years. The greater the proportion surviving, the lower the *risk* for this category of patients. Survival analysis, however, is somewhat more complicated than it first might appear. If one were to measure the length of time between diagnosis and death or record the vital status when last observed for every patient in a selected patient group, one might be tempted to describe the survival of the group as the proportion alive at the end of the period under investigation. This simple measure is informative only if all of the patients were observed for the same length of time.

In most real situations, not all members of the group are observed for the same amount of time. Patients diagnosed near the end of the study period are more likely to be alive at last contact and will have been followed for less time than those diagnosed earlier. Even though it was not possible to follow these persons as long as the others, their survival might eventually prove to be just as long or longer. Although we do not know the complete survival time for these individuals, we do know a minimum survival time (time from diagnosis to last known contact date), and this information is still valuable in estimating survival rates. Similarly, it is usually not possible to know the outcome status of all of the patients who were in the group at the beginning. People may be lost to follow-up for many reasons: they may move, change names, or change physicians. Some of these individuals may have died and others could be still living. Thus, if a survival rate is to describe the outcomes for an entire group accurately, there must be some means to deal with the fact that different people in the group are observed for different lengths of time and that for others, their vital status is not known at the time of analysis. In the language of survival analysis, subjects who are observed until they reach the endpoint of interest (e.g., recurrence or death) are called *uncensored* cases, and those who survive beyond the end of the follow-up or who are lost to follow-up at some point are termed *censored* cases.

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Two basic survival procedures that enable one to determine overall group survival, taking into account both censored and uncensored observations, are the life table method and the Kaplan–Meier method. The life table method was the first method generally used to describe cancer survival results, and it came to be known as the actuarial method because of its similarity to the work done by actuaries in the insurance industry. It is most useful when data are only available in grouped categories as described in the next section. The Kaplan–Meier estimate utilizes individual survival times for each patient and is preferable when data are available in this form.

The specific method of computation, that is, life table or Kaplan–Meier, used for a specific study should always be clearly indicated in the report to avoid any confusion associated with the use of less precise terminology. Rates computed by different methods are not directly comparable, and when the survival experiences of different patient groups are compared, the different rates must be computed by the same method.

The concepts of survival analysis are illustrated in this chapter. These illustrations are based on data obtained from the public-use files of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The cases selected are a 1% random sample of the total number for the selected sites and years of diagnosis. Follow-up of these patients continued through the end of 1999. Thus, for the earliest patients, there can be as many as 16 years of follow-up, but for those diagnosed at the end of the study period, there can be as little as 1 year of follow-up. These data are used both because they are realistic in terms of the actual survival rates they yield and because they encompass a number of cases that might be seen in a single large tumor registry over a comparable number of years. They are intended only to illustrate the methodology and concepts of survival analysis. SEER results from 1973 to 1997 are more fully described elsewhere. These illustrations are not intended and should not be used or cited as an analysis of patterns of survival in breast and lung cancer in the USA.

THE LIFE TABLE METHOD

The life table method involves dividing the total period over which a group is observed into fixed intervals, usually months or years. For each interval, the proportion surviving to the end of the interval is calculated on the basis of the number known to have experienced the endpoint event (e.g., death) during the interval and the number estimated to have been at risk at the start of the interval. For each succeeding interval, a cumulative survival rate may be calculated. The cumulative survival rate is the probability of surviving the most recent interval multiplied by the probabilities of surviving all of the prior intervals. Thus, if the percent of the patients surviving the first interval is 90% and is the same for the second and third intervals, the cumulative survival percentage is 72.9% ($0.9 \times 0.9 \times 0.9 = 0.729$).

Results from the life table method for calculating survival for the breast cancer illustration are shown in Figure 2.1. Two-thousand eight-hundred nineteen (2,819) patients diagnosed between 1983 and 1998 were followed through 1999. Following the life table calculation method for each year after diagnosis, the 1-year survival rate is 95.6%. The 5-year cumulative survival rate is 76.8%. At 10 years, the cumulative survival is 61.0 %.

The lung cancer data show a much different survival pattern (Figure 2.2). At 1 year following diagnosis, the survival rate is only 41.8%. By 5 years it has fallen to 12.0%, and only 6.8% of lung cancer patients are estimated to have survived for 10 years following diagnosis. For lung cancer patients the *median survival time* is 10.0 months. Median survival time is the point at which half of the patients have experienced the endpoint event and half of the patients remain event-free. If the cumulative survival does not fall below 50% it is not possible to estimate median survival from the data, as is the case in the breast cancer data.

In the case of breast cancer, the 10-year survival rate is important because such a large proportion of patients live more than 5 years past their diagnosis. The 10-year time frame for lung cancer is less meaningful because such a large proportion of this patient group dies well before that much time passes.

An important assumption of all actuarial survival methods is that censored cases do not differ from the entire collection of uncensored cases in any systematic manner that would affect their survival. For example, if the more recently diagnosed cases in Figure 2.1, that is, those who were most likely not to have died yet, tended to be detected with earlier-stage disease than the uncensored cases or if they were treated differently, the assumption about comparability of censored and uncensored cases would not be met, and the result for the group as a whole would be inaccurate. Thus, it is important, when patients are included in a life table analysis, that one be reasonably confident that differences in the amount of information available about survival are not related to differences that might affect survival.

THE KAPLAN–MEIER METHOD

If individual patient data are available, these same data can be analyzed using the Kaplan–Meier method. It is similar to the life table method but calculates the proportion surviving to each point that a death occurs, rather than at fixed intervals. The principal difference evident in a survival curve is that the stepwise changes in the cumulative survival rate appear to occur independently of the intervals on the "Years Following Diagnosis" axis. Where available, this method provides a more accurate estimate of the survival curve.

PATIENT-, DISEASE-, AND TREATMENT-SPECIFIC SURVIVAL

Although overall group survival is informative, comparisons of the overall survival between two groups often are confounded by differences in the patients, their tumors, or the treatments they received. For example, it would be misleading to compare the overall survival depicted in Figure 2.1 for the sample of all breast cancer cases with the overall survival for a sample of breast cancer patients who were diagnosed with more advanced disease, whose survival would be presumed to be poorer. The simplest approach to accounting for possible differences between groups is to provide survival results that are specific to the categories of patient, disease, or treatment that may affect results. In most cancer applications, the most important variable by which survival results should be subdivided is the stage of disease. Figure 2.3 shows the *stage-specific* 5-year survival curves of the same breast cancer patients described earlier. These data show that breast cancer patient survival differs markedly according to the stage of the tumor at the time of diagnosis.

Almost any variable can be used to subclassify survival rates, but some are more meaningful than others. For example, it would be possible to provide season-of-diagnosis-specific (i.e., spring, summer, winter, and fall) survival rates, but the season of diagnosis probably has no biologic association with the length of a breast cancer patient's survival. On the other hand, the race-specific and age-specific survival rates shown in Figures 2.4 and 2.5 suggest that both of these variables are related to breast cancer survival. Caucasians have the highest survival rates and African-Americans the lowest. In the case of age, these data suggest that only the oldest patients experience poor survival and that it would be helpful to consider the effects of other causes of death that affect older persons using adjustments to be described.

Although the factors that affect survival may be unique to each type of cancer, it has become conventional that a basic description of survival for a specific cancer should include stage-, age-, and race-specific survival results. Treatment is a factor by which survival is commonly subdivided, but it must be kept in mind that selection of treatment is usually related to other factors that exert influence on survival. For example, in cancer care the choice of treatment is often dependent on the stage of disease at diagnosis. Comparison of survival curves by treatment is most appropriately accomplished within the confines of randomized clinical trials.

CAUSE-ADJUSTED SURVIVAL RATE

The survival rates depicted in the illustrations account for all deaths, regardless of cause. This is known as the *observed survival rate*. Although observed survival is a true reflection of total mortality in the patient group, we frequently are interested in describing mortality attributable only to the disease under investigation. In the past, this was most often calculated using the *cause-adjusted survival rate*, defined as the proportion of the initial patient group that escaped death due to a specific cause (e.g., cancer) if no other cause of death was operating. This technique requires that reliable information on cause of death is available and makes an adjustment for deaths due to causes other than the disease under study. This was accomplished by treating patients who died without the disease of interest as censored observations.

COMPETING RISKS/CUMULATIVE INCIDENCE

The treatment of deaths from other causes as censored is controversial, since statistical methods used in survival analysis settings assume that censoring is independent of outcome. This means that if the patient was followed longer, one could eventually observe the outcome of interest. This makes sense for patients lost to follow-up (if we located them, we might eventually observe their true survival time). However, if a patient dies due to another cause, we will never observe their death due to the cancer of interest. Estimation of the adjusted rate as described previously does not appropriately distinguish between patients who are still alive at last known contact date and those known to have died from another cause. These latter events are called *competing risks*.

When competing risks are present, an alternative to the Kaplan–Meier estimate is the cumulative incidence method. This technique is similar to the Kaplan–Meier estimate in its treatment of censored observations and is identical to the Kaplan–Meier estimate if there are no competing risks. However, in the presence of competing risks, the other causes of death are handled in a different manner.

RELATIVE SURVIVAL

Information on cause of death is sometimes unavailable or unreliable. Under such circumstances, it is not possible to compute a *cause*-adjusted survival rate. However, it is possible to adjust partially for differences in the risk of dying from causes other than the disease under study. This can be done by means of the *relative survival rate*, which is the ratio of the observed survival rate to the expected rate for a group of people in the general population similar to the patient group with respect to race, sex, and age. The relative survival rate is calculated using a procedure described by Ederer et al.

The relative survival rate represents the likelihood that a patient will not die from causes associated specifically with the cancer at some specified time after diagnosis. It is always greater than the observed survival rate for the same group of patients. If the group is sufficiently large and the patients are roughly representative of the population of the USA (taking race, sex, and age into account), the relative survival rate provides a useful estimate of the probability of escaping death from the specific cancer under study. However, if reliable information on cause of death is available, it is preferable to use the *cause*-adjusted rate. This is particularly true when the series is small or when the patients are largely drawn from a particular socioeconomic segment of the population. Relative survival rates may be derived from life table or Kaplan–Meier results.

REGRESSION METHODS

Examining survival within specific patient, disease, or treatment categories is the simplest way of studying multiple factors possibly associated with survival. This approach, however, is limited to factors into which patients may be broadly grouped. This approach does not lend itself to studying the effects of measures that vary on an interval scale. There are many examples of interval variables in cancer, such as age, number of positive nodes, cell counts, and laboratory marker values. If the patient population were to be divided up into each interval value, too few subjects would be in each analysis to be meaningful. In addition, when more than one factor is considered, the number of curves that result provides so many comparisons that the effects of the factors defy interpretation.

Conventional multiple regression analysis investigates the joint effects of multiple variables on a single outcome, but it is incapable of dealing with censored observations. For this reason, other statistical methods are used to assess the relationship of survival time to a number of variables simultaneously. The most commonly used is the Cox proportional hazards regression model. This model provides a method for estimating the influence of multiple covariates on the survival distribution from data that include censored observations. Covariates are the multiple factors to be studied in association with survival. In the Cox proportional hazards regression model, the covariates may be categorical variables such as race, interval measures such as age, or laboratory test results.

Specifics of these methods are beyond the scope of this chapter. Fortunately, many readily accessible computer packages for statistical analysis now permit the methods to be applied quite easily by the knowledgeable analyst. Although much useful information can be derived from multivariate survival models, they generally require additional assumptions about the shape of the survival curve and the nature of the effects of the covariates. One must always examine the appropriateness of the model that is used relative to the assumptions required.

STANDARD ERROR OF A SURVIVAL RATE

Survival rates that describe the experience of the specific group of patients are frequently used to generalize to larger populations. The existence of true population values is postulated, and these values are estimated from the group under study, which is only a sample of the larger population. If a survival rate was calculated from a second sample taken from the same population, it is unlikely that the results would be exactly the same. The difference between the two results is called the sampling variation (chance variation or sampling error). The *standard error* is a measure of the extent to which sampling variation influences the computed survival rate. In repeated observations under the same conditions, the true or population survival rate will lie within the range of two standard errors on either side of the computed rate approximately 95 times in 100. This range is called the *95% confidence interval.*

COMPARISON OF SURVIVAL BETWEEN PATIENT GROUPS

In comparing survival rates of two patient groups, the statistical significance of the observed difference is of interest. The essential question is, "What is the probability that the observed difference may have occurred by chance?" The standard error of the survival rate provides a simple means for answering this question. If the 95% confidence intervals of two survival rates do not overlap, the observed difference would customarily be considered statistically significant, that is, unlikely to be due to chance. This latter statement is generally true, although it is possible for a formal statistical test to yield a significant difference even with overlapping confidence intervals. Moreover, comparisons at any single time point must be made with care; if a specific time (5 years, for example) is known to be of interest when the study is planned, such a comparison may be valid; however, identification of a time based on inspection of the curves and selection of the widest difference make any formal assessment of difference invalid.

It is possible that the differences between two groups at each comparable time of follow-up do not differ significantly but that when the survival curves are considered in their entirety, the individual insignificant differences combine to yield a significantly different pattern of survival. The most common statistical test that examines the whole pattern of differences between survival curves is the *log rank test.* This test equally weights the effects of differences occurring throughout the follow-up and is the appropriate choice for most situations. Other tests weight the differences according to the numbers of persons at risk at different points and can yield different results depending on whether deaths tend more to occur early or later in the follow-up.

Care must be exercised in the interpretation of tests of statistical significance. For example, if differences exist in the patient and disease characteristics of two treatment groups, a statistically significant difference in survival results may primarily reflect differences between the two patient series, rather than differences in efficacy of the treatment regimens. The more definitive approach to therapy evaluation requires a randomized clinical trial that helps to ensure comparability of the patient characteristics and the disease characteristics of the two treatment groups.

Definition of Study Starting Point. The starting time for determining survival of patients depends on the purpose of the study. For example, the starting time for studying the natural history of a particular cancer might be defined in reference to the appearance of the first symptom. Various reference dates are commonly used as starting times for evaluating the effects of therapy. These include (1) date of diagnosis, (2) date of first visit to physician or clinic, (3) date of hospital admission, (4) date of treatment initiation, date of randomization in a clinical trial evaluating treatment efficacy, and (5) others. The specific reference date used should be clearly specified in every report.

Vital Status. At any given time, the vital status of each patient is defined as alive, dead, or unknown (i.e., lost to follow-up). The endpoint of each patient's participation in the study is (1) a specified *terminal event* such as death, (2) survival to the completion of the study, or (3) loss to follow-up. In each case, the observed follow-up time is the time from the starting point to the terminal event, to the end of the study, or to the date of last observation. This observed follow-up may be further described in terms of patient status at the endpoint, such as the following:

- Alive; tumor-free; no recurrence
- Alive; tumor-free; after recurrence
- Alive with persistent, recurrent, or metastatic disease
- Alive with primary tumor
- Dead; tumor-free
- Dead; with cancer (primary, recurrent, or metastatic disease)
- Dead; postoperative
- Unknown; lost to follow-up

Completeness of the follow-up is crucial in any study of survival, because even a small number of patients lost to follow-up may lead to inaccurate or biased results. The maximum possible effect of bias from patients lost to follow-up may be ascertained by calculating a maximum survival rate, assuming that all lost patients lived to the end of the study. A minimum survival rate may be calculated by assuming that all patients lost to follow-up died at the time they were lost.

Time Intervals. The total survival time is often divided into intervals in units of weeks, months, or years. The survival curve for these intervals provides a description of the population under study with respect to the dynamics of survival over a specified time. The time interval used should be selected with regard to the natural history of the disease under consideration. In diseases with a long natural history, the duration of study could be 5–20 years, and survival intervals of 6–12 months will provide a meaningful description of the survival dynamics. If the population being studied has a very poor prognosis (e.g., patients with carcinoma of the esophagus or pancreas), the total duration of study may be 2–3 years, and the survival intervals may be described in terms of 1–3 months. In interpreting survival rates, one must also take into account the number of individuals entering a survival interval.

SUMMARY

This chapter has reviewed the rudiments of survival analysis as it is often applied to cancer registry data and to the analysis of data from clinical trials. Complex analysis of data and exploration of research hypotheses demand greater knowledge and expertise than could be conveyed herein. Survival analysis is now performed automatically in many different registry data management and statistical analysis programs available for use on personal computers. Persons with access to these programs are encouraged to explore the different analysis features available to demonstrate for themselves the insight on cancer registry data that survival analysis can provide and to understand the limitations of these analyses and how their validity is affected by the characteristics of the patient cohorts and the quality and completeness of data.

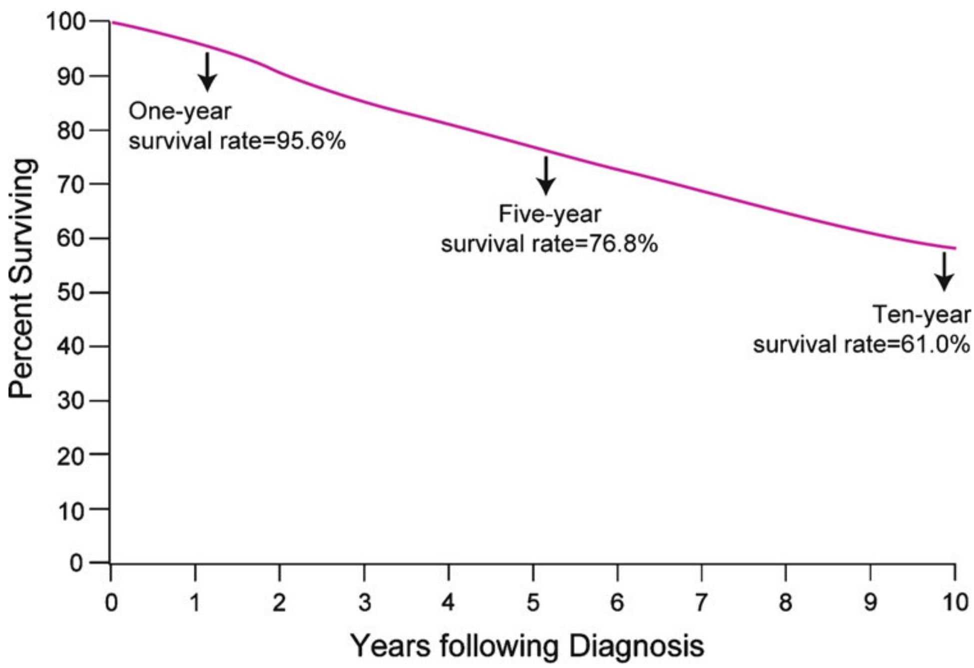

FIGURE 2.1. *Survival of 2,819 breast cancer patients from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1983–1998. Calculated by the life table method.*

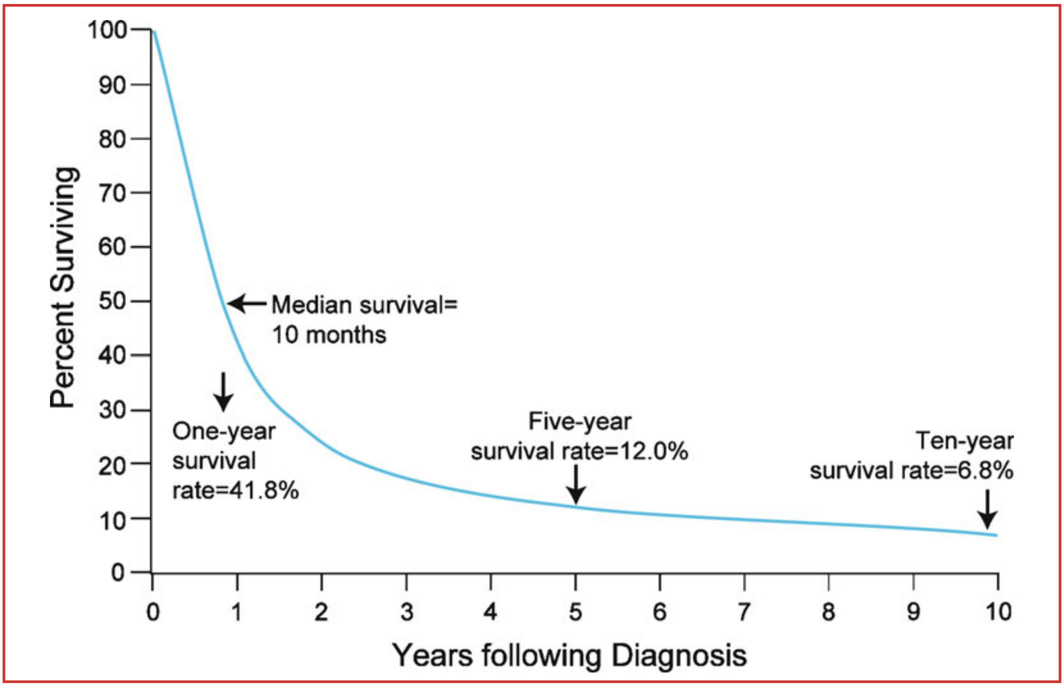

FIGURE 2.2. *Survival of 2,347 lung cancer patients from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1983–1998. Calculated by the life table method.*

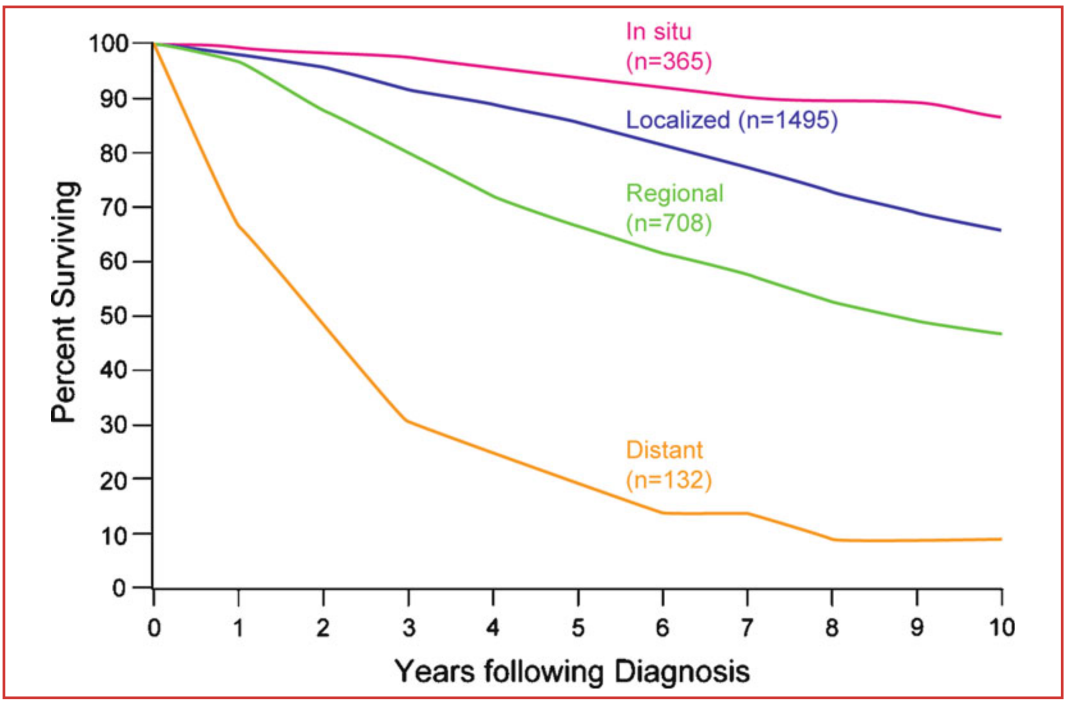

FIGURE 2.3. *Survival of 2,819 breast cancer patients from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1983–1998. Calculated by the life table method and stratified by historic stage of disease. Note: Excludes 119 patients with unknown stage of disease. SEER uses extent of disease (EOD) staging.*

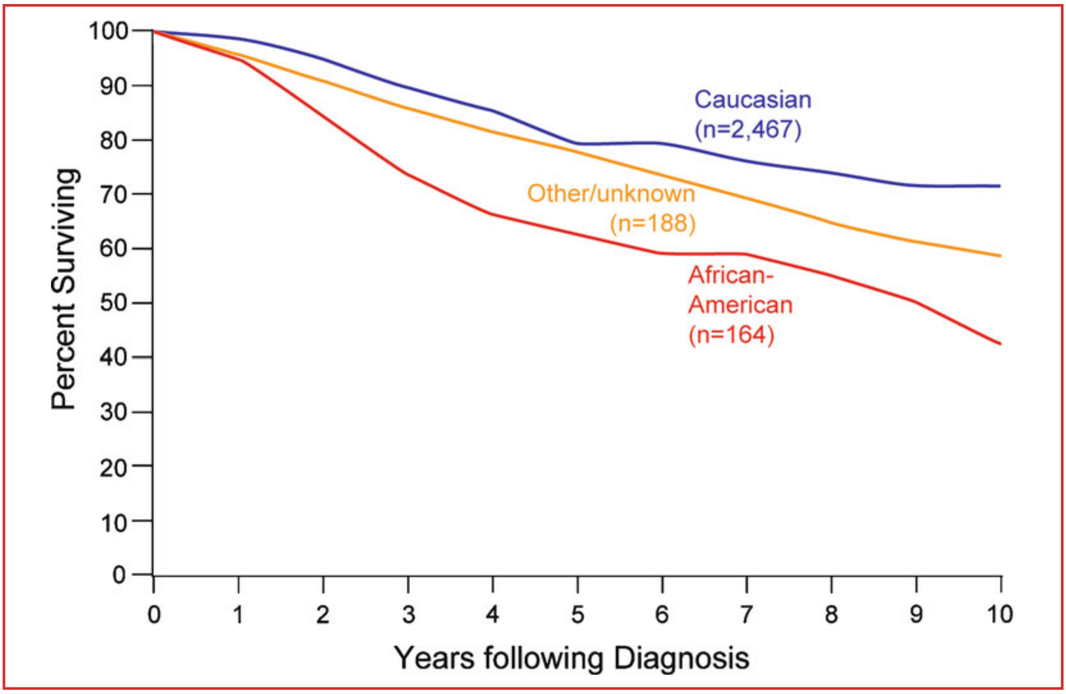

FIGURE 2.4. *Survival of 2,819 breast cancer patients from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1983–1998. Calculated by the life table method and stratified by race.*

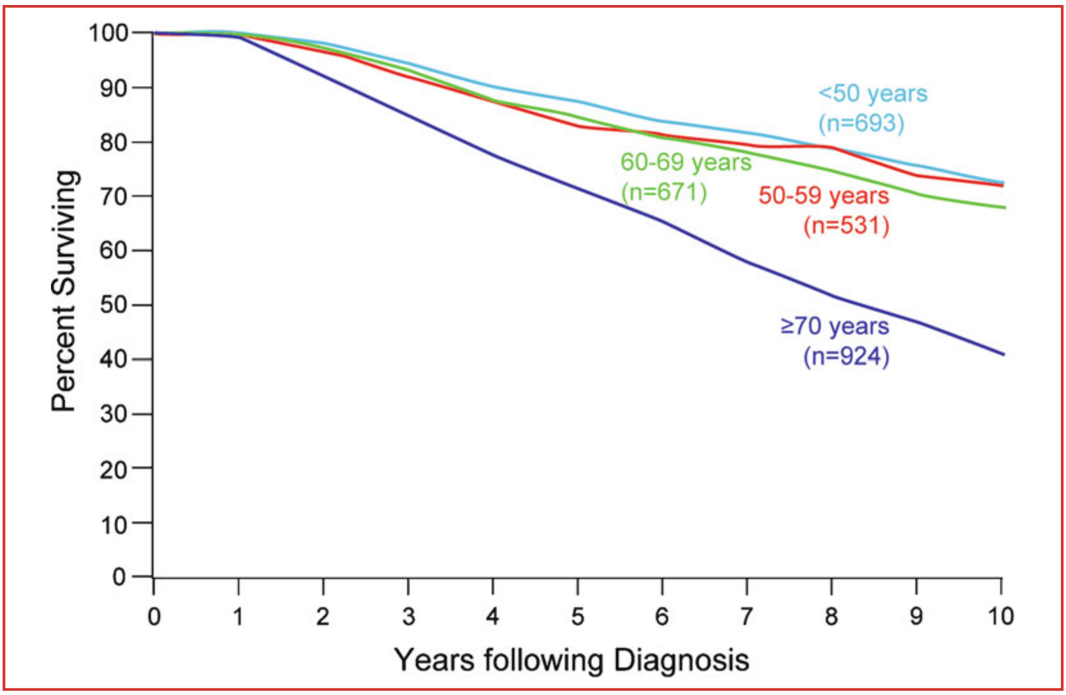

FIGURE 2.5. *Survival of 2,819 breast cancer patients from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1983–1998. Calculated by the life table method and stratified by age at diagnosis.*

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