The Relative Survival Rate: A Statistical Methodology

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TABLE OF CONTENTS

INTRODUCTION

Patient survival is generally accepted as the principal criterion for measuring the effectiveness of treatment in cancer. The American College of Surgeons requires the maintenance of a cancer registration and follow-up program for approval of a hospital cancer program (*1*). The importance of accounting for all cancer patients seen, both treated and untreated, was stressed by the Joint Committee on Reporting Cancer End Results,[2] which formulated minimum rules for reporting survival (*2*).

Although the survival rate, *i.e.*, the proportion of patients surviving a specified interval of time, is a simple concept, there has been a considerable lack of uniformity in computing it. Many physicians exclude deaths from other causes, apparently because they consider it unfair to charge non-cancer deaths to the therapy being evaluated; some only exclude operative deaths; others exclude deaths in which the cancer in question was not known to be present at time of death. When survival rates are used to evaluate the effectiveness of therapy, as they invariably are, the exclusion of operative deaths is hardly defensible. When one series of patients has been treated surgically and a similar series radiologically, the exclusion of

[1] National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

[2] American College of Surgeons, College of American Pathologists, American College of Radiology, American Cancer Society, U.S. Public Health Service,

operative deaths is tantamount to saying that these deaths are not attributable to surgery, *i.e.*, that these patients would have died even if treated by radiotherapy. This is obviously invalid.

The exclusion of "noncancer deaths" is frequently not possible and is conceptually objectionable. Most hospitals operating cancer registries do not obtain copies of death certificates on patients dying outside the hospital. Thus, information on cause of death is not available in many instances in which accurate information on time of death is at hand. Furthermore, the death certificate description of the sequence of events leading to death is frequently incomplete or inaccurate (*3*, *4*). Moreover, aside from the question of accuracy of information, it is often difficult to interpret known facts. Suppose a cancer patient commits suicide. Or, suppose a patient with hyperthyroidism is irradiated and dies of leukemia several years later. Are these or are these not to be considered deaths due to cancer? In discussing the issue of deaths due to "other causes," Paterson, Tod, and Russell (*5*) stated: ". . . no figures which depend on opinion as to the cause of death . . . can be accepted as completely reliable, particularly if they are to be used to compare the value of different methods of treatment. . . . Death from intercurrent disease may be interpreted in two ways: It may mean that at the time when the patient died of another disease or injury no sign of cancer could be found, or it may mean that he died of another cause but with cancer present. Even were agreement on interpretation to be reached, it is still a matter of opinion dependent on skill in examination whether there were signs of cancer or not, and whether the supposed other cause was not itself another manifestation of the disease." In discussing the same issue, Berkson and Gage (*6*) stated: "The determination of whether a death is entirely due to cancer or entirely due to other causes is difficult to establish, if indeed it is even possible to define precisely. Actually, in most cases it is impossible to establish unequivocally. . . ."

Although it may be possible to establish acceptable rules for assigning causes of death, valid interpretation of cause-of-death data requires more detail than is generally available to a cancer registry. Since most cancer patients are past middle age, their risk of dying from other causes is not negligible and it is necessary to adjust for this risk in analyzing their survival experience. This is particularly true when one compares patient groups which differ with respect to factors closely associated with differential mortality risks, *e.g.*, sex, age, race, and calendar period of diagnosis. The *relative survival rate* provides the necessary adjustment for expected mortality from causes other than the disease under study without requiring information on causes of death.

THE RELATIVE SURVIVAL RATE

The actuarial or life-table method for computing survival rates has been described elsewhere (*7–9*). The actuarial computations describe the pattern by which a group is depleted over a series of time intervals.

The method enables one to use all survival information available on the closing date of the study, even the data on patients who entered too late to be observed for the desired length of time, *e.g.*, 5 years. However, in including the data for late entries, one assumes that their survival experience subsequent to the closing date will be similar to that of patients under observation for the entire period. If this assumption is not valid, the procedure is biased (*10*).

The historical development and an explanation of the general methodology of the relative survival rate has been given elsewhere (*11*). We will briefly review the basic concepts and then consider methods for estimating expected survival in a "normal" population, and develop an expression for the standard error of the relative survival rate.

The relative survival rate, which has also been referred to as "the survival ratio" and "the survival rate adjusted for normal life expectancy," provides the answer to Berkson's question: "What is the survival rate so far as cancer is concerned?" (*12*). It is based on the hypothesis that a group of cancer patients is subject to two forces of mortality: *1*) mortality from the specific form of cancer under study, and 2) mortality from all other possible causes of death.[3] We shall define the relative survival rate as the *ratio* of the *observed survival rate* in a group of patients, during a specified interval, to the *expected survival rate*. The expected survival rate is that of a group similar to the patient group in such characteristics as age, sex, and race, but *free of the specific disease under study*. A relative survival rate of less than 100 percent indicates that, during the specified interval, mortality in the patient group exceeded that of persons in the general population free of the disease under study. A relative survival rate equal to 100 percent indicates that, during the specified interval, mortality in the patient group was equal to that in the general population. Thus, analysis of the relative survival rate for successive follow-up intervals permits us to determine whether the mortality rate in a patient group declined in such a fashion so as to approximate a normal level in a specified number of years. The attainment and maintenance of a relative survival rate equal to 100 percent, after a reasonable number of years of follow-up, would indicate that a fraction of the patient group had escaped the force of mortality due to the specific form of cancer under study. This would be presumptive evidence that this fraction had been successfully treated, and it would be possible to estimate the size of this fraction.

The relative survival rate has been referred to as "the age-adjusted survival rate" but it should be noted that the relative survival rate accomplishes age adjustment only in part. It does adjust for the association between age and the risk of dying from other causes, but not for possible association between age and the risk of dying from the specific form of

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[3] As pointed out by Berkson and Gage (*6*), this hypothesis undoubtedly ". . . oversimplifies the facts; that the presence of cancer influences the probability of death from other causes . . . and that the effect of treatment on mortality is more complicated than the sharp dichotomization pictured. But it appears that these complexities do not disturb too violently the effective use of a simplified model."

cancer under study. For example, it has been shown that prognosis in ovarian cancer varies inversely with age. The outlook for younger women, relative to survival in the general population, is clearly better than for older women (*13*). Therefore, in comparing the survival experience of two series of patients with ovarian cancer of unlike age composition, one must age-adjust the observed and relative survival rates by standard statistical methods.

THE EXPECTED SURVIVAL RATE

Use of Population Life Tables

The expected survival rate was defined as the rate for a population similar to the patient group, but *free of the specific disease under study.* Life tables published by the National Office of Vital Statistics are a readily available source of information from which expected survival rates may be estimated. The life-table population may be looked upon as a control group.

Since population life tables reflect the force of mortality from all causes of death, it would seem desirable to adjust the life-table values so as to eliminate deaths due to the disease under study. In practice, this is rarely necessary. Berkson and Gage (*7, 12*) and Cutler *et al.* (*14*) have argued that mortality for a specific site constitutes a negligible fraction of total mortality and that, therefore, survival rates computed from general population life tables provide satisfactory estimates of expected rates in analyzing survival of patients with cancer of a specific site. Milmore (*15*) has shown that eliminating cancer of the breast as a cause of death has, for most age groups, little effect on total mortality of women. Ederer and Heise (*16*) found that eliminating cancer of the stomach as a cause of death has little effect on the expected and relative survival rates, even over an interval of 15 years. Although we generally are not concerned with analyzing the survival of patients with all forms of cancer combined, Ederer and Heise investigated the effect of eliminating all cancer deaths in estimating expected rates from population life tables. They found that this adjustment affected 5- and 10-year relative survival rates to a small degree. Since we are usually concerned with analyzing survival of patients with specific forms of cancer, it appears that we do not need to make an adjustment in estimating expected survival from population life tables. Furthermore, entirely eliminating a specified form of cancer as a cause of death generally overcorrects the estimated expected rate. Although the control group should be free of the disease under study at entry to observation, it does not follow that the control group should not be subject to the risk of subsequently developing the disease and dying therefrom. Unless the organ of origin of the cancer under study is completely removed, even the successfully treated patient is subject to the risk of developing a second cancer at the same site.

It is well known that survival varies with sex, race, and age. These factors present no problem to the person computing expected survival rates because separate life tables are available for white and nonwhite males and females, and the influence of age on life expectancy is specifically described in the life table. Whereas separate life tables are available for individual geographic regions, it is interesting to note that 5-year survival rates for the geographic regions of the United States differ rather little from one another, except that nonwhites in the Mountain and Pacific divisions have higher rates than those in other divisions (table 1).

TABLE 1.—Expected 5-year survival rates at age 60, by sex, race, and geographic division, United States, 1949–51* (rates are expressed as percents; geographic divisions are as defined by U.S. Bureau of the Census)

	White				Nonwhite			
	Males		Females		Males		Females	
Geographic division	Rate	Percent difference from U.S.	Rate	Percent difference from U.S.	Rate	Percent difference from U.S.	Rate	Percent difference from U.S.
United States	86. 8	—	92. 2	—	81. 4	—	84. 8	—
New England Division	86. 3	−0. 6	91. 5	−0. 8	82. 7	1. 6	86. 9	2. 5
Middle Atlantic Division	85. 4	−1. 6	90. 8	−1. 5	81. 0	−0. 5	84. 8	0. 0
East North Central Division	86. 8	0. 0	91. 9	−0. 3	80. 8	−0. 7	84. 6	−0. 2
West North Central Division	88. 7	2. 2	93. 3	1. 2	80. 9	−0. 6	84. 4	−0. 5
South Atlantic Division	86. 7	−0. 1	92. 8	0. 7	79. 2	−2. 7	83. 5	−1. 5
East South Central Division	88. 3	1. 7	93. 1	1. 0	82. 0	0. 7	84. 5	−0. 4
West South Central Division	88. 0	1. 4	93. 7	1. 6	83. 3	2. 3	86. 1	1. 5
Mountain Division	87. 9	1. 3	93. 1	1. 0	86. 8	6. 6	89. 1	5. 1
Pacific Division	86. 7	−0. 1	92. 9	0. 8	85. 3	4. 8	89. 3	5. 3

*Source: National Office of Vital Statistics: Life Tables for the Geographic Divisions of the United States 1949–51. Vital Statistics—Special Reports, Vol. 41, No. 4, July 26, 1956.

Whereas published life tables permit adjustment for sex, race, age, and geographic area, they provide no information on a variety of other factors associated with longevity. Consider two groups of patients with a specified disease, one treated in a research center and the other treated in a county hospital. These two groups would probably differ with respect to socioeconomic status, occupation, and ethnic background. No life tables are available which reflect the differences in mortality in the populations from which these patients were drawn. This does not mean that no useful information can be obtained from available life tables. However, one should keep in mind the possible influence of such factors as socioeconomic status and occupation in interpreting the results.

Some population characteristics are not only associated with longevity, but also with the incidence of cancer. Marital status, urban versus rural residence, income, and smoking are associated with the incidence of at least some forms of cancer (*17–19*). Thus, the distribution of these characteristics among cancer patients differs from that among persons in the general population. For example, one would expect more smokers among patients with lung cancer than in the general population. Since general mortality is higher for smokers, general population life tables, unadjusted for smoking history, will tend to overstate the survival expected in the controls for patients with lung cancer.

It is of interest to explore the effect of associations, such as that between smoking and lung cancer, on the appropriateness of expected survival rates computed from published life tables. One can adjust life-table survival rates for the effect of smoking by using available mortality data for smokers and nonsmokers and data on the distribution of smokers among cancer patients and in the general population.

Columns (1) and (2) of table 2 illustrate the difference in amount of smoking between males in the general population and male lung cancer patients: 56 percent of the general population (ages 55–64) are nonsmokers of cigarettes, compared to only 7 percent for lung cancer patients; smokers of 1 or more packs of cigarettes per day constituted 11 percent of the general population, and 75 percent of the lung cancer population. The mortality rates (all causes) of cigarette smokers (column 3) relative to nonsmokers varied from 1.34 for smokers of less than ½ pack to 2.23 for smokers of 2 or more packs. The effect of adjusting for smoking, as shown in the remaining columns of table 2, is to increase the expected percent dying in 1 year from 2.5 to 3.6, and in 5 years from 13.6 to 19.4. When these percents are translated into survival (*see* table 3), and relative rates for lung cancer, for all cases and those treated by surgery, are computed, the differences, as shown in the last column of table 3, are quite small. The very low survival rates experienced for lung cancer contribute materially to the smallness of the differences. Table 3 also shows that if a hypothetical lung cancer treatment yielded a 1-year survival rate as high as 95 percent, the adjustment for smoking would not materially change the expected rate. However, if this miraculous treatment yielded 75 percent 5-year observed survival, adjusting for smoking would change the relative rate from 87 to 93, a noteworthy difference. Thus, we see that, under certain circumstances, associations between population characteristics with cancer and with general mortality may have significant effects on the accuracy of estimated relative survival rates.

Lung cancer and smoking were purposely chosen in this illustration because of their exceedingly strong association. Aside from age and sex, smoking has been shown to have greater association with cancer than any other factor. Marital status is associated with cancer of the breast, cervix, and ovary. However, since only a small proportion of women over 35 are in the "never married" group (less than 10%) it seems unlikely that adjusting for marital status will appreciably change the relative survival rates for cancer of these sites, especially in view of the facts that

TABLE 2.—Expected mortality among male lung cancer patients, 55–64 years of age, adjusted for amount of cigarette smoking

Packages of cigarettes smoked per day	Percent of total: United States males age 55–64*	Percent of total: Male lung cancer patients†	Mortality ratio (all causes)‡	Expected percent dying In 1 year: Unadjusted§	In 1 year: Adjusted for smoking‖	In 5 years: Unadjusted§	In 5 years: Adjusted for smoking‖
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Total	100	100	1. 31¶	2. 5	3. 6	13. 6	19. 4
None**	56	7	1. 00	1. 9	—	10. 4	—
Less than ½	9	4	1. 34	2. 6	—	13. 9	—
½–1	24	14	1. 70	3. 2	—	17. 6	—
1–2	10	60	1. 96	3. 7	—	20. 3	—
2+	1	15	2. 23	4. 3	—	23. 2	—

* Source: Haenszel, Shimkin, and Miller (20).
† Source: table 4, Breslow *et al.* (21).
‡Mortality relative to nonsmokers. Source, except for "total" line: Hammond and Horn (19).
§ Entry in "total" line computed for age 60 from U.S. Life Tables, 1949–51: entry for each smoking class computed by applying quotient of mortality ratio for smoking class to total mortality ratio to the entry in "total" line of this column.
‖ Weighted average of the expected percents dying, with data of column (2) as weights.
¶ Weighted average of mortality ratios of smoking subgroups, with data in column (1) as weights.
** Includes occasional smokers (less than 1 cigarette per day).

TABLE 3.—Effect of adjustment for amount of smoking on the relative 1- and 5-year survival rates of lung cancer patients

Treatment and survival period	Expected percent dying: Unadjusted	Expected percent dying: Adjusted	Survival rate (%) Expected: Unadjusted	Expected: Adjusted	Observed*	Relative: Unadjusted	Relative: Adjusted	Relative: Difference between adjusted and unadjusted
1-Year								
All patients	2. 5	3. 6	97. 5	96. 4	18. 2	18. 7	18. 9	0. 2
Treated by surgery	2. 5	3. 6	97. 5	96. 4	46. 6	47. 8	48. 3	0. 5
Hypothetical treatment	2. 5	3. 6	97. 5	96. 4	95. 0	97. 4	98. 4	1. 1
5-Year								
All patients	13. 6	19. 4	86. 4	80. 6	4. 1	4. 1	5. 1	0. 4
Treated by surgery	13. 6	19. 4	86. 4	80. 6	13. 4	15. 5	16. 6	1. 1
Hypothetical treatment	13. 6	19. 4	86. 4	80. 6	75. 0	86. 8	93. 1	6. 3

*Source for all cases and surgical treatment: Connecticut, 1947–51 (22).

adjusting for smoking did not materially change the relative survival rate for lung cancer.

Adjustment for Secular Trend

Dublin and Spiegelman (*23*) and Merrell (*24*) have distinguished between the *static* and *fluent* life table. The static life table, also referred to as the *time-specific* life table, is based on age-specific mortality rates as of a given point in time. The fluent life table, also referred to as the *cohort* or *generation* life table, takes into account the change in mortality over calendar time. Thus, constructing a fluent life table for the generation born in 1910, one would use the 1910 mortality rates for the 1st year of life, the 1911 mortality rates for the 2d year of life, the 1912 mortality rates for the 3d year of life, etc. The decline in general population mortality rates during recent decades has been very impressive. The mortality rate, per year per 1,000, for a 50-year-old white female was 9.59 in 1930, 7.62 in 1940, and 5.61 in 1950. Milmore (*15*) has pointed out that use of static life tables during an era of declining general mortality rates can lead to overestimation of improvement in survival for cancer. Table 4 shows that the effect of the decline, since 1930, in general mortality rates on the *expected* survival rates is small for the 5-year rate, but is appreciable for the 10- and 15-year rates, particularly for the older ages. Table 5 compares fluent and static life tables in their effect on the *relative* survival rates for localized and regional breast cancer (Connecticut, 1935–

TABLE 4.—Five-, 10-, and 15-year expected survival rates for white males and white females, computed from U.S. Life Tables 1929–31, 1939–41, 1949–51, and 1957

(rates are expressed as percents)

Age and survival period in years	White males				White females			
	1929–31	1939–41	1949–51	1957	1929–31	1939–41	1949–51	1957
Age 40								
0–5	96.2	97.0	97.6	97.9	97.1	97.9	98.6	98.6
0–10	91.2	92.7	93.9	94.5	93.3	94.9	96.4	96.5
0–15	84.7	86.5	88.3	89.1	88.2	90.8	93.2	93.3
Age 50								
0–5	92.9	93.3	94.0	94.3	94.6	95.6	96.7	96.7
0–10	83.4	84.2	85.5	86.2	87.1	89.4	91.8	92.1
0–15	71.3	72.4	74.2	74.8	77.0	80.6	84.7	85.3
Age 60								
0–5	85.5	86.0	86.8	86.8	88.4	90.2	92.2	92.6
0–10	67.6	68.9	70.7	69.8	72.9	76.6	81.1	81.2
0–15	47.6	49.3	52.1	51.1	54.1	58.6	65.3	66.6
Age 70								
0–5	70.4	71.5	73.7	73.3	74.1	76.6	80.5	81.9
0–10	41.1	42.5	46.4	47.1	46.2	49.5	56.3	60.0
0–15	18.1	19.3	23.2	23.0	21.9	24.8	31.6	33.9
Age 80								
0–5	44.0	45.4	50.1	48.8	47.4	50.2	56.1	56.5
0–10	13.7	14.2	17.5	n.a.*	16.1	17.5	22.8	n.a.
0–15	2.7	2.8	3.9	n.a.	3.5	3.8	5.8	n.a.

* Not available.

TABLE 5.—Comparison of relative survival rates computed from expected rates based on static (1939–41) and cohort life tables, breast cancer localized and regional stages, Connecticut, 1935–44

(rates are expressed as percents)

Age	Follow-up interval (years)	Observed survival rate		Expected survival rate		Relative survival rate				Difference in relative survival rates: static versus cohort life tables	
						Localized		Regional			
		Localized	Regional	Static life table 1939–41	Cohort life table	Static life table 1939–41 (3)÷(5)	Cohort life table (3)÷(6)	Static life table 1939–41 (4)÷(5)	Cohort life table (4)÷(6)	Localized (7)−(8)	Regional (9)−(10)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Under 35											
	0–5	67. 9	21. 7	99. 0	99. 0	69	69	22	22	0	0
	0–10	55. 4	17. 2	97. 6	98. 0	57	57	18	18	0	0
	0–15	48. 5	10. 3	95. 6	96. 7	51	50	11	11	1	0
35–44											
	0–5	74. 5	41. 4	97. 9	98. 0	76	76	42	42	0	0
	0–10	63. 8	27. 7	95. 0	95. 7	67	67	29	29	0	0
	0–15	52. 9	18. 9	90. 4	92. 4	59	57	21	20	2	1
45–54											
	0–5	67. 9	39. 4	95. 1	95. 4	71	71	41	41	0	0
	0–10	54. 7	23. 8	87. 9	89. 8	62	61	27	27	1	0
	0–15	41. 6	19. 0	78. 5	82. 8	53	50	24	23	3	1
55–64											
	0–5	69. 1	32. 2	89. 3	89. 7	77	77	36	36	0	0
	0–10	47. 5	19. 2	75. 5	77. 7	63	61	25	25	2	0
	0–15	34. 0	12. 4	57. 4	63. 3	59	54	22	20	5	2
65–74											
	0–5	58. 6	31. 6	76. 0	76. 9	77	76	42	41	1	1
	0–10	30. 3	16. 4	48. 6	52. 5	62	58	34	31	4	3
	0–15	16. 8	4. 2	24. 6	30. 2	68	55	17	14	13	3
75–84											
	0–5	45. 3	27. 7	50. 5	52. 2	90	87	55	53	3	2
	0–10	18. 5	8. 1	17. 9	22. 3	103	83	45	36	20	9
	0–15	5. 7	0. 0	3. 9	4. 9	146	116	0	0	30	0
85+											
	0–5	30. 0	0. 0	22. 0	21. 6	136	139	0	0	−3	0
	0–10	5. 0	0. 0	2. 7	2. 5	185	200	0	0	−15	0
	0–15	0. 0	0. 0	0. 2	0. 0	0	0	0	0	0	0

44). The last two columns of this table show that the difference between the relative rates computed by the two methods is small for the 5-year but large for the 10- and 15-year rates for the older ages.

Adjustment for Changes in Age Composition of Patient Group

When analyzing the survival experience of a patient group over an extended number of successive follow-up years one needs to take into account not only the changes in general population mortality for individual age groups, but also changes in the age distribution of the surviving members of the patient group. For example, of 1,535 patients with localized breast cancer diagnosed in Connecticut during the period 1935–44, 20 percent were 35–44 years of age and 20 percent were 65–74 years of age. At the end of the 15th year of follow-up, survivors of the 35–44-year cohort account for 32 percent of all survivors, whereas survivors of the 65–74-year cohort account for only 10 percent. Thus, in computing the expected survival rate for those breast cancer patients who survived 15 years, say, for the 15-20-year interval, we ought not to base this on what the age composition of the original patient cohort would have been after 15 years had they all survived, but on the age composition of those who actually survived, otherwise we would understate the expected survival rate by a considerable amount.

Specific Methods of Computing Expected Survival Rates

An exact method.—One can establish the exact expected survival rate for a group of patients by determining the survival probability for each individual, and then taking the average for the entire group. This method can be used to good advantage when expected rates are required not only for the total group, but also for each of a host of subgroups resulting from subclassification according to pertinent variables, such as stage of disease, treatment, age, calendar period of diagnosis, etc. When each patient is represented by a punch card, then, with the help of an electronic computer, one can obtain the survival rate for each subgroup by selecting the appropriate cards and taking the average of the individual survival probabilities. The totality of computations, *i.e.*, the observed, expected, and, if desired, the relative survival rates and standard errors, can then be carried out simultaneously. However, if the number of computations required is large, a small or medium-sized computer may be inadequate, and a large-scale computer may be necessary. If a large-scale electronic computer is not available, or if the number of rates to be computed is small, approximate methods of computation can be used, some of which are quite simple. We shall review several of these.

Approximate methods.—As early as 1908, Brown and Pope computed expected survival rates for tuberculosis patients (*25*). They assumed that all the patients were age 30, and entered Farr's English Life Tables at that age to determine expected survival. Tuberculosis patients in that era had a narrow age range. Also, survival varies little with age at the younger ages; therefore this approximation did not entail a large error. Nathanson and Welch (*26*), in 1936, proposed that the median age of breast cancer patients be calculated and the expected survival rate for that age be determined from published life tables. Berkson and Gage (*27*) suggested using the average[4] (rather than the median) age, but added that a more precise result is sometimes obtained by weighting the age-specific expected rates in proportion to the age distribution of the patients. We have found that using the mean or median of the entire patient group does give a satisfactory estimate of the expected survival rate for the 1-year, but not necessarily for the 5-year interval, particularly when a disease affecting a wide age range, such as breast cancer, is concerned.

Cutler *et al.* (*11*, *13*, *28*), in a recent analysis of cancer survival data from the Connecticut Tumor Registry, obtained accurate expected rates with the following approximate method.[5]

1. A central year was chosen to represent the calendar period during which the patients entered observation, *e.g.*, 1940 for 1935–44.
2. The cases were divided into seven age groups: under 35, 35–44, 45–54, . . ., 85+.
3. A central age was chosen for each of the age groups: 30, 40, . . ., 90.
4. For each of the central ages, the expected survival rate was determined from published life tables for the general population. This yielded the age-specific expected rates.
5. The age-specific rates obtained in step 4 were weighted in proportion to the number of cases alive and under observation at the beginning of the follow-up interval for which the rate was computed. The average of the weighted rates was the expected rate for all ages combined.

This method served two purposes: 1) to compute the age-specific expected survival rates for an analysis of survival by age and 2) to compute the expected rate for all ages combined. The rather lengthy calculations were carried out by a medium-sized electronic computer. However, one is not always interested in analyzing age-specific survival rates. Usually the over-all rate is the primary concern. We shall present a method for calculating expected survival rates for all ages combined, which can be used by investigators who do not have access to an electronic computer. The method we propose can also be useful to investigators who have access to an electronic computer, but desire interim results until the program is written and the computations are scheduled. The calculations can be carried out on a desk calculator, or even with pencil and paper.

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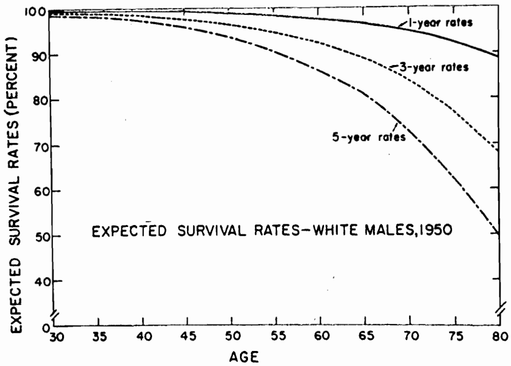
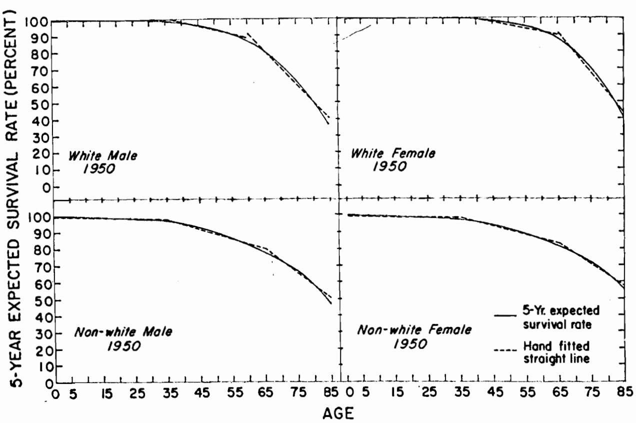
[4] We use the terms "average," "arithmetic mean," and "mean" synonymously.

[5] The accuracy of this method was recently tested in an analysis of 436 breast cancer patients. The exact 5-year expected survival rate was 93.1 percent, compared with 92.5 as computed by Cutler's method.



TEXT-FIGURE 1.—Expected 1-, 3-, and 5-year survival rates for white males, 1950. (From U.S. Life Tables, 1949–51.)



TEXT-FIGURE 2.—Expected 5-year survival rates for white and nonwhite males and females, 1950. (From U.S. Life Tables, 1949–51.)

A simple approximate method for calculating expected survival rates.—Text-figure 1 shows that expected 1-year survival rates are approximately linear over the entire age range, with but slight curvature after age 65, but that the 3- and 5-year rates curve sharply after age 45. Text-figure 2 shows that 5-year survival rates can well be represented by three straight lines; one for under age 30, one for 30–65, and one for 65+. When the expected survival rate is linear over an age interval, the expected rate for a group of patients in that interval is given exactly by the rate for the average age in that interval.[6] *We therefore recommend using either the*

---

[6] Consider n patients age $x_1, x_2, \ldots, x_i, \ldots x_n$, where the ages lie in the interval from a to b. Let $\bar{x}$ be the average age of the patients, and $p(x)$ the expected survival probability at age x. If $p(x)$ is linear over the interval from a to b, then it can easily be shown that the average value of $p(x)$ for the n patients is exactly equal to the value of the function at the average value of x, *i.e.*,

$$\frac{1}{n}\sum_{i=1}^{n} p(x_i) = p(\bar{x}).$$

average or the median age for determining the expected 1-year survival rate, and the weighted average of the age-specific expected rates of each of two or three age groups divided at ages 30 and 65 to determine the 3- or 5-year survival rate. When most of the patients are over 30, as for most types of cancer, two age groups are sufficient: under 65, and 65 or more.[7] The following is a step-by-step procedure for calculating the expected 3- or 5-year survival rate for all ages:

1. Divide the patients into three age groups, under 30, 30–64, and 65 or more, and for each group determine the mean (or median) age.

2. Determine the expected rate for each of the three ages obtained in step 1, either by calculation from published life tables for the general population, or directly from table 6. The use of table 6 will be explained later.

3. Compute the average of the three rates obtained in step 2 by weighting each rate in proportion to the number of cases alive at the beginning of observation.

In computing the 1-year expected rate it is not necessary to divide the patients into groups, thus steps 1, 2, and 3 can be combined into a single step: compute the average (or median) age of the entire group and use table 6.

We will illustrate the 3 steps of this method by calculating the relative 5-year survival rate for 180 patients with cancer of the uterine corpus with regional spread of disease, diagnosed in Connecticut, 1945–54. We are indebted to the Connecticut Tumor Registry for providing us with these data.

Of the 180 patients, 113 were under age 65, and the remaining 67 were 65 or older. Only 1 patient was under 35, hence we will use only two age groups. The number of cases by 10-year age group is:

Total, all ages	180
Subtotal, under 65	(113)
Under 35	1
35–44	13
45–54	42
55–64	57
Subtotal, 65+	(67)
65–74	51
75–84	16
85+	—

[7] In empirical tests of 13 cohorts of cancer patients, the average age ranging from 46 to 72, we found that dividing the cohort into two age groups at age 60, 65, or 70 yielded very satisfactory estimates of the expected survival rate. In this paper we are arbitrarily recommending age 65, although 60 or 70 would also be satisfactory.

TABLE 6.—Expected percent surviving 1, 3, and 5 years in the United States, by sex, race, and age: 1940, 1945, 1950, and 1955*

Age	Male								Female							
	1940		1945		1950		1955		1940		1945		1950		1955	
	White	Non-white	White	Non-white	White	Non-white	White	Non-white	White	Non-white	White	Non-white	White	Non-white	White	Non-white
	1-Year survival rates															
30	99.7	99.1	99.8	99.4	99.8	99.5	99.8	99.6	99.8	99.3	99.8	99.5	99.9	99.6	99.9	99.7
35	99.6	98.9	99.7	99.1	99.8	99.4	99.8	99.4	99.7	99.1	99.8	99.2	99.8	99.5	99.9	99.6
40	99.5	98.6	99.5	98.9	99.6	99.1	99.7	99.2	99.6	98.8	99.7	99.1	99.8	99.2	99.8	99.4
45	99.2	98.1	99.3	98.5	99.4	98.7	99.4	98.9	99.5	98.4	99.5	98.7	99.6	98.9	99.7	99.2
50	98.8	97.5	98.9	97.8	99.0	98.1	99.1	98.4	99.2	97.8	99.3	98.2	99.4	98.4	99.5	98.7
55	98.3	96.8	98.3	97.2	98.4	97.2	98.5	97.7	98.9	97.1	99.0	97.7	99.1	97.8	99.3	98.1
60	97.5	96.1	97.5	96.6	97.6	96.3	97.8	96.7	98.3	96.5	98.5	97.0	98.7	97.0	98.9	97.6
65	96.3	95.3	96.3	95.5	96.6	95.4	96.5	95.1	97.4	95.9	97.5	96.1	97.9	96.3	98.0	96.2
70	94.5	94.2	94.7	94.1	95.0	94.4	95.0	93.7	95.8	95.1	96.2	95.2	96.6	95.4	96.9	95.2
75	91.7	92.2	92.1†	92.6†	92.5	92.9	92.8	93.2	93.1	93.7	93.5†	94.0†	94.3	94.2	94.9	94.8
80	87.5	89.3	88.3†	90.5†	89.0	90.9	89.2	91.9	89.2	91.9	89.9†	92.4†	90.9	92.7	91.5	93.8

3-Year survival rates

30	99.1	97.3	99.3	98.0	99.4	98.5	99.5	98.8	99.3	97.7	99.5	98.4	99.6	98.8	99.7	99.1
35	98.8	96.7	99.0	97.1	99.2	97.9	99.3	98.2	99.1	97.1	99.2	97.5	99.5	98.3	99.6	98.5
40	98.3	95.7	98.5	96.5	98.7	97.2	98.9	97.6	98.8	96.3	99.0	97.1	99.2	97.5	99.3	98.2
45	97.5	94.2	97.7	95.1	97.9	95.9	98.1	96.5	98.3	95.0	98.5	95.9	98.8	96.4	99.0	97.2
50	96.3	92.2	96.4	93.1	96.7	93.9	96.9	94.8	97.5	93.2	97.8	94.5	98.2	95.0	98.5	95.8
55	94.5	90.2	94.7	91.4	94.9	91.4	95.3	92.6	96.4	91.3	96.8	92.7	97.2	93.0	97.7	94.2
60	92.0	88.3	92.2	89.8	92.5	88.9	92.8	89.9	94.5	89.6	95.1	90.7	95.6	91.0	96.3	92.5
65	88.5	86.1	88.6	86.2	89.3	86.4	89.1	85.0	91.5	87.8	92.1	88.1	93.3	88.8	93.5	87.9
70	83.2	82.7	83.9	82.8	84.5	83.4	84.9	81.9	86.6	85.4	88.0	85.8	89.0	86.4	90.4	86.2
75	75.2	77.0	76.2†	78.5†	77.5	79.2	78.2	80.8	78.9	81.4	80.3†	82.2†	82.4	82.9	83.9	84.9
80	64.7	69.7	66.5†	72.5†	68.4	73.9	68.7	75.4	68.6	76.5	71.0†	77.8†	73.1	78.6	74.3	81.1

5-Year survival rates

30	98.5	95.4	98.7	96.5	99.0	97.3	99.1	97.9	98.8	96.1	99.0	97.1	99.3	97.8	99.5	98.4
35	97.9	94.2	98.1	95.0	98.5	96.4	98.7	96.8	98.5	95.0	98.7	95.7	99.1	96.9	99.2	97.4
40	97.0	92.5	97.2	93.9	97.6	95.0	97.9	95.7	97.9	93.5	98.2	95.0	98.6	95.6	98.8	96.8
45	95.5	89.8	95.8	91.3	96.2	92.6	96.5	93.7	97.0	91.2	97.3	92.8	97.8	93.6	98.2	95.0
50	93.3	86.7	93.6	88.2	94.0	89.3	94.4	90.8	95.6	88.3	96.2	90.5	96.7	91.2	97.2	92.5
55	90.2	83.6	90.6	85.6	90.9	85.3	91.6	87.2	93.5	85.4	94.3	87.6	95.0	88.0	95.8	90.0
60	86.0	80.7	86.3	82.7	86.8	81.4	87.3	82.5	90.2	82.8	91.2	84.2	92.2	84.8	93.2	86.7
65	80.2	77.0	80.4	76.9	81.4	77.5	81.2	75.0	85.0	79.9	86.0	80.2	88.0	81.4	88.5	79.7
70	71.5	71.4	72.9	72.3	73.7	72.7	74.4	71.4	76.6	75.7	79.1	77.1	80.5	77.4	82.9	77.8
75	59.5	62.6	61.0†	65.0†	63.0	66.4	63.9	69.6	64.6	69.5	67.8†	70.9†	69.9	71.9	72.1	75.4
80	45.4	52.9	47.9†	56.2†	50.1	58.6	50.1	60.3	50.2	62.3	54.2†	64.4†	56.1	65.6	56.8	66.8

*Source: 1940 rates computed from National Office of Vital Statistics, U.S. Life Tables and Actuarial Tables, 1939–41, tables 5, 6, 8, and 9; 1945 rates computed from Metropolitan Life Insurance Company interpolation of National Office of Vital Statistics Abridged Life Tables, United States, 1945; 1950 rates computed from National Office of Vital Statistics, U.S. Life Tables and Actuarial Tables, 1949–51, Vol. 41, No. 1; 1955 rates computed from Metropolitan Life Insurance Company interpolation of National Office of Vital Statistics Abridged Life Tables, United States, 1955.

†Estimated by extrapolation.

From these data, the average age of the patients under 65 can be determined as 53.7 years, and for the older group as 72.4 years.[8] The respective median ages are 55.1 and 71.6.[9]

Table 6 shows 1-, 3-, and 5-year survival rates by age, sex, and race for 1940, 1945, 1950, and 1955, computed from life tables for the United States. We select, from table 6, the values for calendar year 1950, because this is the midpoint for our group, which was diagnosed 1945–54. In general, it is not necessary to interpolate between calendar years in table 6, because the differences between values for successive 5-year calendar intervals are small. For example, if the patients entered the study, *i.e.*, were diagnosed, admitted, or treated, during the period 1944–50, inclusive, we would select the values for 1945 from table 6, 1945 being the year nearest 1947, the midyear of 1944–50.

The ages in table 6 are given in 5-year intervals, and here it is necessary to interpolate. Using the table of 5-year expected survival rates for white females (virtually all the Connecticut patients are white) for 1950, we interpolate between ages 50 and 55 and between ages 70 and 75 to obtain, respectively, rates of 95.4 and 75.4 percent for the average ages 53.7 and 72.4.

We now compute the average of 95.4 and 75.4, weighting each by the number of cases, 113 and 67, respectively.

$$\frac{(113 \times 95.4) + (67 \times 75.4)}{113 + 67} = 88.0$$

We shall use the 5–10-year interval of follow-up to illustrate the calculation of the expected survival rate for an interval subsequent to the starting point of the study. We have to consider two items: the average age of the patients alive and under study at the beginning of the 6th year, and the calendar year of the life table for looking up the expected rate.

Of the original 180 patients with cancer of the corpus, 38 were alive and under study 5 years after diagnosis (92 had died, 6 were lost to follow-up, and 44 were alive but under observation for less than 5 years at the closing

[8] In computing the average ages, we assumed that the cases were concentrated at the midvalues of the 10-year age intervals, *e.g.*, 40, 50, etc. For the group under age 35, we arbitrarily assumed age 30 as the midvalue; there were no cases 85 or older, otherwise we would arbitrarily assume a midvalue of 90 for this group. The average ages can, of course, be computed more exactly from *un*grouped data. However, grouped data are sufficiently accurate, and often more convenient to work with, especially when the number of cases is large and punched cards are used. The method of computing the arithmetic mean for both grouped and ungrouped data is explained in introductory textbooks in statistics.

[9] It may, in certain instances, be easier to compute the median than the mean. For example, if each patient is represented by a card, then one can easily determine the median age by arranging the cards in order of age of the patient. The middle card, or the average of the middle two cards, is the median. The method for computing the median from grouped and ungrouped data is explained in introductory texthooks in statistics.

date of the study). The distribution by age *at diagnosis* for these patients was as follows:

Total, all ages	38
Subtotal, under 65	(30)
Under 35	1
35–44	4
45–54	14
55–64	11
Subtotal, 65+	(8)
65–74	8
75–84	—
85+	—

From these data, the average age at diagnosis is 51.7 years for the patients under 65 and 70.0 for those 65+, thus the average ages 5 years after diagnosis are 56.7 and 75.0, respectively. Whereas we used the 1950 life-table values for determining the expected rates at diagnosis, we now, 5 years later, use the 1955 values. From table 6 we obtain 94.9 and 72.1, respectively, as the expected 5-year rates for ages 56.7 and 75.0. We now average these rates, weighting them in proportion to the number of cases alive at the beginning of the interval, to obtain the expected 5–10-year survival rate:

$$\frac{(30 \times 94.9) + (8 \times 72.1)}{30 + 8} = 90.1$$

It will be noted that, in the preceding calculations, the dividing line was at age 70, *i.e.*, 65 at diagnosis plus 5 years, rather than at age 65. However, as explained in footnote 7 on page 113, this procedure is acceptable.

When computing long-term expected survival rates, one needs to take into account the secular trend in general population life-table values. Whereas differences in mortality rates between successive calendar years tend to be small, they become appreciable over, say, a 10-year period. Thus, when calculating expected survival rates for intervals greater than 5 years, we recommend subdividing the follow-up interval into 2 or more intervals of 5 years or less. This is a modified application of the cohort, or generation life table (*23*, *24*). We will illustrate the calculation of the 10-year expected rate for the 180 patients, of the previous example, with cancer of the corpus. We subdivide the 0–10-year follow-up interval into two 5-year intervals, 0–5 and 5–10, and subdivide the patients into two age groups, under 65 and 65+. From the average age at diagnosis of the patients in each age group (53.7 and 72.4) we determine the 0–5-year expected rates from the 1950 life-table values, as shown in the preceding section. We now add 5 years to these average ages, and determine the 5–10-year expected rates from the *1955* life tables and have the following:

Follow-up interval	Life table	Under 65		65+	
		Average age	Expected rate	Average age	Expected rate
0–5	1950	53. 7	95. 4	72. 4	75. 4
5–10	1955	58. 7	93. 9	77. 4	64. 8
0–10			89. 6		48. 9

We obtain the 0–10-year rate for each age group by multiplying the 0–5-year rate by the 5–10-year rate, and obtain the 0–10-year rate for all ages by weighting the age-specific 0–10-year rates in proportion to the number of cases alive at diagnosis. Note that we use the number of cases *at diagnosis* as weights because we are concerned with the proportion of expected survivors measured *from diagnosis*. The rationale for this approach has been explained in detail (*29*). The expected 10-year survival rate is:

$$\frac{(113 \times 89.6) + (67 \times 48.9)}{113 + 67} = 74.5$$

THE STANDARD ERROR OF THE RELATIVE SURVIVAL RATE

The standard error provides a measure of the confidence with which one may interpret a statistical result. Thus, the standard error of the survival rate indicates the extent to which the computed rate may have been influenced by sampling variation. For example, by adding and subtracting twice the standard error to and from the computed survival rate, one obtains an approximate 95 percent confidence interval. This means that in repeated observations, under the same conditions, the true survival rate will lie within a range of two standard errors on either side of the computed rate an average of 95 times in 100.

When the survival rate has been calculated by the life-table method, the standard error may be computed from Greenwood's formula (*30*); detailed explanations of this formula, with applications, have been given (*8*, *9*). When the observed survival rate has been computed by the direct method (*7*, *12*, *27*), the standard error may be computed from the binomial formula $\sqrt{p(1-p)/n}$, where p is the survival rate and n is the number of patients exposed to the risk of death. The latter formula can also be used for single intervals of follow-up when the life-table method has been used. Approximate values of twice the standard error of the 1-, 3-, and 5-year survival rate, based on Greenwood's formula, as well as values of twice the standard error for any interval computed by the binomial formula, have been conveniently tabled (*31*). Standard errors of the 1-, 2-, . . . , and 10-year survival rates, based on Greenwood's formula, can be quickly computed from tables published recently (*32*).

The standard error of the *relative* survival rate can be computed directly from the standard error of the *observed* survival rate by simply dividing the latter by the expected survival rate. The proof for this will be developed in the subsequent paragraphs.

Let r = the relative survival rate, p = the observed survival rate, and $\tilde{p}$ = the expected survival rate. Then, by definition, $r = p/\tilde{p}$.

The standard error of the relative interval survival rate can be derived from its rel-variance,[10] V_r^2:

$$V_r^2 = V_p^2 + V_{\tilde{p}}^2 - 2\rho_{p\tilde{p}} V_p V_{\tilde{p}}$$

Since the observed and expected rates are drawn from independent populations, the correlation between p and $\tilde{p}$ is zero, and

$$V_r^2 = V_p^2 + V_{\tilde{p}}^2$$

The expected survival rate is computed from life tables for the general population, hence its rel-variance will usually be very small in comparison with that of the observed survival rate. In practice we may therefore neglect it, and

$$V_r^2 = V_p^2$$

or

$$\sigma_r^2/r^2 = \sigma_p^2/p^2.$$

Thus

$$\sigma_r = r\sigma_p/p = \sigma_p/\tilde{p} \qquad \text{Q.E.D.}$$

SUMMARY

The relative survival rate is defined as the ratio of the observed survival rate in a group of patients to the survival rate expected in a group similar to the patients in such characteristics as age, sex, and race, but free of the specific disease under study. The relative survival rate adjusts for deaths from causes other than the disease under study and thus provides an estimate of the survival rate so far as the disease under study is concerned. In lieu of computing the relative survival rate, some physicians exclude deaths from other causes; it is argued here that this method has conceptual and practical objections. Several features and applications of the relative survival rate as a tool in the analysis of patient survival are discussed. A number of methods, and pitfalls in these methods, for computing expected survival rates from population life tables are reviewed, and a simple approximate method, along with tables of 1-, 3-, and 5-year expected survival rates, is presented. Finally, a formula for the standard error of the relative survival rate is derived.

[10] The rel-variance is the square of the coefficient of variation. Hansen, Hurwitz, and Madow (*33*) show how the formula for V_r^2 is derived.

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