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Interpreting Cancer Survival Rates

The available data on survival are not a sensitive measure of progress in cancer control.

James E. Enstrom and Donald F. Austin

Recently there has been much discussion about the progress or lack of progress in cancer research and control in the United States during the last 25 years. Various authors (1-4) have employed cancer survival rates to support their opinions. For instance, Greenberg says (2):

The lay press is unduly gullible in reporting 'progress'' in cancer treatment. The basis for this contention [is] that cancer survival rates, as reported by the National Cancer Institute, have shown little improvement over the past two decades or so, and that the frequent claims of markedly improved survival rates ignore or blur the fact that most of the changes occurred before 1950, and can probably be attributed to lower mortality from operations. . .

Statisticians at the National Cancer Institute respond (3):

The picture is neither as dull nor as bright as some have claimed. The improvement in patient survival observed during the 1940's and 1950's has generally slowed since then. However, continuing improvement in survival rates took place during the 1960's and is continuing into the 1970's for a substantial segment of cancers. In fact, prognosis for more than half of all patients with cancer is better now than it was 10 years ago. The recent upward trend is less dramatic, but it is nonetheless real and consequential.

One oncologist concludes (4):

One measure of the very real and increasing progress that has occurred in applied and basic cancer research has been the controversy that it has engendered.

The purpose of this article is to put this discussion in perspective by pointing out the many limitations and qualifications in the interpretation of survival rates and their trends. This is not meant to be a comprehensive review of cancer survival rates, but rather a summary of several points necessary for understanding their meaning and their use.

Any discussion of "progress" must first state the goals toward which progress is to be measured. The National Cancer Act of 1971 created the National Cancer Program, for which the goals are specifically detailed in a National Cancer Plan (5–7). In general, the overall goal is 'to develop the means to reduce the incidence, morbidity, and mortality of cancer in humans" (5). More specifically, it is to reduce the burden of cancer in the population by intervening in all of the following effects of cancer: premature

death, presence of disease, persistent disability, somatic discomfort, subjective dissatisfaction, and social disruption. Thus any judgment regarding progress or lack of it must be based upon a measurement of change in one or more of these effects. Whether survival rates and their trends can be used to measure progress against any of the effects of cancer in the population is at issue.

A consideration of cancer survival rates and their trends should begin with an explanation of what these rates measure. Basically, they give the probability of a person's remaining alive for a specified period after being diagnosed as having cancer. The rates are expressed as the percentage of patients still alive at some specified time after the diagnosis. Thus, for any individual patient, survival is equivalent to a period of observation, the start being the point of diagnosis and the end being death or the completion of a specified number of years. Survival rates are most often used to evaluate the effectiveness of therapy in curing cancer, cure being usually defined as survival for at least 5 years. It is common to use relative survival rates, which adjust for the probability of dying from other causes.

Factors Influencing Survival Rates

A number of factors enter into the determination of survival rates. For the patient destined to terminate observation through death due to cancer, survival can be lengthened in either of two ways: first, the endpoint (death) can be displaced distally in time; second, the starting point (diagnosis) can be displaced proximally in time. For instance, every patient could be under observation 1 year longer if the diagnosis could be made 1 year earlier in the course of the disease. This would have the effect of creating a 5-year survival rate equivalent

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to what was previously a 4-year survival rate with no change in efficacy of treatment.

Paradoxically, because survival rates are necessarily based only on patients with invasive cancer, earlier diagnosis can also create an opposite effect. Cases diagnosed in the in situ stage (prior to invasion) are not eligible for inclusion in survival calculations because of the possibility of spurious diagnosis, invasion being the sine qua non of cancer (8). But cases correctly diagnosed in situ represent the group with the best expectation of life. Thus, an increase in the proportion of cancer cases correctly diagnosed in the in situ stage may result in a corresponding increase in the proportion of individuals cured of that cancer which will not be reflected in the survival rates. This situation has been cited as an explanation for the lack of improvement in the 5-vear survival rate over a 20-year period for women with invasive cervical cancer, in spite of a dramatic decrease in the mortality rate of that disease (3).

Cancer survival rates vary as a function of age, sex, race, social class, degree of histological confirmation, and type of treatment, in addition to cancer site, the stage of disease, and host resistance. The survival rate for any given cancer site can vary substantially depending on the combined influence of these various factors. For instance, although survival rates are calculated separately for several stage categories of the disease (localized, regional spread, remote metastasis), the combined rate (all stages) is not adjusted to any standardized stage proportions and therefore is affected by differences in stage proportions that actually occur for various reasons (9). Unfortunately it is this combined rate that is frequently used as a basis of comparison. A similar situation exists for the other variables listed above. Likewise, the survival rate for all sites is not adjusted for varying proportions of specific sites. Thus, it is not appropriate to attach great importance to comparisons of total (all sites) survival

rates, although it is reasonable to use the total survival rate as one measure of the overall cancer problem, just as the total incidence and mortality rates are used as other measures.

Additional factors can complicate the interpretation of trends in survival rates. Because the science of cancer diagnosis is imperfect, inevitably some patients with noncancerous disease are included among patients being observed for cancer survival. However, as diagnostic technology advances, so presumably does the accuracy of diagnosis. Thus, if all other factors remained constant one would expect survival rates to decrease over time as more and more benign conditions were eliminated from the computations.

Improving follow-up methodology can create an opposite trend in survival rates. The usual means of maintaining observation of a cancer patient for survival determination is through an active follow-up procedure. This usually entails review of hospital inpatient and out-

Table 1. Five-year relative survival rates, by site, for cancer of both sexes and all stages, based on data from the California Tumor Registry (CTR) and the End Results Evaluation Program (EREP) for periods of diagnosis from 1942 to 1969. The relative survival rate, expressed in percent, adjusts for the probability of death from other causes, being the ratio of the observed survival rate to the rate expected in a group in the general population matched to the patient group in sex, age, and time of observation (21). The CTR data are based on all races (whites, 95 percent); EREP data are based on whites only. Blanks indicate that no data are available, usually because of an insufficient number of cases.

Cancer sites	California Tumor Registry								End Results Evaluation Program		
	1942–56								····		
	County hospi- tals	Private hospi- tals	Total	1945–49	1950–54	1955–59	196064	1965–69	1950–54	1955–64	1965–69
All sites*											
All stages	19†	41†	34†	33	39	40	40	41	39	39	39
Localized	50	67	64	65	71	69	68	71	68	67	68
Esophagus	1	2	2						4	3	$3 \pm 1 \ddagger$
Stomach	6	13	10	11	11	11	13	13	11	12	12 ± 1
Colon	20	41	35	33	41	46	44	47	42	46	44 ± 1
Rectum	18	41	34	32	42	41	40	42	41	40	40 ± 2
Liver	2	5	4						1	3	5 ± 2
Pancreas	1	3	2	2	1	1	2	2	1	1	1
Larynx	23	56	43						53	55	61 ± 3
Lung	2	7	5	4	6	7	8	9	7	8	9 ± 1
Breast	35	62	56	56	60	63	63	65	59	62	64 ± 1
Cervix uteri*	39	63	54	45	59	60	56	58	57	60	56 ± 2
Corpus uteri	42	70	64	64	71	73	71	72	71	72	74 ± 2
Ovary	18	27	24	25	28	31	34	36	28	32	32 ± 2
Prostate				38	42	49	56	59	44	51	56 ± 2
Kidney	14	35	28						32	36	41 ± 2
Bladder	21	51	42	43	51	51	53	53	54	56	60 ± 3
Hodgkin's	12	20	24						22	20	54 + 2
disease	12	28	24	7	10	10	15	12	33	39	34 ± 3
Leukemia	4	/	0	/	12	19	15	12			
Number of cases, all sites* Percent local- ized cases*	33,112	64,714	97,826	26,066 34	39,762 38	50,649 40	55,441 42	59,404 40	82,884	219,493	~110,000
Data source	(12, 13)	(12, 13)	(12, 13)	(23)	(23)	(23)	(23)	(24)	(20, 22)	(21)	(3, 22)
	(==) ==)	())	()		(-)	/	(-)	· · · /	() ==)	/	· / == /

*In situ cases are excluded from all but the 1942–56 data, and nonmelanomic skin carcinomas are excluded from all the data. *Ext). +Estimated for both sexes by the figure shown with the rate in this column equals twice the standard error (see text).

patient records and periodic querying of the treating physician regarding the patient's status or, when that is not possible, a direct query to the patient to determine vital status. Inevitably some proportion of cases become lost to follow-up. Death records are used as a final check for lost patients. In the usual life table method of calculating survival rates, patients lost to follow-up are removed from the calculation at the time of last known contact (10, 11). This has the same effect as assuming that the survival rate of those lost is not different from that of those remaining under observation. However, because of death registration checks, lost patients who die become "found" much more easily than those who remain alive. A bias is thus created which has the effect of producing a computed survival rate that is lower than the actual rate. The discrepancy is greatest for cancers with poor survival, because the methodology assumes most lost patients are dead when in fact lost patients are most likely alive. As the follow-up system improves and a smaller proportion of patients remain in the "lost" category, the survival rates should increase, especially for those sites with poor survival.

Another important consideration is that the data collection, processing, and analysis procedures be reliable and remain uniform over time. Some of the elements that must be considered are completeness of case reporting, abstracting errors, coding errors, procedural changes in registry operation, accuracy and confirmation of diagnosis, definition of staging, completeness of case followup, and method of calculation. These matters are discussed in detail elsewhere (11-13), but their quantitative effects on the available survival trend data have not been stated. When attempting to ascertain real time trends in survival rates, it is essential that these systematic effects be assessed.

Thus, a number of factors guite separate from the efficacy of treatment can affect survival rates and their trends. When survival rates are used to evaluate the effects of a clinical trial, where patients are randomly assigned to treatment groups and followed by one followup system, the rates become a sensitive means of identifying advances in treatment. When survival rates are computed with pooled follow-up data from a variety of sources, they offer the best available probabilistic prognostication of an individual cancer patient's expectation of life. There are several limitations with this use. First, their applicability to the 4 MARCH 1977

general run of cancer patients depends upon the actual representativeness of the pooled data. Second, the probabilities are, of necessity, several years out of date.

Finally, in order for a survival rate following treatment to be most meaningful, it must be compared with the corresponding survival rate that would be expected from the natural history of the disease, and not be interpreted solely as an absolute number (14). Such comparisons require proper clinical trials, as has been emphasized by Shimkin (15). In the absence of these clinical trials, survival rates will continue to serve primarily the function of prognostication.

End Results Evaluation Program

Up until 1956 there was no organized system for the collection of data on cancer survival rates in the United States. In fact at that time Shimkin stated, "We cannot be proud of either the survival figures, or of the reporting mechanisms on cancer patients which must serve as our guide in the treatment of these diseases" (16). Subsequently the National Cancer Institute established the End Results Evaluation Program (EREP) in order to gather data systematically (17). As described in 1961 (18),

The End Results Group is made up of representatives from 4 central and 10 individual hospital tumor registries, with a broad geographic distribution... The central registries collect information from more than 250 hospitals and clinics in all parts of the United States....

Furthermore (17),

The institutions cooperating in the End Results Evaluation Program were selected on the basis of ability and willingness to participate. The extent to which they are representative of all hospitals treating cancer patients in the United States is not known.

Actually, in all the reports so far (18-22), the data presented are based on the experience of cancer patients treated since 1940 in about 100 hospitals, consisting of all the hospitals in the state of Connecticut, hospitals treating approximately 20 percent of the cancer patients in the state of California, a group of hospitals in the Boston metropolitan area, and six large university hospitals in various parts of the United States (22). For each of the reports about 45 percent of the cases were supplied by the California Tumor Registry, about 25 percent by the Connecticut Tumor Registry, the remainder by the other hospitals. There are no data on cancer cases in about 40

states. In fact, only about 1.5 percent (100 out of 7000) of the hospitals and about 3 percent (20,000 out of 650,000) of the annual cancer cases in the United States are included. The National Cancer Institute recently replaced the EREP with the Surveillance, Epidemiology, and End Results (SEER) program through which cancer incidence and survival data are being collected on entire designated populations totaling approximately 10 percent of the U.S. population (7), but no survival data are yet available from it. Hitherto the only source of data on a well-defined and completely covered population in the United States has been the Connecticut Tumor Registry.

California Tumor Registry

Cancer survival data are also available from the California Tumor Registry (CTR), which was established in 1947 and has been the major contributor to the EREP. It is useful to consider CTR here because it indicates the amount of variation which exists between its survival rates and those of the total EREP. The registry is described in detail elsewhere (12, 13, 23, 24). Shown in Table 1 are CTR 5-year relative survival rates for a number of major sites and for all cancer, in 5-year periods of diagnosis from 1945 to 1969 (23, 24). Included for comparison are the EREP 5-year relative survival rates for the periods of diagnosis 1950 to 1954 (20), 1955 to 1964 (21), and 1965 to 1969 (22). Also included are 1942 to 1956 CTR rates for county hospitals, private hospitals, and the total (12, 13). The EREP cases are white only, whereas the CTR cases are about 95 percent white, almost all of the remainder being black. In addition, the total number of cancer cases and the percentage of localized cases is given for each time period.

From this table several interesting comparisons can be made. First, while there has been a steady rise in the CTR survival rates for several sites, since 1950 there has been no increase in the total survival rate for localized cases and only a slight increase for cases of all stages. Second, the CTR rates are quite similar, as might be expected, to the corresponding EREP rates for the period 1950 to 1969. Indeed, since 1950 the total 5-year relative survival rate for the EREP data has remained constant: 39 percent for all stages and about 68 percent for localized cancer (21, 22). Third, the 1942-56 CTR data for private and public (county) hospitals show a large (factor of 2) social class variation in survival rates, with cancer patients in private hospitals (higher social class) surviving cancer better than patients in public hospitals (lower social class) for almost every site and stage of disease (12, 13). The survival rates in the private hospitals during this early (1942–56) period are very close to the CTR and EREP rates

Table 2. Changes in annual age-adjusted cancer mortality and incidence rates and 5-year relative survival rates for whites. The mortality rates are based on all U.S. deaths (26), the incidence rates on the Second and Third National Cancer Surveys (26, 27); these rates are ageadjusted by the direct method using the 1950 U.S. population as the standard, and then rounded off. The survival rate changes are based on EREP data given in Table 1.

	Dea	ths per 1	00,000	Inc	idence per	Five-year rel- ative surviva	
Cancer site	1950	1970	Change (%)	1947	1969–71	Change (%)	rates: change (%), 1950–54 to 1965–69
Esophagus	2.5	2.5	0	4	3	-25	-25
Stomach	15	6	-60	24	9	-63	9
Colon	15.5	15	-3	25	27	8	5
Rectum	7	4.5	-36	17	12	-29	-2
Pancreas	6	7.5	25	7	8	14	0
Lung	12	30	150	17	36	112	29
Breast	13	13.5	4	38	39	3	8
Uterus (total)	10	5	-50	32	20	-38	1
Cervix uteri	5.5	3	-45				-2
Corpus uteri	4.5	2	-56				4
Ovary	4	4.5	13	8	7	-13	14
Prostate	7.5	7	-7	17	21	24	27
Kidney	2.5	3	20	5	6	20	28
Bladder	4	3.5	-13	13	12	-8	11
Hodgkin's disease	1.5	1.5	0	3	3	0	64
Leukemia	6	6.5	8	8	9	13	0
All sites	135	140	4	290	275	-5	0

Table 3. Three-year relative survival rates and distribution of cases for leukemia by morphologic classification, based on data from the End Results Evaluation Program (21).

Morphologic classification	Rate	es (%)	Distribution of cases (%)		
	1955-64	1965–69	1955–64	1965–69	
All leukemia	20	20	100	100	
All acute leukemia	3	7	50	61	
Acute lymphocytic leukemia	5	15	14	17	
Acute myelocytic leukemia	1	2	15	25	
Monocytic leukemia	3	3	11	9	
Acute, not otherwise specified	4	9	10	10	
All chronic leukemia	39	41	50	39	
Chronic lymphocytic leukemia	51	53	29	23	
Chronic myelocytic leukemia	25	26	19	15	
Chronic, not otherwise specified			2	1	

for 1965–69. An additional analysis of breast cancer cases taking stage, age, race, and type of treatment into account still showed greater survival among private hospital patients (12), and a recent study further identifies different survival between social class groups treated at the same hospital (25). These survival differences are most likely due to differences in the host resistance of patients and illustrate another source of variation in the rates.

Interpretations and Conclusions

In order to evaluate whether there are meaningful trends in data such as those presented in Table 1, it is important to consider systematic and statistical error inherent in survival rates. As an example, twice the standard statistical error (corresponding to the 95 percent confidence limits) is shown in Table 1 for the 1965–69 EREP data: it is about 2 percent for most sites. The methodology for estimating the statistical error is presented elsewhere (11). The effects of the systematic error are more difficult to assess, as has been noted earlier, but they are probably greater than the statistical error. However, the trends in cancer survival can be indirectly inferred from concurrent trends in cancer incidence and mortality. It may be seen in Table 2 that both the age-adjusted total cancer incidence rate and the age-adjusted total cancer mortality rate changed by only a few percent between 1950 and 1970 (26, 27). Because of the somewhat different survey populations and classification definitions on which they are based, the incidence and mortality rates are not precisely comparable; but the fact that neither has changed significantly since 1950 implies that the total cancer survival rate has also remained essentially constant. This is an independent confirmation of



Fig. 1. Trends in rectum cancer (left) and lung cancer (right) for white males in the United States. The incidence and mortality rates are against to the 1950 U.S. population. Data are based on (21) and (27), as updated by unpublished EREP results summarized in (29).

the direct data on total survival rates given in Table 1.

The same phenomenon holds for individual cancer sites even though the survival changes given in Table 2 appear to have little relationship to concurrent changes in mortality rates. This is because for most sites the relative changes in survival result from rather small absolute changes. For instance, the 29 percent relative increase in lung cancer survival is only an absolute increase from 7 percent to 9 percent, which is insignificant in view of the inherent errors. So long as incidence and mortality remain unchanged or change proportionately, no genuine change in survival can occur. This is what has happened for sites such as lung, stomach, rectum, and esophagus. The large increase in the prostatic cancer survival rate has occurred because the incidence rate has increased markedly while the mortality rate has declined negligibly (28).

An approach advocated by Linden is helpful in presenting four of the factors that should be considered when evaluating progress in cancer control. Figure 1, taken from his work (29), shows four trends in cancer of the rectum in white males in the United States: the incidence rate, the mortality rate, the 5-year survival rate, and the percentage of cancer cases that were localized at the time of diagnosis. The same four measurements are also shown for cancer of the lung. Both sets of data illustrate the burden of mortality and its close correspondence to the rate of occurrence. Both also show the close relationship between the survival rate and the percentage localized at diagnosis. And for both these sites the risk of getting or dying from cancer has changed independently of the 5-year survival rates. Whether these changes could be taken as measures of "progress" depends upon the correct attribution of their cause.

The fact that mortality rates and incidence rates are highly correlated while neither is related to survival rates might lead one to suspect that if progress in cancer control is related to how many people get cancer and how many people die from it, then survival rates are not a

sensitive measure. The suspicion is strengthened by a different phenomenon, demonstrated in Table 3, in which the EREP 3-year relative survival rates for leukemia for 1955-64 and 1965-69 (21) are summarized by morphologic classification. Although significant increases in leukemia survival are often cited as evidence of great progress in cancer control, and though there have in fact been survival improvements for essentially all forms of leukemia, the survival rate for leukemia with all forms combined has remained constant. This is due to the increasing proportions of the highly fatal forms of leukemia. If one uses the differentiated survival rates as the criterion of progress, then in this instance progress has been negated by a changing incidence.

In summary, survival rates should not be used as a sole or primary measure of progress in cancer control, because factors unrelated to the efficacy of treatment play an important role in the determination of those rates and their trends. If cancer control is related to how many people get and die from cancer, then progress can better be measured by the use of incidence and mortality rates.

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