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Non-parametric comparison of relative versus cause-specific survival in Surveillance, Epidemiology and End Results (SEER) programme breast cancer patients

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Cancer-related mortality can be measured by two dissimilar methods: *cause-specific survival* (based on mortality attributed to a specific cause), and *relative survival* (based on mortality relative to a matched cohort). We used both methods to determine actuarial survival in a population of 119 502 breast cancer patients from the Surveillance, Epidemiology and End Results (SEER) programme data set, with 20 years of follow-up. The population was divided into four strata by patient age and tumour stage. In all strata, there was only minimal deviation between the two survival methods. Of particular interest was the cause-specific treatment of patients recorded as dead of unknown cause, i.e. those deaths that could not be attributed with certainty to either 'breast cancer' or to 'other causes'. Findings suggest that the most reliable results may be obtained by apportioning these deaths between 'dead of cause' and 'withdrawn at the time of death'. This apportionment is based on the relative number of deaths attributed to 'breast cancer' versus 'other causes'.

1 Introduction

In assessing survival, researchers prefer a secure measure of failure. Death is perhaps the most secure of all survival endpoints, since the fact that a patient died on a specific date can often be determined with a high level of confidence. In contrast, the cause of death may be uncertain or difficult to determine. Thus death from a specific cause may provide a less reliable measure of failure than overall mortality.

In some studies, however, our goal is to measure the association of prognostic covariates with a specific cause of death, such as breast cancer. Like many cancers, this tumour affects primarily older adults, who suffer competing mortality from a wide variety of diseases. In such a setting, the total of all deaths may provide a biased measure of mortality from breast cancer. Bias would be especially great when the covariates include age of the patient.

To address this problem, we can use cause-specific survival analysis. That is, we can use death from breast cancer as our survival endpoint, while treating patients who died of other causes as withdrawn at the time of death.[1] Although researchers look with suspicion on many of the methods for analysing multiple failure models, there is support for the approach of decomposing overall failure into cause-specific failure components.[2] For such

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analysis, the Kaplan and Meier estimation technique is easily generalized for estimation of hazards for cause-specific endpoints.[3] In general, the cause-specific endpoint seems most appropriate with high quality follow-up information, such as that obtained in prospective, carefully structured clinical trials.

Even in clinical trials, however, there are a number of potential pitfalls in determining the specific cause of death. One such pitfall is record keeping. For example, there may be disparity between the hospital record and the death certificate. Error rates of approximately 70% were found by Percy *et al*. for certain cancers of the oral cavity and central nervous system.[4] With other cancers, however, the error rate was much lower. For breast cancer in particular, they found a concordance of greater than 95% between the hospital record and the death certificate.

In addition to record keeping, other problems are encountered in determining the cause of death. Even if all records indicate that death was due to breast cancer, should we demand histologic confirmation? What if we have histologic evidence of primary breast cancer, but no biopsy was taken to prove that the patient died of disseminated disease? 'Respiratory failure', a commonly recorded cause of death, could result from metastasis, or from pneumonia in a patient long cured of her primary tumour.

The issue is further clouded by the impact of therapy. Could modern therapy cure some patients, and yet increase mortality in those who otherwise would have survived their disease? In patients who die from the complications of therapy, should we record the treated cancer as the cause of death?

Moving on to the effect of biologic mechanisms, could the genetic and environmental factors that lead to a specific cancer also predispose patients to fatal non-malignant diseases? This last possibility raises a fundamental question: if patients with breast cancer do have an especially high mortality from (for example) pneumonia, how should we handle these 'associated' deaths? Should we include them in our analysis as cause-specific deaths, if we hope to measure the long-term impact of this cancer on survival?

Particularly useful insight into these issues is provided by Brown *et al*., who examined non-cancer deaths in the same Surveillance, Epidemiology and End Results (SEER) programme database used for our study.[5] Patients with various cancers demonstrated an excessive hazard rate from non-cancer causes, in comparison to matched cohorts. This excess was in the range of 1–108 standard deviations above the expectation. The reported data offer no insight into mechanism, and thus we do not know what proportion of the excess is due to miscoding the cause of death, versus a propensity among cancer patients toward other fatal diseases. With respect to female breast cancer, however, the excessive non-cancer relative hazard rate, though significantly greater than 1.0, measured only 1.09.[5]

To avoid some of the dilemmas posed by cause-specific survival, we can turn to the technique of relative survival. That is, we can compare total mortality in the study population with total mortality in a matched cohort.[6] This approach, of course, presents its own set of difficulties. Chief among these is obtaining an appropriate cohort population. In the current study, patients were matched for age, race, sex and calendar year, using tables published by The National Center for Health Statistics. Despite the value of this resource, there is no way to assure or test for a perfect match between the study population and its cohort.

Since relative and cause-specific survival were derived from different assumptions, we might reasonably ask whether the two methods yield comparable results. Also to be

considered is a dilemma frequently encountered when performing cause-specific analysis: how do we handle those deaths that are recorded as due to unknown causes, that is, deaths that can be confidently attributed neither to the cancer under study nor to other causes?

In addressing these various issues, this paper is organized as follows. Section 2 provides a brief overview of cause-specific survival and issues related to competing risks. Section 3 gives a review of some of the previous work related to relative survival analysis. Section 4 applies both cause-specific and relative survival methods to the same data set, using various methodologies for handling deaths coded as due to unknown causes.

2 Overview of cause-specific survival and competing risks

The underpinnings of cause-specific survival and the theory of competing risks can be traced to the memoir presented by Daniel Bernoulli to the French Academy of Sciences in 1760. Bernoulli addressed the following problem: if in a given population smallpox could be eradicated, what would be the effect on the population mortality at different ages?[7,8] In Bernoulli's treatise, he assumed that if an individual was saved from smallpox, then that individual would be subject to other causes of death in exactly the same manner as the rest of the population.[7] The assumption is not true if smallpox had selectively eliminated the weakest members of the population. This assumption has proved to be one of the key areas of controversy in cause-specific survival analysis and in the theory of competing risks. Bernoulli's solution to the problem was to simply dismiss the issue.

To paraphrase Jerome Cornfield,[9] in any study with two or more mutually exclusive ways to achieve some endpoint, these mutually exclusive ways will compete with each other. Thus if death is the endpoint, then death by heart failure will compete with death from a malignant neoplasm. Alternatively, in the study of breast cancer, local recurrence will compete with distant recurrence and with death from causes other than breast cancer. The most direct approach is to consider patients as censored when the endpoint, or 'cause of failure', is not the one under study. For example, if one wishes to measure the effect of treatment on local recurrence, one might classify as censored those patients who suffer a distant recurrence without a local recurrence, or those who die of other causes. For this methodology to avoid serious errors, however, these various causes of failure must be independent. The remainder of this section will deal with some of the problems and proposed solutions that arise in cause-specific and competing risk survival methodology.

In their applications of cause-specific survival, several recent authors attempt to address rather than simply dismiss the assumption of independence among the various causes of failure.[10–12] Panzarella and Meakin[11] advocate the two-step procedure suggested in Gelman *et al*.[12] With this procedure, one can determine whether treatment alters time to local versus distant relapse from breast cancer. In the first step of the procedure, the treatment groups are compared using Kaplan–Meier analysis, with first failure (regardless of failure type) as the survival endpoint. In the second step, the treatment groups are compared using chi-square analysis of the distribution of 'failure types' at a common follow-up time. This approach decomposes the time to first failure by failure types, and yet preserves the independent censoring assumption. Gelman *et al*. also point out that when traditional methods are applied to multiple failure types, the assumption of independence is often violated, leading to serious errors.[12] Such violations are especially

prevalent when the failure types are biologically related, as with local versus distant failure of breast cancer.

Cutler and Ederer[13] describe a life table method for addressing partial survival information. Chiang[14,15] provides a refinement to the Cutler and Ederer method that addresses the problem of incomplete follow-up data. In these articles, Chiang also becomes the first to provide a systematic method for assessing the probability of death from specific causes in the presence of competing risks. This method incorporates what is known as the 'proportionality assumption', which is described in detail in David and Moeschberger.[7]

Gail[16] provides a review and critique of some of the models used in competing risk analysis. His review introduces a notation that facilitates the definition of competing risk models and allows examination of their underlying assumptions. Elandt-Johnson[17] also provides an overview of competing risks. Furthermore, she argues that the theory of competing risks, which is based on the concept of a joint survival function of hypothetical times to death, is not sufficient to make meaningful statements about the mechanisms that cause death. She also suggests that 'multiple cause' coding on death certificates provides useful information that should be incorporated into survival models.

Wong[18] proposes a non-parametric competing risk model that takes relative susceptibility into account, thereby eliminating the independence assumption. His proposed model also adjusts the survivors and deaths in one interval when one of the competing causes of death is eliminated in the previous interval. As Berry[19] points out, however, the Wong model allows all deaths from other causes to occur at the beginning of the previous interval. This causes a potential bias, which Berry suggests can be overcome if those who die of other causes are considered as survivors until the middle of the previous interval.

Prentice *et al.*[20] provide the most complete summary of the difficulties associated with competing risks and causes for specific failures. In this landmark paper, the authors examine three of the major problems that can arise when there are competing causes of death.

The first problem arises when we attempt to estimate the effects of therapies and covariates in the presence of competing risk. As a result of competing risks, estimates of the effects due to treatment may be incorrect. To demonstrate this point, the authors cite the University Group Diabetes Program,[21] which found that Tolbutamide use, in addition to affecting diabetes, was associated with increased cardiovascular mortality. Thus treatment may introduce confounding by affecting two or more of the competing risks.

The second problem arises in the study of interrelations among risks or failure types. Most competing risk problems are formulated in terms of potential failure times $Y_1, \ldots, Y_k$ which correspond to the k types of failure. One observes in each patient the cause of failure and its corresponding failure time, $Z = \min\{Y_1, \ldots, Y_k\}$.[7] If our goal is to show that, for example, failure type 1 is independent of failure type 2, then we must show that failure time Y_1 is statistically independent of failure time Y_2. Unfortunately, in any individual patient we can observe only the time to that failure which occurs first. Thus it is impossible to obtain the data necessary for determining the independence of failure times Y_1 and Y_2.

The third problem pointed out by Prentice *et al.*[20] is the estimation of failure rates for some causes, given the removal of some or all other causes. The classic example is that given by Bernoulli of the competition between smallpox and other causes. In addressing this problem, the authors show that cause-specific hazards and hence cause-specific

survivals are the basic estimable quantities. They also argue that the problem of estimating failure rates under the removal of certain causes is not well posed until a mechanism for cause removal is specified.

An additional problem is disclosed by Slud and Byar,[22] who demonstrate that survival curves can easily be reversed when censoring is appreciable due to an alternative cause of death. In this same vein, Schatzkin and Slud[23] describe a type of relation bias that may arise when a second disease selectively removes from the population patients who are susceptible to the disease of primary interest.

Benichou and Gail[24] attempt to estimate the absolute risk of an event in a time interval, given that the individual is at risk at the beginning of the interval and there are competing risks. They define the absolute risk, π, as the crude probability of experiencing the event of interest, in the presence of competing risks

$$\pi(t;x) = \int_0^t h_1(u;x) \exp\left[-\int_0^u \{h_1(v;x) + h_2(v;x)\}\mathrm{d}v\right]\mathrm{d}u$$

where $h_1(u;x)$ is the cause-specific hazard of interest for an individual with covariates x and $h_2(u;x)$ is the cause-specific hazard for other risks.

These authors point out that absolute risk may be more meaningful than the cause-specific survival curve for evaluating some issues in public health and clinical management. They also note that absolute risk has a valid interpretation as a probability, even when the independence assumption fails to hold.

Given the numerous difficulties created by competing risks, and the limited progress in addressing these difficulties, it appears that the comment of Jerome Cornfield in 1957 may still hold today: 'With respect to actual knowledge of the magnitude of possible empirical effects of competing risks, we seem to have made no advance beyond Bernoulli'.

3 Overview of relative survival rates

As an alternative to the methods described above, we can correct overall survival to obtain an estimate of disease-specific survival by using the relative survival rate. Berkson[25] introduced the concept of the relative or corrected survival rate, which he defined as the ratio of an observed survival rate to an expected survival rate within a specific population. This method has been advanced by Ederer *et al.*,[6] Axtell *et al.*,[26] Hakulinen *et al.*,[27] Hakulinen[28] and Brown.[29] Unlike cause-specific survival, which requires exact knowledge of the individual causes of death, relative survival adjusts the observed survival rates by using the expected general population mortality rates as the correction mechanism.

The relative survival rate can be interpreted as the probability of survival until the end of the follow-up period, provided the only cause of death is the disease under study. This interpretation is based on the assumption that patients are subject to two independent forces of mortality. These independent forces are: (i) the specific disease under study, and (ii) all other causes. If the independence assumption is false, that is, if the presence of the disease alters the risk of death from other causes, then errors can arise in the estimation of the relative survival rates. Provided there are no violations of the necessary underlying assumptions, relative survival rates can be used to measure patient survival, adjusted for

the effect of mortality from the competing risk of death, but without using information on the individual's specific cause of death.

Ederer *et al*.[6] defined the relative survival as the ratio of the observed probability of survival in the patient group to the expected probability in a sample of individuals from the general population. Subjects are selected for this sample based on two criteria: (i) they are without the disease under study, and (ii) they are matched to the disease group at the beginning of the follow-up time with respect to covariates that might effect survival. In cause-specific terms, the relative survival rate corresponds to the probability of survival, given that causes of death associated with the disease under study are the only risks acting on the population of patients.

A current example of the use of relative survival can be found in the report on breast cancer mortality in Australian women between 1982 and 1994.[30] This report focuses on the breast cancer survival patterns in Australia at the population level. Rates are reported in terms of relative survival, using the RELSURV[31] computer program to derive estimates. Other computer programs are available for this purpose. Hakulinen and Abeywickrama[32] describe a computer program that was used to study female colon cancer patients in Finland between 1967 and 1979. This program has evolved into SURV2[33] and is now available via the Internet.

Relative survival rates are vulnerable to a number of limitations. One limitation is the independence assumption, i.e. that survival from the disease under study is independent of survival from other causes. In addition, Buckley[34] points out that accuracy in estimating relative survival is dependent on the choice of the hazard rates for determining expected survival. He also notes that, if the independence assumption is false, disease-specific survival rates are affected by changes in the sample composition.

Some advances in the use of relative survival risks can be found in Andersen *et al*.[35] These authors extend the basic idea of relative survival and construct a Cox-type regression model, which is applied to insulin-dependent diabetes in Denmark. Hakulinen and Tenkanen[36] demonstrate how a proportional hazards regression model may be used for relative survival rates using GLIM. They apply this method to a population of lung cancer patients in Finland from 1968 to 1970. Hakulinen *et al*.[37] construct maximum likelihood tests on aggregated data to test for equality of survival rates. Their work introduces a method for testing hypotheses that was proposed in Brown[29] and Buckley.[34] Another refinement in the area of relative survival can be attributed to Andersen and Vaeth.[38] These authors demonstrate that the multiplicative hazard model allows the estimate for relative mortality to be generalized into the standardized mortality ratio. This generalization is useful, since the standardized mortality ratio is the traditional method for comparing mortality across workers in various occupations.

An especially interesting approach to relative survival is presented by Cronin and Feuer.[39] They present methods for computing both net survival (in the absence of death from other causes) and crude survival (in the presence of death from other causes). They also point out that crude survival may be the best measure of long-term benefit from cancer therapy, since it allows for the fact that a proportion of patients with persistent cancer will nevertheless die of other causes. This is especially true for older patients, whose mortality from other causes may overshadow any benefit from therapy.

In spite of the usefulness of relative survival rates, especially for those working with registries, relative survival, like cause-specific methods, suffers from basic limitations. The

greatest of these is the ever present independence assumption, i.e. that deaths from the cause under study are unrelated to other causes.

4 Analysis of SEER data

We applied both cause-specific and relative survival methods to the same data set. The cause-specific method was then further explored by testing various alternative techniques for handing those patients coded as dead of unknown cause.

4.1 Study population

Data were obtained from the SEER programme via a public-use CD-ROM. This disk was produced by the National Cancer Institute (NCI), DCPC, Surveillance Program, Cancer Statistics Branch. It contains data for over 200 000 patients who were treated for breast cancer between 1973 and 1993. The staging system used (SEER historical system) classifies disease as localized, regional, or distant spread based on combined pathologic and clinical data. Localized disease corresponds approximately with stage I of the American Joint Committee on Cancer (AJCC) TNM staging system (axillary lymph nodes tumour-free), and regional disease corresponds with stage II (axillary metastasis present with no known distant metastasis). Patients with *in situ* disease or with distant metastasis were excluded from analysis. Follow-up ranged from 1 to 20 years in 1-year increments. Further details on the data set are contained in the report by Henson *et al*.[40]

For relative survival analysis, as described below, expected survival (E_{ij}) was computed for stratum i in interval j using tables published by The National Cancer for Health Statistics. Cohorts for comparison were grouped by age, race, gender, and calendar year. Analysis for each interval included all individuals in the cohort at time zero.[6] Patients were divided into four strata based on the age of the patient and stage of the tumour. The strata were

- Stratum 1: age <55 years, stage I = local;
- Stratum 2: age ≥ 55 years, stage I = local;
- Stratum 3: age <55 years, stage II = regional;
- Stratum 4: age ≥ 55 years, stage II = regional.

4.2 Actuarial survival analysis

Actuarial survival from breast cancer was estimated by two methods for stratum i, interval j

A_{ij} = relative survival, comparing all-cause survival with matched cohort
$= B_{ij}/E_{ij}$
$B_{ij} = \prod_{k=1,\,j}[1 - D_{ik}/(R_{ik} - \frac{1}{2}L_{ik})]$
R_{ik} = total number of patients at risk at beginning of interval
D_{ik} = total number of deaths from any cause
L_{ik} = total number of patients withdrawn
E_{ij} = all-cause survival in matched cohort

C_{ij} = cause-specific survival, measured by deaths attributed to breast cancer
$= \prod_{k=1,\,j}[1 - d_{ik}/(r_{ik} - \frac{1}{2}l_{ik})]$

r_{ik} = cause-specific number of patients at risk at beginning of interval
d_{ik} = number of deaths *attributed* to breast cancer
l_{ik} = cause-specific number *attributed* to withdrawn or dead of other causes

$f_{ik} = c_{ik} + o_{ik}$
c_{ik} = patients coded as dead of breast cancer
o_{ik} = patients coded as dead of causes other than breast cancer
u_{ik} = patients coded as dead of unknown cause

Note that these symbols apply to overlapping data sets. For *relative* survival, D_{ik} indicates all deaths that occurred during the interval, while L_{ik} indicates all patients withdrawn. For *cause-specific* survival, d_{ik} includes those deaths 'attributed' to breast cancer, while l_{ik} includes those patients 'attributed' to withdrawal. The methods by which these attributions were made will be described below.

4.3 Cause-specific treatment for deaths of unknown cause

In cause-specific survival analysis, deaths due to causes other than the cancer under study are treated during computation as withdrawn at the time of death.[1] Problems arise, however, when patients are known to have died during the course of study, but the cause of their death cannot be securely attributed to either the cancer under study or to other causes. When such events contaminate a significant proportion of the study population, the researcher must choose from among a variety of possible alternatives. This study examines four alternatives for the cause-specific treatment of deaths from unknown cause. The alternatives, each of which is based on a corresponding hypothesis, will be referred to by the following notation:

4.3.1 CS-1

Hypothesis: Among patients recorded as dead of unknown cause, the distribution of mortality is identical to that of the remainder of the stratum. Thus, omission of these patients from the study set will have no impact on the conclusions drawn.

Action: Patients recorded as dead of unknown cause were omitted from the study population. That is, u_{ik} was omitted from computation, and

$$d_{ik} = c_{ik} \qquad l_{ik} = L_{ik} + o_{ik}$$

4.3.2 CS-2

Hypothesis: Patients recorded as dead of unknown cause actually died of breast cancer.

Action: Patients recorded as dead of unknown cause were treated during computation as having died of the cancer under study. That is

$$d_{ik} = c_{ik} + u_{ik} \qquad l_{ik} = L_{ik} + o_{ik}$$

4.3.3 CS-3

Hypothesis: Patients recorded as dead of unknown cause actually died of causes other than breast cancer.

Action: Patients recorded as dead of unknown cause were treated during computation as withdrawn at the time of death. That is

$$d_{ik} = c_{ik} \qquad l_{ik} = L_{ik} + o_{ik} + u_{ik}$$

4.3.4 CS-4

Hypothesis: A proportion of deaths recorded as due to unknown cause are due to breast cancer, while the remainder are due to other causes. To determine the proportion attributable to breast cancer, we divide the number of cases coded as dead of breast cancer (c_{ik}) by the total number of deaths from breast cancer and other causes ($f_{ik} = c_{ik} + o_{ik}$). In a complementary fashion, to determine the proportion of deaths due to unknown cause that are attributable to other causes (and should be treated as withdrawn at the time of death), we divide the number of cases coded as dead from other causes (o_{ik}) by the same denominator (f_{ik}).

Action: Deaths recorded as due to unknown causes were apportioned between d_{ik} and l_{ik}, based on the formula

$$d_{ik} = c_{ik} + u_{ik}c_{ik}/(c_{ik} + o_{ik}) = c_{ik}(1 + u_{ik}/f_{ik})$$
$$l_{ik} = L_{ik} + o_{ik} + u_{ik}o_{ik}/(c_{ik} + o_{ik}) = L_{ik} + o_{ik}(1 + u_{ik}/f_{ik})$$

4.4 Comparison of relative versus cause-specific survival

Actuarial survival analysis was performed using each of the four *cause-specific* modifications shown above. Findings with each of these four methods were compared to the results obtained when *relative* actuarial analysis was performed on the same data set. The following comparisons were performed separately for each of the four strata described above

- the per cent survival difference after 20 years of follow-up;
- the mean per cent difference taken over the entire 20 years;
- the sum of squared error taken over 20 years.

For three of the four strata, cause-specific estimates of survival were slightly higher than relative estimates (Figure 1a, b). Cause-specific survival was greater than relative survival for younger patients with both stage I and stage II disease, and for older patients with stage II disease. This trend was reversed, however, for older patients with stage I disease.

Both relative and cause-specific survival are vulnerable to error, and thus neither can be used as the 'gold standard' by which to measure the other. For cause-specific survival, a major potential source of error is miscoding the cause of death. For relative survival, a major potential source of error is a mismatch between the study population and the population used to estimate underlying mortality.

In searching for a possible explanation for the differences noted, it is useful to examine the relative distribution of death from various causes among the four strata. Deaths from breast cancer are more numerous for stage II than for stage I disease, while deaths from other causes are more numerous among older than among younger patients (Table 1). There is also substantial variation in the relative distribution of deaths over the 20 years of follow-up (Figure 2a–d). Among younger patients with either stage I or stage II disease,

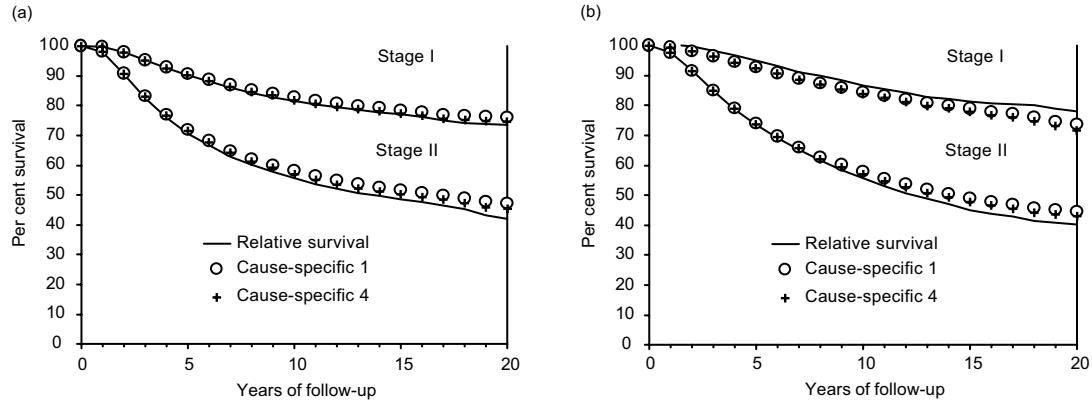

Figure 1 Relative and cause-specific survival for patients: (a) <55 years of age; (b) ≥55 years of age

Table 1 Summary of clinical data from SEER data set

Stage	Age	At risk	Withdrawn	Deaths (per cent of all deaths)			
				Total	Breast cancer	Other causes	Unknown causes
I	< 55	22 300	17 728	4 290	3 123 (72.8)	854 (19.9)	313 (7.3)
I	≥ 55	46 234	29 368	16 669	4 891 (29.3)	10 630 (63.8)	1 148 (6.9)
II	< 55	19 309	10 922	8 214	6 894 (83.9)	895 (10.9)	426 (5.2)
II	≥ 55	31 659	13 215	18 343	10 214 (55.7)	7 118 (38.8)	1 011 (5.5)

deaths from breast cancer greatly exceed those due to other causes. This predominance continues until near the end of follow-up. A similar predominance is noted among older patients with stage II disease, but only during the first few years of follow-up. Among older patients with stage I disease, however, this predominance is completely reversed. Deaths from other causes greatly exceed those due to breast cancer, and this predominance persists throughout the entire duration of follow-up.

Thus, of the four strata in the study population, it is only among older patients with stage I disease that: (i) relative survival exceeds cause-specific survival; and (ii) deaths from other causes consistently predominate over deaths from breast cancer. These findings do not provide an explanation for disparities between relative and cause-specific survival. The findings do suggest, however, that this explanation may be dependent on the relative proportion of deaths from breast cancer versus other causes. In speculating about specific mechanisms, one could propose that a certain proportion of deaths attributed to breast cancer are actually due to other causes. Thus as deaths from other causes increase with advancing age, there is a corresponding increase in the number of deaths erroneously attributed to breast cancer. The impact of this error mechanism would be greatest when relatively few older patients were dying of breast cancer, as in that population with stage I disease.

Another possible explanation for the disparity between relative and cause-specific survival may be found in the comparison cohort used for relative survival. We made no

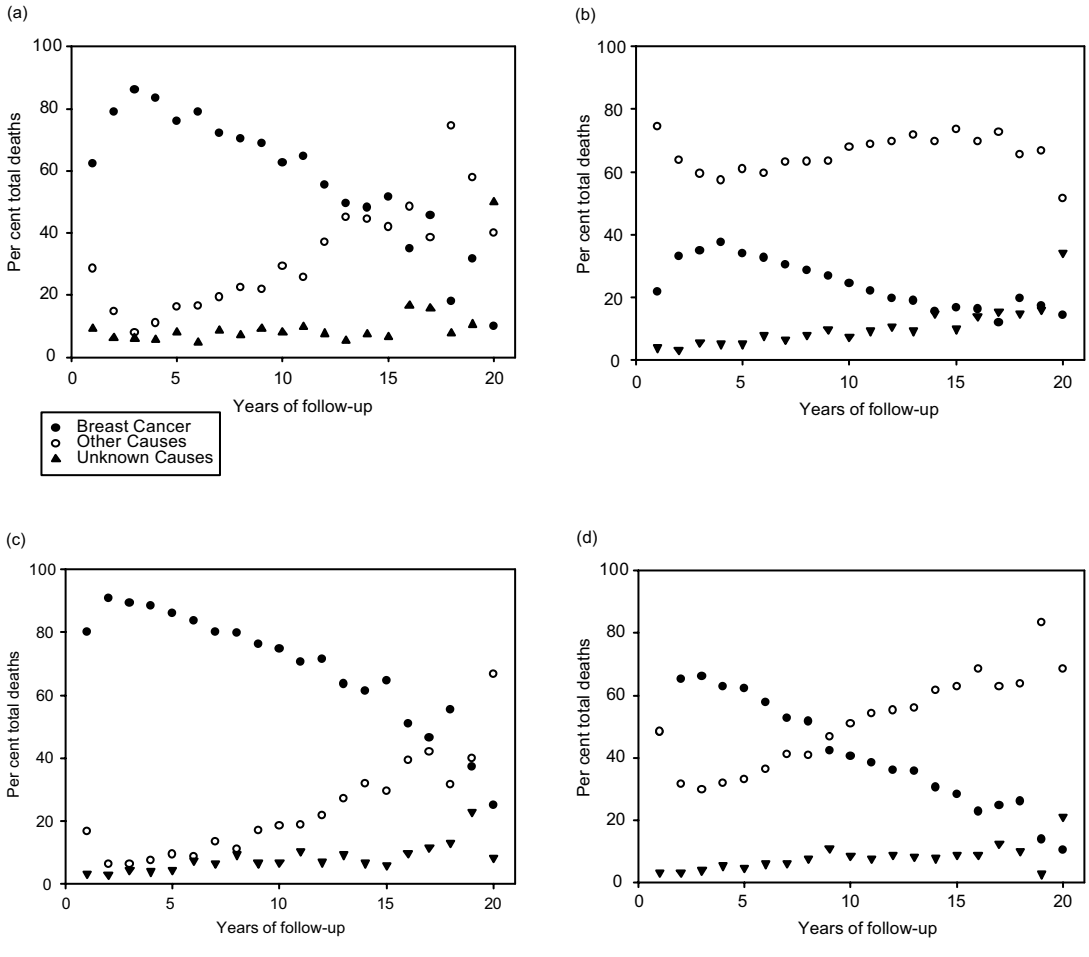

Figure 2 Proportion of deaths for patients: (a) <55 years of age and (b) ≥55 years of age with stage I disease; (c) <55 years of age and (d) ≥55 years of age with stage II disease

effort to 'extract' breast cancer mortality from this cohort. Since breast cancer is a significant contributor to overall mortality among women, this 'contamination' could affect our findings. Specifically, including breast cancer deaths in the control cohort could cause a decrease in expected survival, leading to a compensatory increase in estimates of relative survival. Despite this factor, however, relative survival was less than cause-specific survival for three of the four strata.

In general, we are impressed more with the consistency rather than the disparity between these two methods. The differences shown in Figure 1a, b are relatively small, especially considering the extended follow-up of 20 years.

In the data set studied, CS-4 gave results similar to those found with CS-1 (Figure 1a, b, Table 2). This reflects to some degree the small per cent of deaths from unknown cause, which varied from 5.2 to 7.3% of all deaths. Nevertheless, in three out of the four strata,

Table 2 Cause-specific versus relative survival from breast cancer in SEER data

Stage	Age	Survival method	20-year survival (%)	Difference between relative and cause-specific 20-year survival		
				Relative minus cause-specific	Mean deviation	Sum of squared error
I	<55	REL	73.5			
		CS-1	76.1	−2.6	1.2	40
		CS-2	72.9	0.5	0.2	1
		CS-3	76.3	−2.9	1.3	50
		CS-4	74.5	−1.0	0.3	4
I	≥55	REL	78.1			
		CS-1	73.7	4.5	2.5	142
		CS-2	63.6	14.5	6.0	979
		CS-3	74.3	3.8	2.2	103
		CS-4	71.7	6.5	3.2	243
II	<55	REL	42.0			
		CS-1	47.3	−5.3	2.4	152
		CS-2	44.4	−2.3	1.1	29
		CS-3	47.9	−5.9	3.0	219
		CS-4	45.4	−3.3	1.4	51
II	≥55	REL	40.2			
		CS-1	44.6	−4.4	2.2	150
		CS-2	39.3	0.9	0.3	2
		CS-3	45.6	−5.5	3.1	263
		CS-4	43.0	−2.9	1.5	66

Relative survival: REL. Cause-specific survival: CS-1 – deaths of unknown cause (d.u.c.) omitted; CS-2 – d.u.c. coded as dead of breast cancer (d.o.b.c.); CS-3 – d.u.c. coded as withdrawn; CS-4 – d.u.c. apportioned between d.o.b.c. and withdrawn.

CS-4 gives results closer to those found with relative survival than any of the other cause-specific methods. Thus CS-4 may be the method of choice for handling deaths from unknown cause when performing cause-specific survival analysis, provided there is no evidence against the hypothesis on which it is based.

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