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REVIEW

Interpreting trends in cancer patient survival

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Abstract Dickman PW, Adami H-O (Karolinska Institutet, Stockholm, Sweden; and Harvard University, Boston, MA, USA). Interpreting trends in cancer patient survival (Review). *J Intern Med* 2006; **260**: 103–117.

Data on cancer patient survival are an invaluable tool in the evaluation of therapeutic progress against cancer as well as other lethal diseases. As with all quantitative information routinely used in evidence-based clinical management – including diagnostic tests, prognostic markers and comparisons of therapeutic interventions – data on patient survival require evaluation based on an understanding of the underlying statistical methodology, methods of data collection and classification, and, most notably, clinical and biologic insight. This article contains an introduction to the methods used for estimating cancer patient survival, including cause-specific survival, relative survival and period analysis. The methods, and their interpretation, are illustrated through presentation of trends in incidence, mortality and patient survival for a range of different cancers. Our aim was to lay out the strengths and limitations of survival analysis as a tool in the evaluation of progress in the diagnosis and treatment of cancer.

Keywords: cancer, survival, excess mortality, relative survival prognosis, survival analysis.

Introduction

'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' [1]. Enstrom and Austin's opening sentence to their article 'interpreting cancer survival rates' [1], published almost 30 years ago, is equally applicable today and not only in the United States. Their arguments that data on cancer survival are not a sensitive measure of progress in cancer control have also been voiced by others [2–4]. We argue that in order to evaluate progress against cancer one must simultaneously interpret trends in incidence, mortality and survival. A search for a 'single best measure' is misdirected; all three measures are valuable and none are fully interpretable without knowledge of the other two. The aim of this paper was to discuss the role of patient survival rates in evaluating progress against cancer.

Until primary prevention programmes succeed to the point of eradicating cancer, doctors must effectively diagnose and treat the cancers that arise and require a means of measuring progress in this specific area. Patient survival rates provide such a measure whereas population mortality rates may not as they also reflect changes in incidence. For example, lung cancer mortality rates are decreasing in many countries, not because we have become better at diagnosing and treating those individuals that develop lung cancer but because successful primary prevention has reduced lung cancer incidence.

The ultimate goal in cancer treatment is to cure the patient. Intuitively, monitoring temporal trends in patient survival is an ideal approach to assessing our performance in this area. We would expect introduction of novel therapeutic modalities – or more efficient use of existing ones – to result in improved survival rates and interpret such findings as evidence of real progress. More often than not, however, such a straightforward interpretation needs several, sometimes many, reservations [5]. The difficulties in interpreting estimates of patient survival have led to the utility of the measure being questioned [1–3]. We argue that patient survival rates provide useful information for doctors, patients, and policy-makers although estimates must be interpreted with care.

Our purpose is to lay out the strengths and limitations of survival analyses as a tool in the evaluation of progress in the diagnosis and treatment of cancer. Needless to say, the same principles apply to other nonmalignant disease that may be fatal. We offer readers two alternatives to approach our text. Besides reading conventionally from beginning to end, those who are less interested in principles and methods can start directly by reading our concrete examples. We present these examples in order to illustrate the principles discussed in the text but hope they are also informative in their own right.

Measuring survival

What does patient survival measure?

'Survival curves', such as that shown in Fig. 1, are commonplace in the medical literature. Cancer patient survival is typically measured as the time from diagnosis until death (Fig. 2a). The '5-year survival rate' is often used as a summary measure of the survival of a group of patients (e.g. patients diagnosed with a specific malignancy at one clinic during 1998). If the outcome is death due to any cause, this represents the proportion of patients alive 5 years after diagnosis. The 'survival rate' is therefore not strictly a rate; it is a proportion [6]. If the outcome is death due to the cancer of interest, the '5-year cause-specific survival rate' represents the proportion of patients who did not die of cancer within the period 5-years subsequent to diagnosis. From Fig. 1, for example, we see that approximately 70% of patients without distant metastases at diagnosis survived 5 years without dying due to colon carcinoma. In subsequent sections we will discuss other measures of patient survival, including relative survival.

Because the survival time is a difference between two dates, it is sensitive to changes in either of the dates. If, for example, diagnosis is made in a patient who presents with symptoms (Fig. 2a) then the

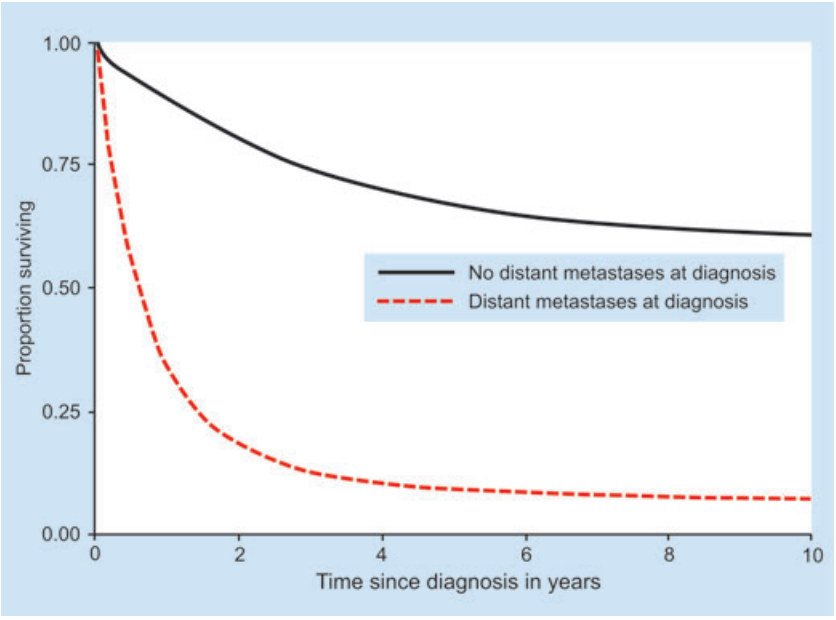

Fig. 1 Cumulative cause-specific survivor function for patients diagnosed with colon carcinoma in Finland 1985–1994.

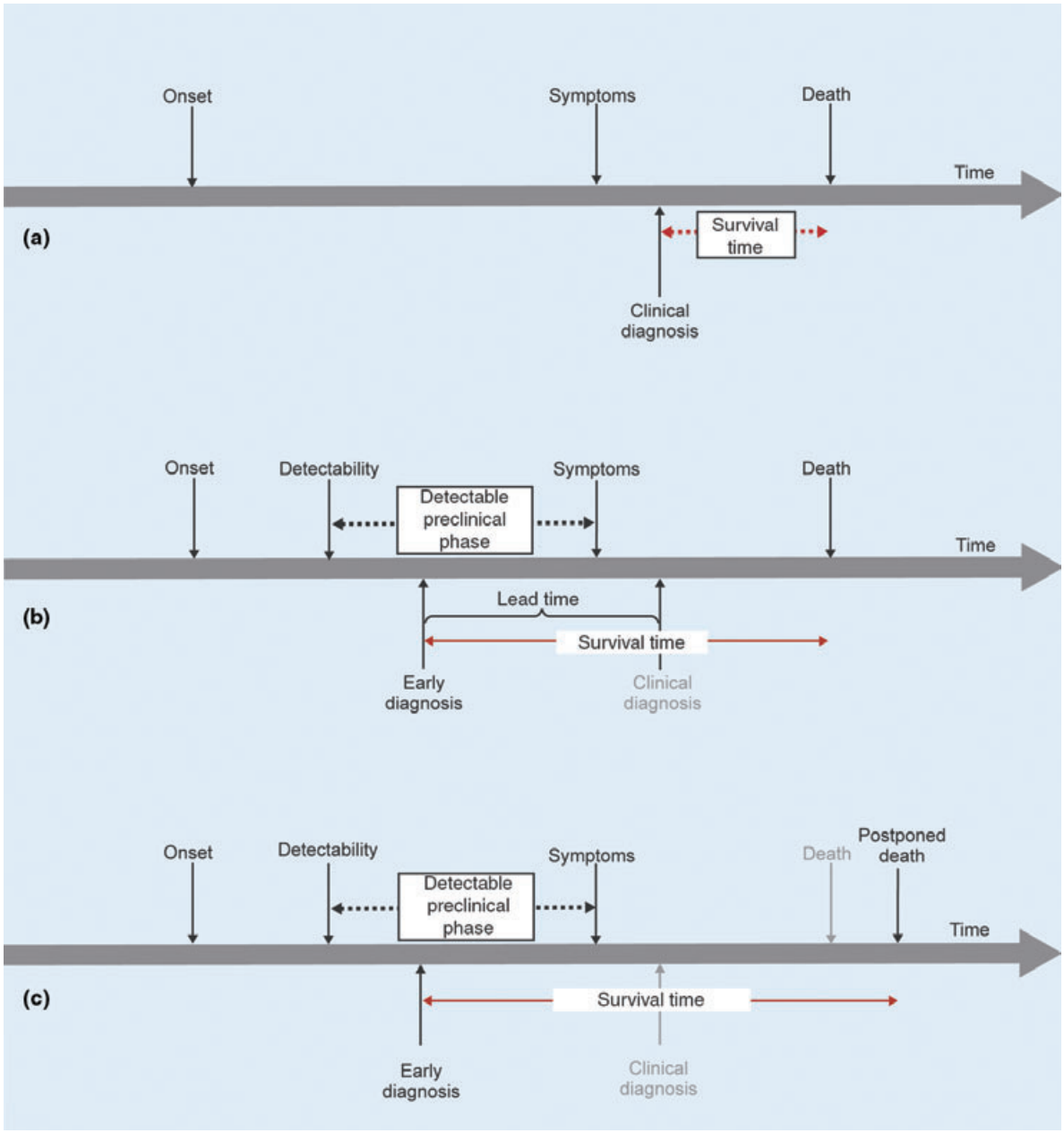

Fig. 2 Natural history of cancer and calculation of survival time for (a) a patient diagnosed clinically, (b) an asymptomatic patient diagnosed through screening where the early diagnosis has not postponed the time of death, and (c) an asymptomatic patient diagnosed through screening where the early diagnosis has postponed the time of death.

survival time is the time between this diagnosis and the date of death. If, however, the cancer was detected by screening (Fig. 2b) the survival time will be increased by an amount, called the lead time, even if the date of death remained unchanged. We would hope, however, that the early diagnosis would increase the potential for cure so that death would be postponed and survival time further increased (Fig. 2c). It is this improvement in survival resulting from postponing death that is of real interest although this component of the trend in patient survival cannot be easily separated from other components such as lead time.

Even in the absence of screening of asymptomatic patients, diagnosis will not occur at the same point in the natural history of cancer for all patients.

Consider, as one extreme, a patient developing breast cancer in a remote rural area where women have limited autonomy, with considerable social and economic barriers to obtaining health care, low awareness of the disease and its early symptoms, no easy access to primary care, and long delays for referral to centres where diagnosis and treatment can be provided. Consider at the other extreme, the same patient living in a highly developed and affluent society which allows her breast cancer to become detected without any delay when it has given rise to symptoms. The time between symptoms and clinical diagnosis in Fig. 2a will be longer in the latter than in the former situation and survival time will differ even if time of death remains the same. We can easily imagine that similar differences, although less extreme, exist when survival is measured during different time periods in the same population. For many malignancies, public and professional awareness as well as access to adequate diagnosis and treatment will improve over time. The corollary here is not that early treatment has no benefit (it often has); only that longer survival is not necessarily proof of such benefit.

What do we wish to measure?

A statistical measure can be considered desirable if it reflects the underlying quantity of interest. So what is it we want to measure? A public health goal is to prevent the occurrence of cancer and doctors play a large part in these endeavours. The goal of the clinician is to reduce morbidity and mortality amongst those individuals who will experience morbidity and mortality due to cancer. To assess progress towards the goal of reducing cancer mortality we would ideally like to be able to measure cancer mortality amongst individuals who are destined to experience increased mortality due to cancer.

Population mortality rates do not serve our purpose as they measure mortality in the entire population during a specified period of time. The published cancer mortality rates for, for example, the year 2005 are calculated by counting the number of deaths due to cancer amongst patients diagnosed over a period of many years, for some malignancies during several decades. The denominator includes the entire population, irrespective of whether or not they have been diagnosed with cancer. Mortality rates will therefore be subject not only to trends in cancer patient survival but also to trends in cancer incidence. As such, they are not an ideal measure of the progress in diagnosis and treatment of cancer. Estimates of patient survival are based upon 'patients diagnosed with cancer'; not identical to 'individuals who will experience increased mortality due to cancer' but close. This difference between the desired study base and the actual study base should be kept in mind when interpreting the estimates.

There is an exact mathematical relationship between survival proportions and mortality rates. Estimates of patient survival can, and we will argue often should, be presented as mortality rates. The question of 'should we present mortality rates or survival rates?' can therefore be rephrased as 'should we present mortality rates among the entire population or mortality rates among the patients'? From a clinical perspective, mortality amongst the patients is of greater interest.

Methods for estimating cancer patient survival

Given we are interested in estimating mortality amongst patients diagnosed with cancer (i.e. cancer patient survival) there are a wide range of statistical methods at our disposal. The most common methods are summarized in Table 1. We will assume that we are interested in estimating mortality due to the specific cancer and therefore wish to correct for mortality due to other causes. The obvious approach is to calculate so-called cause-specific mortality

Table 1 Measures of cancer patient survival

Measure	Advantages	Issues
Observed survival	Measures total mortality. May be more relevant to the patient and/or clinician	Comparisons (e.g. of temporal trends) may be confounded by age
Cause-specific survival	Measures mortality directly due to cancer	Requires accurate classification of cause-of-death
Relative survival	Measures mortality due to cancer, capturing both direct and indirect mortality	Requires estimates of expected survival of a comparable general population

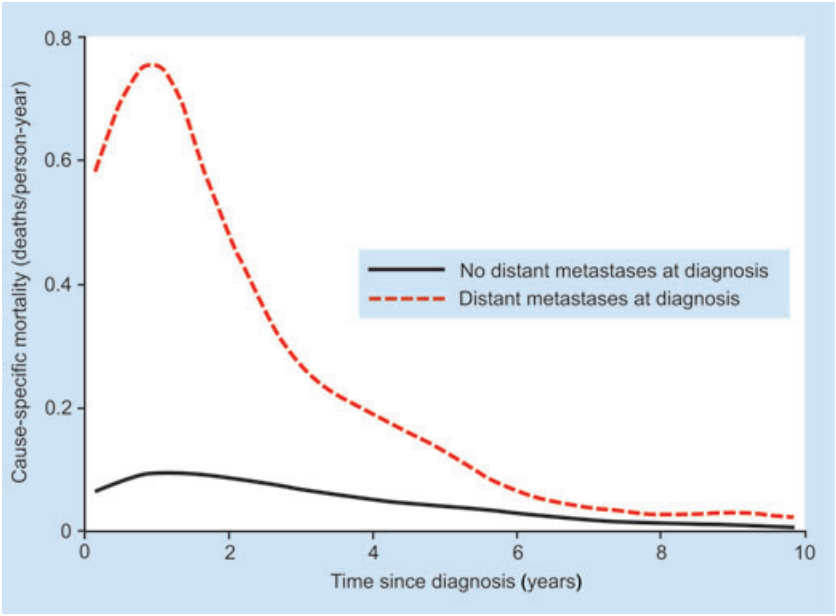

Fig. 3 Cause-specific mortality rates for patients diagnosed with colon carcinoma in Finland 1985–1994 for those with and without distant metastases at diagnosis.

rates, calculated as the number of deaths due to the cancer of interest divided by the number of person-years at risk. We can calculate these mortality rates for small intervals of time since diagnosis and plot the rates as a smoothed function of time since diagnosis (Fig. 3).

The scale on the *Y*-axis in Fig. 3 is deaths due to cancer per person-year at the specific point since diagnosis. Note that these are rates which can theoretically assume any positive value, although when the rates are small they are approximately equal to the probability of death during a 1-year interval. We can see that patients with distant metastases at diagnosis experience considerably higher mortality and that mortality within both groups is highest approximately 1 year following diagnosis. Patients experience very little cancer mortality once they have survived 6 years, even those classified as having distant metastases at diagnosis.

The term 'hazard rate' is used in survival analysis to refer to the 'event rate'. If the event is death then the hazard rate is a mortality rate. A mathematical statistician might think of Fig. 3 as representing cause-specific hazard rates whereas others would be more familiar with the term cause-specific mortality rates. When modelling patient survival using multivariable models it is always the mortality rate (hazard rate) that is modelled.

Most statistical models for survival analysis, the Cox proportional hazards [7] model being the most widely applied in medicine, assume that mortality rates are proportional over follow-up time (the so-called proportional hazards assumption). In other words, the mortality of patients with distant metastases at diagnosis is assumed to be a fixed multiple of the mortality of patients without distant metastases at diagnosis at each and every time-point following diagnosis. This fixed multiple is known generically as the hazard ratio (or relative hazard or relative risk) but could more accurately be called a (cause-specific) mortality rate ratio. A proportional hazards assumption appears reasonable for the data shown in Fig. 3 and using a Cox model the estimated hazard ratio is 7.3 with a 95 confidence interval (6.9–7.6). That is, patients with distant metastases at diagnosis are estimated to experience 7.3 times higher mortality due to colon carcinoma, at each and every point during follow-up, than patients without distant metastases at diagnosis.

Although we always model mortality rates it is more common to present descriptive statistics in terms of survival proportions (i.e. survival curves) rather than mortality rates. Figure 1 shows the cumulative cause-specific survival proportions amongst patients with colon carcinoma in Finland. The slope of the survival curve is proportional to the height of the mortality curve at the same point in time. It is much more difficult, however, to see pattern of mortality as a function of time in Fig. 1 than it is in Fig. 3.

Relative survival (excess mortality)

In order to estimate cause-specific mortality (or, equivalently, cause-specific survival) we require accurate information on cause-of-death. When working with data collected by cancer registries, cause-of-death information is generally based on death certificate coding and may not be sufficiently reliable [8–10]. Welch and Black [11] studied deaths amongst surgically treated cancer patients that occurred within 1 month of diagnosis. They found that 41% of deaths were not attributed to the coded cancer. It is not reasonable to think that such a high proportion of these individuals would die of causes unrelated to the condition for which they underwent surgery; the most likely explanation is that the death certificates did not accurately reflect the cause of death.

When working with cause-specific survival we must classify each and every death as being either entirely due to the cancer in question or completely unrelated to the cancer in question, a dichotomy that does not always reflect the clinical reality. How do we classify, for example, the cause-of-death of a man diagnosed with prostate cancer, treated with oestrogen, who dies following a thromboembolism?

An alternative is to estimate excess mortality, the difference between the total (all-cause) mortality of the patients and the mortality that would be expected in the absence of cancer. Expected mortality is typically estimated based on age, sex and calendar year mortality rates in the general population. Excess mortality provides a measure of the mortality associated with a diagnosis of cancer irrespective of whether the excess mortality is directly or indirectly attributable to the cancer. Deaths due to treatment complications or suicide are examples of deaths which may be considered indirectly attributable to cancer. A major advantage of working with excess mortality is that information on cause of death is not required, thereby circumventing problems with the inaccuracy or nonavailability of death certificates.

The crucial assumption in working with excess mortality is that we can accurately estimate expected mortality. For most types of cancer, patients diagnosed with cancer are representative of the general population, so their expected mortality can be estimated using general population mortality rates. The most notable exceptions are smoking-related cancers where patients will have higher mortality than the general population due to numerous other smoking-related conditions (e.g. cardiovascular disease). The survival analogue of excess mortality is relative survival which is calculated as the ratio of the observed (all-cause) survival proportion to the expected survival proportion.

Cause-specific mortality and excess mortality are two different measures of the same underlying theoretical quantity, namely the estimated mortality due to cancer after adjusting for mortality due to other causes. The two measures should be similar in practice. Any differences will be due to the appropriateness of the relative assumptions (accurate classification of cause-of-death in the case of cause-specific mortality and accurate estimation of expected mortality in the case of excess mortality). Similarly, cause-specific survival and relative survival estimate the same underlying theoretical quantity and should be similar in practice, as they often are.

Statistical cure

It is possible and very common to estimate cumulative relative survival resulting in graphs analogous to that shown in Fig. 1. It is also possible, but less common, to estimate relative survival for each year of follow-up (Fig. 4). Such estimates are known as interval specific or conditional relative survival ratios and provide information that is not easily accessible in the cumulative estimates.

For patients diagnosed with cancer of the stomach we see from Fig. 4 that the relative survival ratio for the first year following diagnosis is only 0.4. This implies that 60% of all newly diagnosed patients will die due to stomach cancer already during the first year of follow-up. Amongst those who survive the first year, the relative survival ratio for the second year is 0.7. Patients who survived 6 years following diagnosis experienced an interval specific relative survival for subsequent intervals that approximates 1.

The attainment and maintenance of an interval-specific relative survival ratio of 1 indicates that there is no excess mortality due to cancer and the patients are assumed to be 'statistically cured'. For many cancers, the pattern of excess mortality is similar to that shown for stomach cancer, with high excess mortality soon after diagnosis and

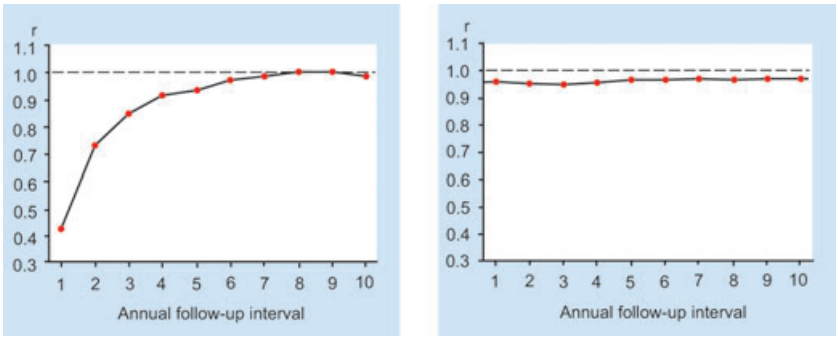

Fig. 4 Interval-specific (conditional) estimates of relative survival for patients diagnosed with cancers of the stomach (left graph) and female breast (right graph) in Finland.

statistical cure reached after approximately 6–8 years [12]. A notable exception is female breast cancer where excess mortality remains at a relatively constant level for many years following diagnosis.

Plots of the interval-specific relative survival ratio, such as those shown in Fig. 4, are also useful for assessing the quality of follow-up procedures of the cancer registry. If the interval-specific relative survival ratio levels out at a value greater than 1, this generally indicates that some deaths have been missed in the follow-up process. An interval-specific relative survival ratio of unity is generally not achieved for smoking-related cancers, such as cancer of the lung and kidney due to excess mortality associated with other smoking-related conditions, malignant and nonmalignant.

Period analysis: predicting survival of newly diagnosed patients

Published estimates of cancer patient survival are based on grouped data and are not necessarily good indicators of the prognosis of individual patients. Even though we attempt to estimate survival for groups that are as clinically homogeneous as possible, there is still a great deal of diversity amongst, for example, the group of 60- to 69-year-old women diagnosed with node-negative, oestrogen-receptor positive, well differentiated breast carcinomas of diameter 11–20 mm. Only the treating doctor can estimate how representative this group may be for predicting the prognosis of an individual patient. A further complication is that the available estimates of patient survival are based on patients diagnosed many years in the past. Period analysis is an approach whereby it is possible to obtain estimates of patient survival for patient groups that more accurately predict the survival of newly diagnosed groups of patients.

Estimates of cumulative survival in the presence of censoring are constructed by taking the product of conditional (interval specific) survival probabilities over short intervals of follow-up. Both the life table (actuarial) and Kaplan–Meier methods use this principle. That is, to estimate the probability of surviving 5 years following diagnosis we might estimate the probability of surviving the first year, multiplied by the probability of surviving the second year (given survival through the first year), multiplied by the probability of surviving the third year (given survival through the first 2 years), and so on. This approach is applied because the assumptions made to account for censored data are appropriate for small intervals (such as 1 year) but not for intervals as long as 5 years.

In order to estimate cumulative 10-year survival, traditional methods require a cohort of patients where at least some individuals are diagnosed more than 10 years in the past. With the traditional approach for estimating cumulative survival, the cohort approach, all patients contribute to the estimated conditional survival proportion for the first year (even those diagnosed more than 10 years ago). Brenner *et al.* [13] suggested that it might be more appropriate to estimate each of the conditional survival proportions using only the most recently diagnosed patients. For example, the conditional survival proportion for the first year would be based on patients diagnosed during the previous year; the conditional survival proportion for the second year would be based on patients diagnosed the year before that, and so on. Patients diagnosed many years in the past would only contribute to the estimates of conditional survival proportions for later intervals.

What demographers refer to as a period life table is used to estimate expectation of life at birth; we estimate the expectation of life for a newborn by assuming he or she will experience the same age-specific probabilities of death of the present population. We know (or hope) that these figures will underestimate the true life expectancy of newborns as we expect mortality rates to decline. The period approach to cancer patient survival applies the same principle; we estimate the survival of newly diagnosed patients by assuming they will experience the same interval-specific probabilities of survival as those patients currently alive and at risk today.

This suggestion was initially met with scepticism. However, studies based on historical data [13] have shown that period analysis very accurately predicts the prognosis of newly diagnosed patients. It also highlights temporal trends in patient survival sooner than traditional cohort methods. So why does period analysis underestimate expectation of life for newborns but provide remarkably accurate predictions of the survival of newly diagnosed cancer patients? Age-specific mortality rates have been decreasing – and will hopefully continue to decrease – for all ages. Temporal improvements in cancer patient survival, however, are generally most pronounced in the first few years following diagnosis. Unfortunately, not all of the patients who would previously have died early are cured but their deaths are delayed to subsequent intervals. This results in period estimates of survival that are overly optimistic. This bias, however, is cancelled by the fact that we expect a general improvement to continue so expect period estimates to be pessimistic in the same manner as when estimating expectation of life.

Possible explanations for temporal trends in patient survival

In addition to predicting survival of newly diagnosed patients, clinicians are interested in using estimates of patient survival for assessing performance in diagnosing and treating patients. In addition to improvements in diagnosis and treatment, temporal improvements in patient survival may be the result of a range of additional factors [5]. We have previously discussed screening and will briefly mention some additional issues.

Changes in definition of disease

A systematic designation of premalignant conditions as invasive disease will inevitably inflate estimates of survival, and therefore the possible impact of changes over time in the histopathological classification and coding of tumours must be considered when interpreting survival trends.

Stage migration

The accuracy of the classification of clinical stage has increased as more sensitive diagnostic technologies are introduced, giving rise to what is commonly known as stage migration [14]. For example, the use of computerized axial tomography scanning and magnetic resonance imaging has resulted in the diagnosis of metastatic disease that would have been undetectable some years ago. The patients who 'migrate' typically have worse survival than those with truly localized disease but better survival than those patients with obvious metastatic disease. Reclassifying these patients from the localized to the nonlocalized group will therefore result in apparent improvements in patient survival in both groups even when there has been no change in survival. It is tempting to perform stage-specific or stage-adjusted analyses in an attempt to disentangle the relative contribution of therapeutic improvements, earlier diagnosis, and lead-time effects to temporal improvements in survival. Such analyses may, however, be confounded by the effect of stage migration whereas all-stage analyses will not.

Trends in survival and their interpretation

To illustrate strengths and limitations of survival analyses, we now present concomitantly incidence, mortality, and survival rates for individuals aged less than 85 years. We use the public database of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute [15]. These data cover nine cancer registries in the United States of America. Incidence and mortality rates were age-standardized to the 2000 US population and 5-year relative survival ratios were calculated using the method proposed by Hakulinen for calculating expected survival [16]. All calculations were performed using SEER*Stat version 6.2.1 [17]. We present estimates aggregated over broad age ranges

for both sexes and all races in order to illustrate some of the issues involved in interpreting estimates of patient survival. A more complete presentation of these data is available on the SEER website (http://seer.cancer.gov/).

Trends demonstrating therapeutic progress

- Childhood leukaemia (Fig. 5)
- Testicular cancer (Fig. 6)

The five year survival amongst patients with childhood leukaemia (Fig. 5) and testicular cancer (Fig. 6) improved dramatically during the last decades of the 20th century. Could such trends arise spuriously even in the absence of real therapeutic progress and improved long-term cure rates? This appears inconceivable for several reasons. First, enormous bias would be needed to create trends of this magnitude. Secondly, the trends coincide with introduction of new therapeutic modalities, chiefly

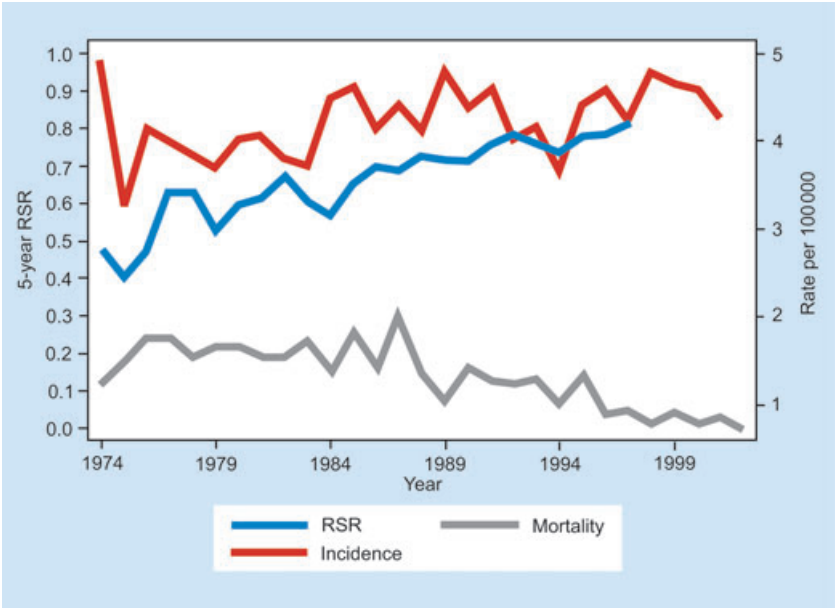

Fig. 5 Leukaemia amongst males and females aged 0–14 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

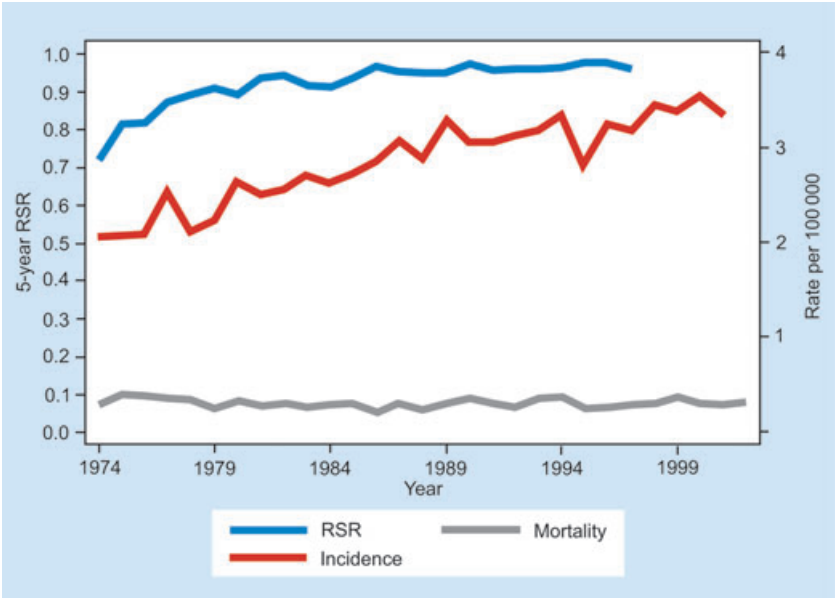

Fig. 6 Cancer of the testis amongst males aged 0–50 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

cis-platinum-based chemotherapy for testicular cancer and successively refined combination chemotherapy for childhood leukaemia. Thirdly, the malignant phenotypes are distinct with little or no room for changes in diagnostic criteria over time. Fourthly, there have been no screening efforts that spuriously increase the observation time between diagnosis and a fatal outcome. Finally, unlike several solid malignancies in adulthood, 5-year survival rates are good approximates of long-term cure because late fatalities are rare events. Hence, we conclude that treatment of testicular cancer and childhood leukaemia represents success stories in cancer cure, and that this accomplishment is effectively captured and adequately quantified by temporal trends in survival.

Trends demonstrating lack of progress

- Lung cancer (Fig. 7)
- Pancreatic cancer (Fig. 8)

Lack of therapeutic progress is nowhere more obvious than for cancers of the lung and pancreas. Notwithstanding an extraordinary number of clinical trials for lung cancer (a literature search indicated that over 900 such trials have been published) the gloomy prognostic outlook has remained largely unaltered over several decades. Indeed, amongst lung cancer patients, the 5-year relative survival remained virtually horizontal whilst the mortality rate closely mimicked the incidence rate. This is exactly the pattern one would expect when case fatality remains constant. No conceivable bias could have concealed any real progress.

Attempts to achieve early diagnosis of lung cancer by means of screening high-risk individuals (chiefly heavy smokers) have not documented benefit [18]. The aggressive nature of this malignancy leaves only a small fraction of patients – apparently stable over time – where disease is localized to the lung at the time of diagnosis and therefore curable by surgical removal of the primary tumour. It might be timely to ask whether resources spent on studies of new chemotherapy regimens would save more lives if spent on primary prevention; smoking continues to account for about 90% of all lung cancer cases – and deaths.

As if it were possible, pancreatic cancer – less preventable, surgically inaccessible, early metastasing – seems even more elusive for curative treatment than lung cancer. Over a 25-year period, 5-year relative survival varied little around 5%.

Some spurious trends might have arisen because over time, new technologies have improved diagnostic sensitivity and specificity. It is hard to predict whether this would increase survival rates because some disseminated cancers with origin in organs other than the pancreas can now be identified and excluded from analyses. Or whether improved

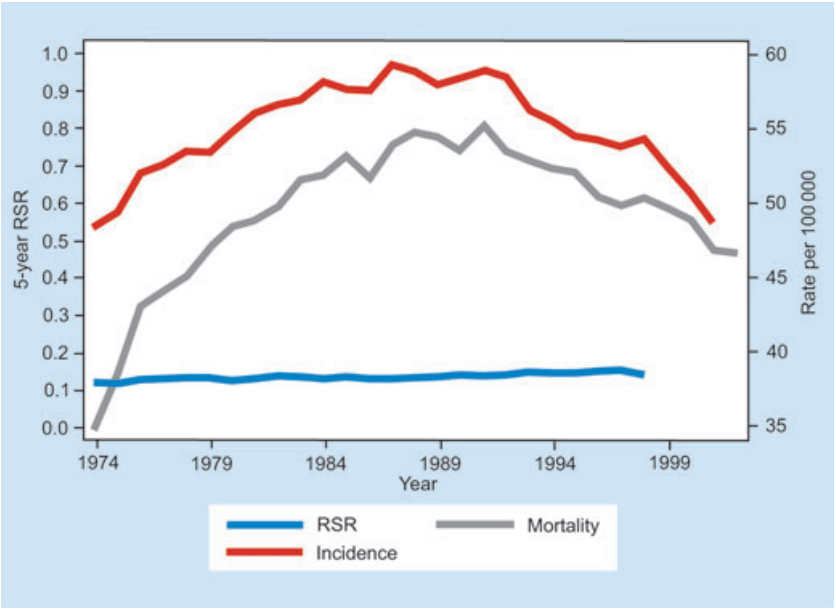

Fig. 7 Cancer of the lung and bronchus amongst males and females aged 0–84 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

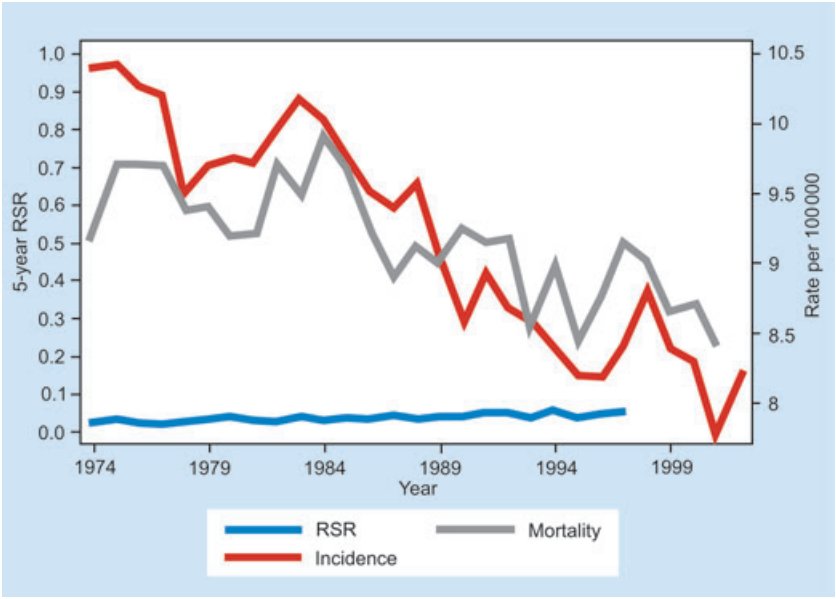

Fig. 8 Cancer of the pancreas amongst males and females aged 0–84 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

diagnosis has reduced survival estimates because now some pancreatic cancers are correctly included that in earlier years became histopathologically confirmed first at autopsy and therefore excluded from survival analyses. Overall, however, the lack of convincing improvement in survival accords with clinical knowledge and lack of therapeutic breakthroughs.

We conclude that survival rates convey a grim but true message concerning frustrating lack of progress in the cure of lung and pancreatic cancer. For both these malignancies, however, reduced incidence due to primary prevention – chiefly reduced tobacco smoking – has reduced the disease burden for the population.

Trends arising without improved cure

- Prostate cancer (Fig. 9)

Interpretation of trends in prostate cancer survival is one of the most elusive goals in contemporary

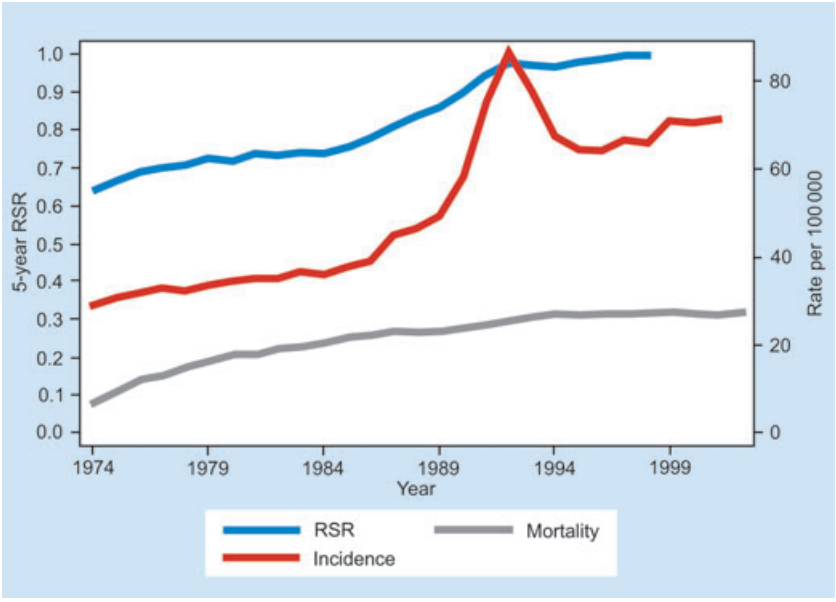

Fig. 9 Cancer of the prostate amongst males aged 0–84 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

oncology. One unique benchmark exists, however, namely the fact that no treatment with a curative intent existed for prostate cancer until the late 1980s when radical prostatectomy begun to be used. Until then, the mainstay of treatment was hormonal manipulation, offering effective but transient palliation with no cure. Hence, prior to about 1990, no survival trend could be attributed to improved cure because no such treatment was in use. Yet, trends in survival did clearly exist (Fig. 9) and we must ask why. Conceivably, some deaths due to side effects of high-dose hormonal treatment (chiefly oestrogen) might have been avoided when these treatments begun to be used more carefully.

More recently, the increasingly widespread use of radical prostatectomy has likely influenced survival rates favourably [19]. Probably, however, overall survival rates have increased marginally at most, because only a fraction of all incident cases undergo treatment with a curative intent (those with a most favourable prognosis) and it takes several years for the benefit to become manifest [19]. Instead, two other factors may explain most of the trend, namely lead time bias and overdiagnosis of nonfatal disease [20].

Diagnostic intensity was shown already before the introduction of testing with prostate-specific antigen (PSA) to profoundly influence the incidence but (as expected) not the mortality from prostate cancer [21]. This situation has become greatly exaggerated following widespread PSA testing, starting around 1990 and still escalating. Although there is no empirical evidence for any true underlying upward trend in prostate cancer incidence, the annual number of newly diagnosed cases has almost doubled in little more than a decade in the USA (Fig. 9), Sweden [22] and elsewhere [23]. This would imply that the yearly cohort of patients newly diagnosed with prostate cancer is now substantially 'diluted' with nonfatal cases. In addition, clinically significant, potentially fatal cases are diagnosed earlier during their natural course. This lead-time phenomenon (Fig. 2b) will, by definition, increase survival time between diagnosis and death.

In summary, prostate cancer represents an extreme in terms of complex dynamics over time. As a corollary, trends in survival do not allow any conclusion concerning therapeutic progress to be drawn with confidence. Only mortality rates can help us understand the net effects of increased diagnostic intensity, lead time, overdiagnosis and novel therapeutic modalities.

Trends attributable to several factors in combination

- Breast cancer (Fig. 10)

Beyond any doubt, survival rates amongst women with breast cancer have improved gradually, but importantly, over several decades. A substantial amount of solid scientific evidence helps us conclude

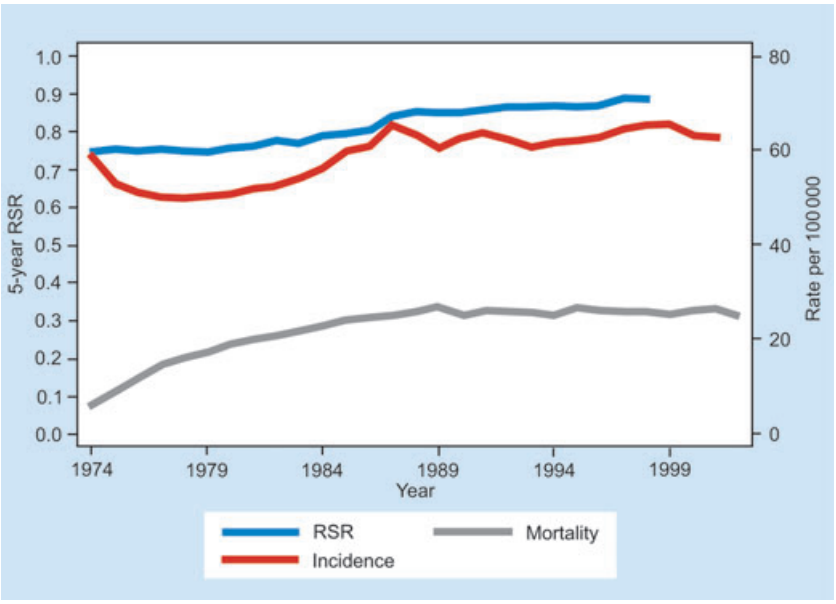

Fig. 10 Cancer of the breast amongst females aged 0–84 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

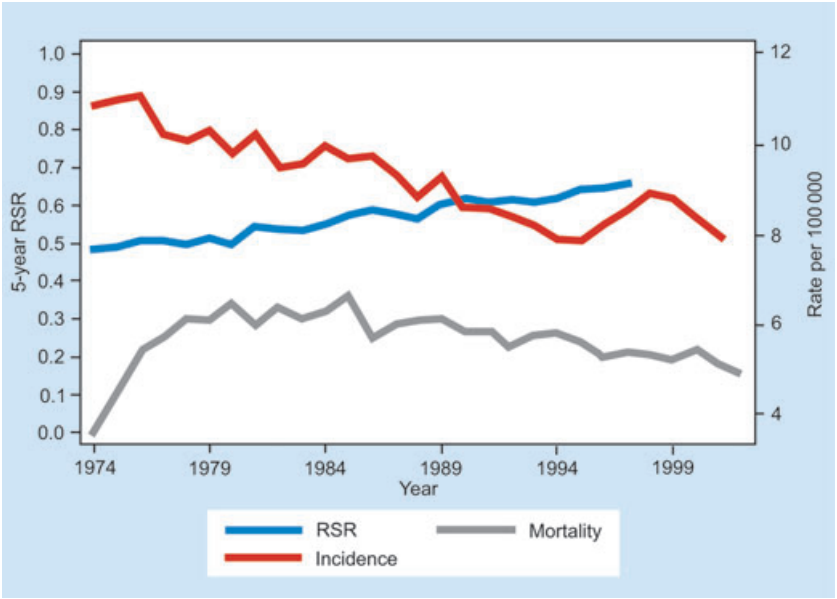

Fig. 11 Cancer of the rectum amongst males and females aged 0–84 years. Trends in incidence, mortality and 5-year relative survival for nine US states participating in the SEER program.

that these trends represent real progress in several areas – and that favourable trends might indeed continue in future [24]. The main contributions come from early diagnosis by means of mammography screening and from widespread use of systemic adjuvant treatment with chemotherapy, anti-oestrogens or both [24, 25]. Second-generation aromatase inhibitors may herald further progress. Early clinical diagnosis through increased public and professional awareness might contribute too, but randomized trials of breast self-examination have failed to document any measurable benefit [25].

Some bias arising due to widespread screening with mammography might also exaggerate the improved trend in survival, at least slightly. First, screening entails some overdiagnosis of breast cancers that would otherwise not have surfaced clinically, and thus are nonfatal. Such over diagnosis seems, however, modest [25, 26] and far lower that that associated with PSA testing for prostate cancer [21]. Secondly, screen detection adds lead time to the observed interval between diagnosis and death. Again, however, this effect is much smaller than that associated with PSA, and usually in the order of a few years.

- Rectal cancer (Fig. 11)

Rectal cancer is a rewarding example of substantial progress, achieved within the constraints of existing therapeutic principles. Although screening interventions amongst asymptomatic individuals using faecal occult blood testing or endoscopic visual inspection, can likely improve cure rates through early diagnosis, such programmes have had limited penetration in the USA [27]. Instead, the combined effects of two other developments have improved the prognostic outlook for patients with rectal cancer. Unlike most other efforts in oncology that concentrate on adjuvant systemic treatment to eliminate distant micro metastases, the main conduit to increasing survival from rectal cancer is improved local tumour control.

In the past, many patients – often around 30% and sometimes more – suffered from local recurrence of their rectal cancer following surgical treatment. This incurable stage often entailed enormous suffering. During the last decades, randomized clinical trials demonstrated a clear benefit when surgical treatment was preceded by radiation therapy [28, 29]. Concomitantly, awareness about the fundamental role of the surgical technique grew amongst surgeons [30]. As a corollary, rectal cancer surgery begun to be concentrated to fewer surgeons who mastered the technique of a meticulous and extensive local dissection. This technique allowed radical removal of the tumour without contamination of the surgical field. In many settings, local recurrence rates went down to 10% or even lower [31]. These developments are obvious, and major biases appear unlikely. Therefore, we conclude, as others [32], that the favourable temporal trends in rectal cancer survival reflect real progress, probably with about equal contributions from improved surgical technique and from preoperative

radiotherapy. This conclusion can only be reached with confidence when appropriate statistical analyses and clinical insights are used in combination.

Discussion

For reasons outlined earlier [33] we deliberately avoided addressing whether there is any overall progress in cancer patient survival. Cancer comprises a large group of disease that – although sharing some biological hallmarks – differs in virtually every other aspect: etiological, prognostic and clinical.

Unlike some others, we consider estimates of cancer patient survival an invaluable tool in the evaluation of therapeutic progress against cancer as well as other lethal diseases. We feel this tool has been unfairly dismissed based on exaggeration of its limitations. As with all quantitative information routinely used in evidence-based clinical management – including diagnostic tests, prognostic markers and comparisons of therapeutic interventions – data on patient survival require evaluation based on an understanding of limitations, biases, stochastic processes and, most notably, clinical as well as biological insight.

Conflict of interest statement

No conflict of interest was declared.

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