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Review

Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications

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Abstract

Long-term survival rates are the most commonly used outcome measures for patients with cancer. However, traditional long-term survival statistics, which are derived by cohort-based types of analysis, essentially reflect the survival expectations of patients diagnosed many years ago. They are therefore often severely outdated at the time they become available. A couple of years ago, a new method of survival analysis, denoted period analysis, has been introduced to derive more 'up-to-date' estimates of long-term survival rates. We give a comprehensive review of the new methodology, its statistical background, empirical evaluation, computational realisation and applications. We conclude that period analysis is a powerful tool to provide more 'up-to-date' cancer survival rates. More widespread use by cancer registries should help to increase the use of cancer survival statistics for patients, clinicians, and public health authorities.

Keywords: Neoplasms; Prognosis; Registries; Survival

1. Introduction

Long-term survival rates are the most commonly used outcome measures for patients with cancer. They are widely used to monitor progress in cancer care over time, or to compare quality of cancer care between different populations (e.g. [1–4]). Furthermore, cancer survival statistics are increasingly accessible through the Internet to clinicians and cancer patients, and their knowledge has a strong impact on both clinicians' management of the disease as well as patients' coping strategies.

However, traditional long-term survival rates, which have been derived by cohort-based types of analysis [5–7], have essentially reflected the survival expectations of patients diagnosed many years ago. They have often been severely outdated at the time they became available as they failed to account for ongoing improvements in survival over time. A few years ago, a new method of survival analysis, denoted period analysis, has been introduced to derive more up-to-date estimates of long-term survival rates [8,9]. Meanwhile, this methodology has undergone extensive empirical evaluation [10–14], which showed that the method provides much more up-to-date estimates of long-term survival rates than traditional methods of survival analysis indeed. Furthermore, software has been developed which allows easy implementation of this new analytical tool for both absolute and relative survival rates [15]. The method is now applied to derive more up-to-date long-term survival rates in an increasing number of countries [16–24]. These analyses suggest that long-term survival rates achieved by the end of the 20th century are much higher than previously suggested by traditional cohort-based analysis. For example, a recent period analysis of cancer patient survival in the United States [22] indicated that 20-year relative survival rates for all cancers combined are now approximately 51% rather than 40% as suggested by traditional cohort-based analysis (see Fig. 1). Even larger differences are seen for many common forms of cancer, such as breast cancer (65% versus 52%) or ovarian cancer (50% versus 35%).

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In this review, a comprehensive presentation of the new methodology, its statistical background, empirical evaluation, computational realisation and applications is given. We thereby hope to expedite widespread availability of more up-to-date cancer survival statistics.

2. Theory

The methodological principle of period analysis, which has been described in detail by Brenner and Gefeller [8,9] is very simple. In order to provide up-to-date estimates of long-term survival for some recent time period, all observations included in the analysis are left-truncated at the beginning of the period of interest in addition to being right censored at its end. This is illustrated in Fig. 2 for 5-, 10-, 15-, and 20-year survival estimates that might be obtained for a recent time period, say 1995–1999 (the most recent time period for which data from the Finnish Cancer Registry, which were used for the empirical illustration given below, were available at the time this paper was written).

With traditional, cohort-based survival analysis, the most recent estimates of 5-, 10-, 15-, and 20-year survival rates would have pertained to patients diagnosed in 1990–1994, 1985–1989, 1980–1984, and 1975–1979, respectively (areas marked by black grid in Fig. 2), if 5 calendar years are combined to provide reasonably precise estimates of survival (which is common practice in the cancer registry world). However, given that most cancer deaths occur during the first few years following diagnosis, these survival estimates would essentially reflect levels of prognosis achieved many years ago. They may therefore be outdated in cases of recent improvement in survival. By contrast, period analysis exclusively considers survival experience in recent years, i.e. in the 1995–1999 period in this example (grey area in Fig. 2). With that approach, survival experience during the first year following diagnosis is provided by patients diagnosed between 1994 and 1999. Survival experience in the 2nd year following diagnosis is provided by patients diagnosed between 1993 and 1998 and so on, until survival experience during the 20th year following diagnosis, which is provided by patients diagnosed between 1975 and 1980. These conditional survival probabilities within single years are then multiplied to calculate cumulative survival rates, such as 5-, 10-, 15-, and 20-year survival rates, in the same way as in a traditional life table analysis.

Whereas the period approach has been introduced for the analysis of long-term patient survival only a few years ago, it has been widely used for a very long time in other science fields. Probably the best known example is the estimation of life expectancy. Estimates of current life expectancy are commonly based on period life tables, which include survival probability by age during a given recent calendar period. For example, in a life table for the 1995–1999 period, survival probability in the first year of life is provided by people born in 1994–1999, survival probability in the second year of life is provided by people born in 1993–1998, and so on. This implies that the survival probabilities in defined years after birth are obtained in exactly the same way as the period-based survival probabilities of cancer patients in

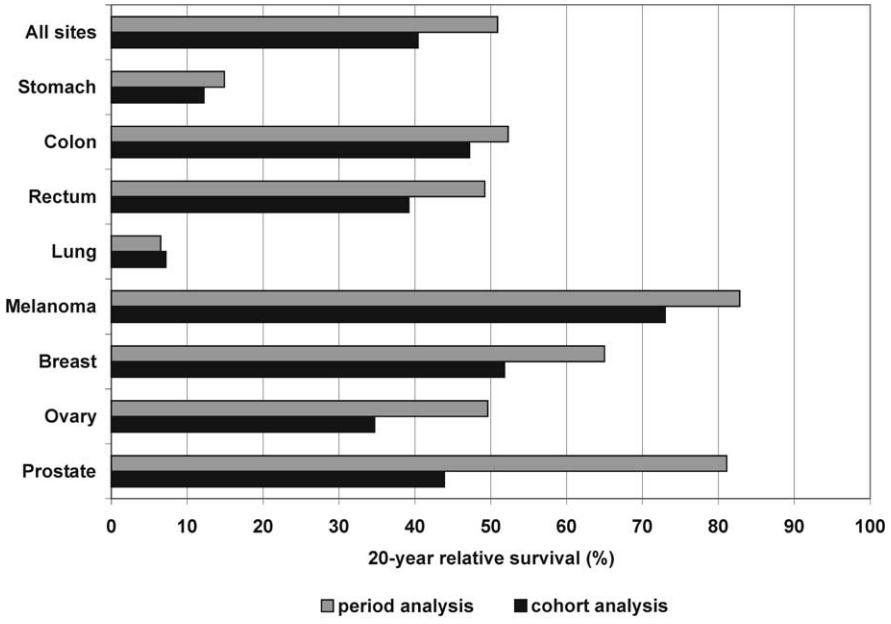

Fig. 1. 20-year relative survival rates of cancer patients achieved by the end of the 20th century in the United States: Results of a period analysis for the year 1999 compared with the results of a cohort-based analysis (pertaining to a cohort of patients diagnosed in 1979 and followed, with respect to vital status, for up to 20 years until 1999) [22].

defined years following diagnosis. The life expectancy is then derived as a summary measure from these age- and period-specific survival probabilities. Although estimates of life expectancy are occasionally also derived from cohort life tables which pertain to cohorts of people born a lifespan ago, these estimates are mainly of historical interest. In particular, they do not reflect major advances achieved in population survival rates during the past decades in most parts of the world.

The life expectancy derived from some recent period life table reflects the average length of life to be expected by newborn people assuming that the age-specific mortality rates observed during that period remain constant over time. Likewise, the period estimates of cancer patient survival for some recent time period reflect the cumulative survival rates to be expected by newly-diagnosed cancer patients assuming that the conditional survival probabilities within defined time intervals following diagnosis observed in that time period prevail.

In practice, conditional survival probabilities often tend to increase further over time thanks to advances in early detection, therapy, or both. Therefore, the survival expectations of cancer patients diagnosed within some calendar period are usually even higher than the period estimates for that period (just like the average length of life of people born in some calendar period is usually longer than the life expectancy estimated from a life table for that period due to further reductions in mortality rates in the population over time).

However, in theory, period estimates of long-term cancer patient survival may also become (transiently) overly optimistic, if advancements in early detection or therapy do not increase the chance of cure, but merely postpone cancer deaths. In this hypothetical situation, the increased survival rates during the early years following diagnosis will show up before the reduced conditional survival rates in later years. This theoretical possibility has often been forwarded as a caveat against the use of period analysis before the results from thorough empirical evaluations became available. However, as outlined in more detail below, it turned out to be of little if any relevance in practice.

In the analysis of cancer registry data, relative survival rates are often reported along with or rather than absolute survival rates. Relative survival rates, which are derived as the ratios of absolute survival rates and the expected survival rates of subjects of the corresponding age and gender in the general population, as estimated from population life tables, reflect the 'net survival' of patients with cancer. They can be inter-

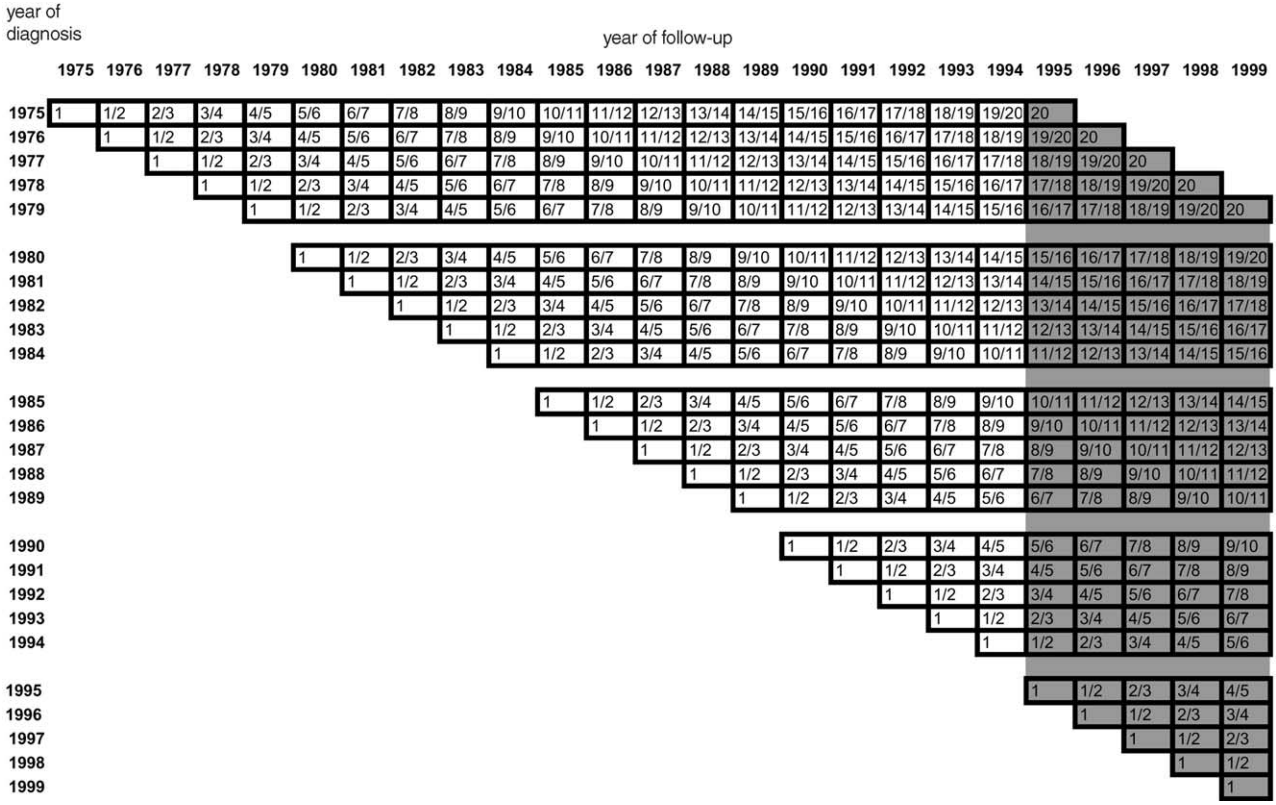

Fig. 2. Principle of derivation of recent period versus cohort estimates of long-term survival rates illustrated in the context of a cancer registry with incidence and follow-up-data up to and including 1999. The areas marked by black grid indicate the database needed for obtaining recent cohort estimates of 20-, 15-, 10-, and 5-year survival rates in 1995–1999 (pertaining to patients diagnosed in 1975–1979, 1980–1984, 1985–1989 and 1990–1994, respectively). The grey area indicates the database needed for deriving recent period estimates for the 1995–1999 period. The numbers within the cells indicate the years of follow-up since diagnosis.

preted as expected survival rates of patients with cancer in the hypothetical situation in which cancer is the only cause of death [7]. There are different methods to calculate expected survival rates from the population life tables. The most commonly used methods are the so-called Ederer II method [25] and Hakulinen's method [26].

Like traditional survival analysis, period analysis can be employed for both absolute and relative survival rates. In all of the examples given in this paper relative survival rates derived according to Hakulinen's method are shown.

3. Empirical evaluation

Two major avenues have been followed for empirical evaluation of the performance of period analysis.

In one approach, it was evaluated how well survival estimates obtained by period analysis (compared with estimates obtained by traditional survival analysis) within some calendar period actually agree with the survival rates later observed for patients diagnosed with cancer in that period. This approach is of particular relevance in the clinical setting, where the prognosis of newly-diagnosed patients is usually of most interest to patients, their families and clinicians.

In a second approach, it was assessed how timely changes in survival rates over time were disclosed by monitoring cancer survival rates using the period method compared with traditional methods of survival analysis. This approach is of particular relevance from a public health point of view, where one is clearly interested to disclose trends in cancer patient prognosis, e.g. by advances in cancer care or early detection, in as timely manner as possible.

Following these approaches, extensive empirical evaluations have been carried out for all of the most common forms of cancer using data from the nationwide Finnish Cancer Registry (population base: approximately 5 million people), which is ideal for this purpose due to its long history of cancer registration and very high level of data quality and completeness since the early 1950s [27,28]. The principle of these evaluations will be illustrated below in different age groups of patients for all forms of cancer combined (excluding non-melanoma skin cancer), again using data from the Finnish Cancer Registry.

3.1. Accurate reflection of survival expectations of newly-diagnosed patients

In Fig. 3, 10-year relative survival curves actually observed for patients diagnosed with cancer in 1985–1989 (upper black lines) are shown. This is the most recent cohort of patients for whom 10-year follow-up was complete at the time of this analysis. These are compared with the most up-to-date estimates of 10-year relative survival curves that could have been obtained in 1985–1989 (i.e. at the time of diagnosis of these patients) using either period analysis (grey lines) or traditional cohort analysis (lower black lines). The period survival curves are much closer, in both shape and levels of survival, to the survival curves later observed for newly-diagnosed patients than the cohort survival curves (although even the period survival curves are slightly too pessimistic). The advantage of period analysis over traditional cohort analysis is seen in all age groups, but it is largest for childhood cancers where the improvements over time have been largest.

Very similar patterns have been demonstrated in more detailed analyses specifically addressing each of the 15 most common forms of cancer in Finland [10], as well as major forms of childhood cancer in the United States [14]. The only exception were cancers for which no improvements were seen over time, such as pancreatic cancer and lung cancer. For these cancers, both period and cohort based survival curves agreed equally well with the 10-year survival curves later observed. The advantage of period analysis over traditional cohort analysis was even greater when 20-year rather than 10-year survival curves were considered for each of the most common forms of cancer [13].

In an additional analysis, a more comprehensive evaluation was performed in which the entire database of the Finnish Cancer Registry from 1953 on was included and in which the 'so-called' complete analysis was also evaluated along with period and cohort analysis [11].

'Complete' analysis is a modification of traditional cohort analysis, in which more recently diagnosed patients are also included, even if they could not possibly have completed the entire follow-up interval of interest and thus would have to be censored at the closing date of follow-up. For example, in Fig. 2, a complete estimate of 20-year survival available in 1995–1999 would pertain to the survival experience in 1975–1999 of patients diagnosed in 1975–1999, as opposed to the survival experience in 1975–1999 of patients diagnosed in 1975–1979 only included in the cohort estimate, and the survival experience in 1995–1999 only of patients diagnosed in 1975–1999 included in period analysis. Thus, estimates from complete analysis should be somewhat more up-to-date than those from cohort analysis, but still much less so than those from period analysis. This pattern was empirically confirmed for each of the 16 most common forms of cancer in Finland [11].

3.2. Timely monitoring of progress in long-term cancer patient survival

In Fig. 4, a time series analysis of 5-, 10-, 15-, and 20-year relative survival rates of patients with any form of

cancer in Finland between 1955 and 1999 is shown. For each 5-year calendar interval from 1960–1964 to 1995–1999, the most up-to-date relative survival estimates available by period analysis (grey lines) or by traditional cohort analysis (black lines to the right) in that calendar interval are shown (with the 1955–1999 database used for this analysis, the time series for 5-, 10-, 15-, and 20-year survival estimates start with calendar intervals 1960–1964, 1965–1969, 1970–1974, and 1975–1979, respectively). As Fig. 4 illustrates, relative survival rates of patients with cancer have substantially improved over time. The figure also illustrates that the time trends disclosed by period analysis are very similar in shape to those disclosed by cohort analysis. However, detection of time trends is advanced considerably by the use of period analysis rather than traditional cohort analysis. Achievements in 5-, 10-, 15-, and 20-year relative survival rates are disclosed almost 5, 10, 15, and 20 years earlier, respectively, by period analysis compared with cohort analysis. This can be seen from the fact that the

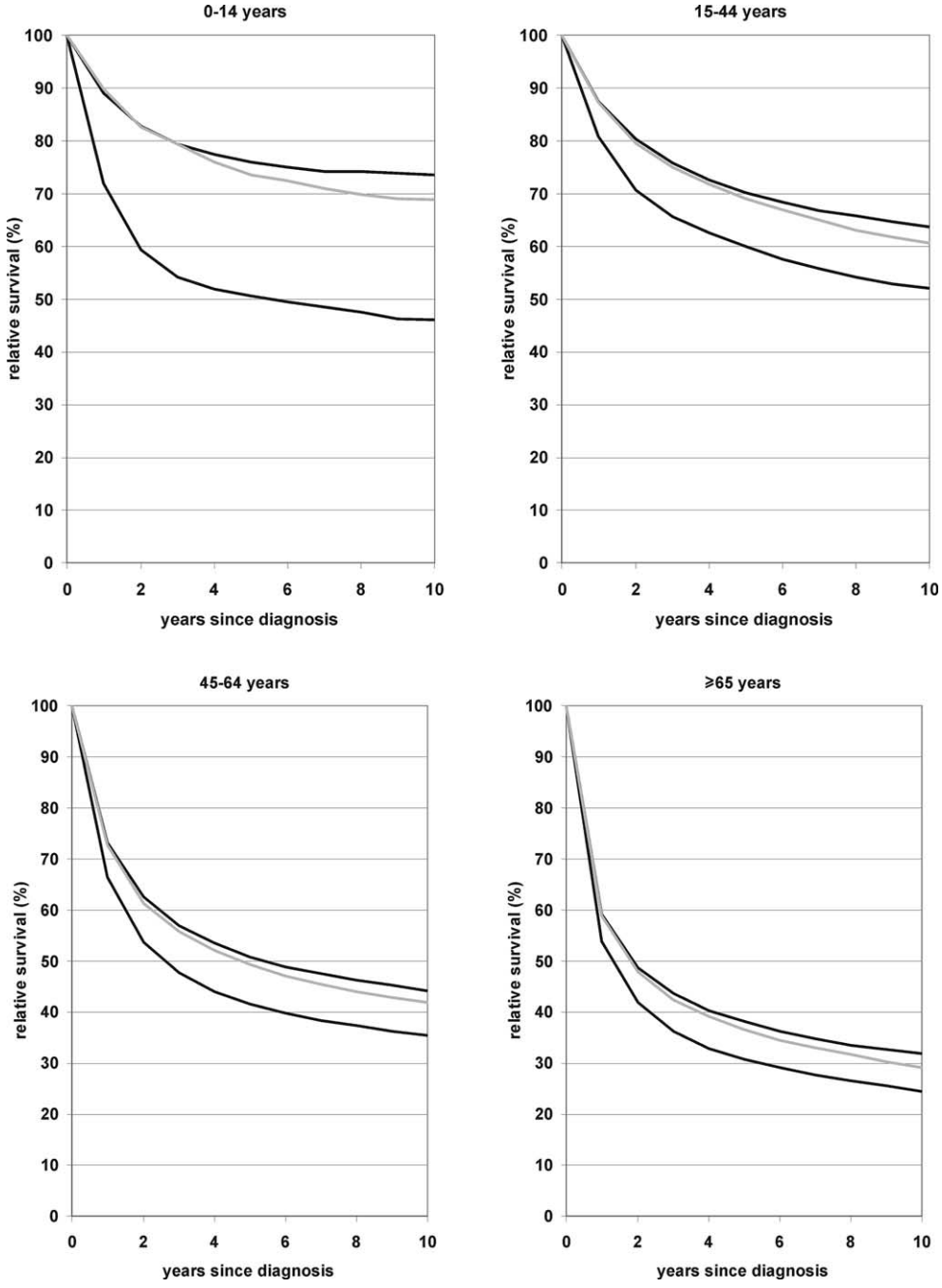

Fig. 3. Observed 10-year relative survival curves of patients diagnosed with cancer at various ages in 1985–1989 (upper black lines) compared with the most up-to-date survival curves available in 1985–1989 by period analysis (grey lines) and cohort analysis (lower black lines).

period trend curves almost coincide with and provide natural extensions of the cohort trend curves of 5-, 10-, 15-, and 20-year relative survival rates shifted by 5, 10, 15, and 20 years to the left, respectively (black lines to the left in Fig. 4).

Essentially the same patterns regarding the advantages of period analysis over cohort analysis were seen in more detailed analyses for each of the 15 most common forms of cancer in Finland [12], despite the strong variation in survival rates and their trends between various cancer sites. Obviously, the type of analysis makes little difference to the results for those cancers for which essentially no changes in survival rates have occurred over time, such as lung cancer or pancreatic cancer.

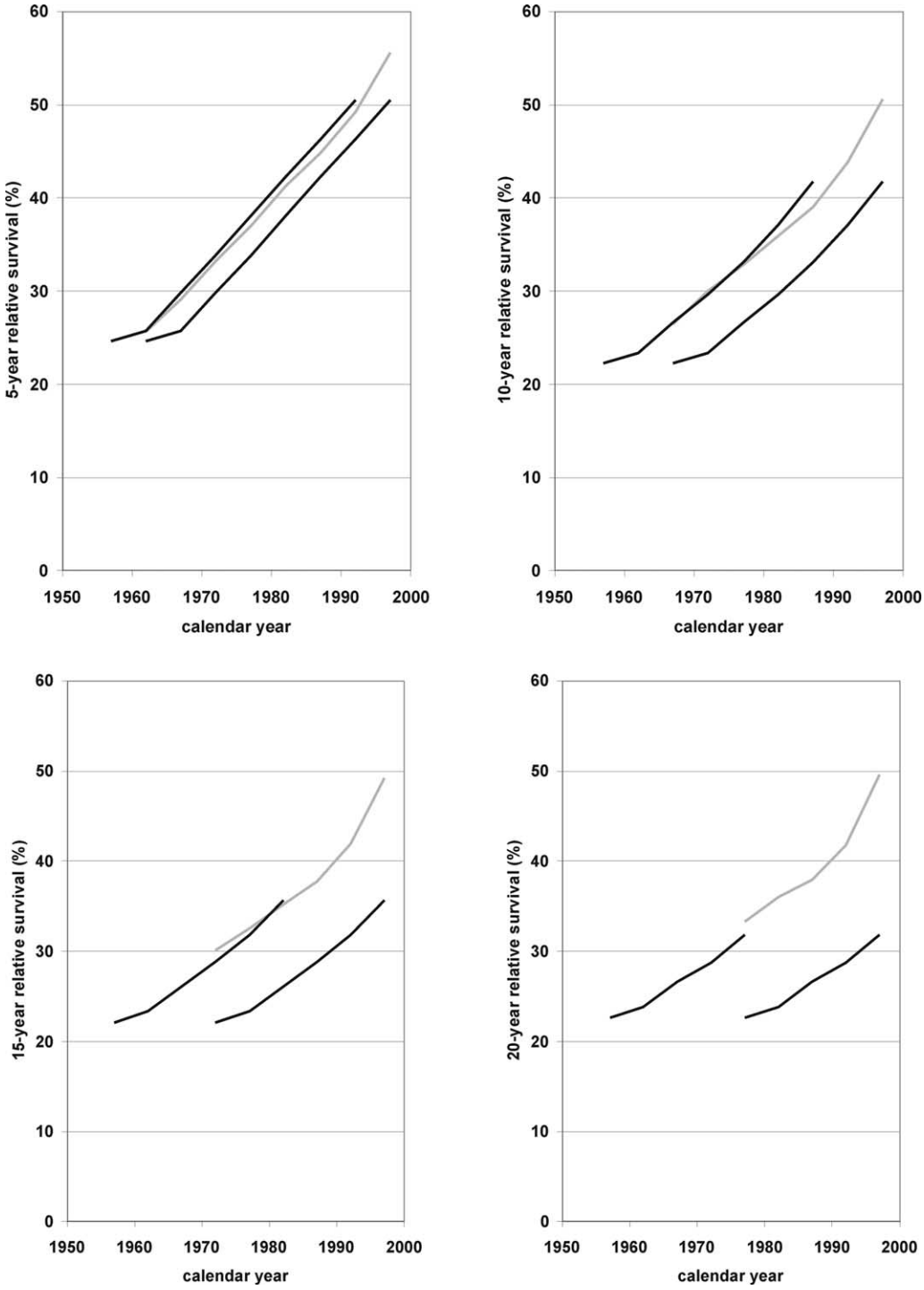

Fig. 4. Trends in 5-, 10-, 15- and 20-year relative survival rates for patients with all forms of cancer in Finland disclosed in various calendar years by period analysis (grey lines) versus cohort analysis (black lines to the right). The black lines to the left indicate the trends that could have been disclosed if the cohort estimates of 5-, 10-, 15-, and 20-year survival rates could have been obtained 5-, 10-, 15- and 20 years in advance.

4. Computational realisation

The previously available special software for relative survival analysis used by most cancer registries has not included options to perform period analysis [29,30]. Recently, easy to use SAS macros have been developed and made publicly available, by which both traditional analysis as well as period analysis of both absolute and relative survival rates can be performed. Two macro versions are currently available. They provide identical results for absolute survival rates, but they differ in the way the expected survival rates in the absence of cancer (as derived from population life tables), and hence the relative survival rates, are derived. In one version, the expected survival rates are derived according to the Ederer II method [15], in the other version, Hakulinen's method is used [31].

A detailed description of the macros has been given elsewhere [15,31]. Briefly, a life table methodology is employed, in which numbers of deaths, patients at risk and conditional survival rates are derived for 1-year intervals of follow-up after diagnosis. These conditional survival rates are then multiplied to derive cumulative survival rates. Standard errors of survival estimates are derived according to Greenwood's method [32].

For the derivation of expected survival rates, 1-year survival probabilities by gender and single years of age (and possibly other covariates, such as race, where applicable) must be read in from population life tables. These population life tables can easily be updated (e.g. by invoking pertinent macros) if extended calendar periods are included in the calculations.

The macros can be run with the SAS statistical software package version 8 or older. The macros and their documentation can be downloaded free of charge from the statistical archive network maintained by the Department of Medical Informatics, Biometry and Epidemiology at the University of Erlangen-Nuremberg (http://www.imbe.med.uni-erlangen.de/issan/SAS/period/period.htm). The source code of the macros is open code under the conditions of the GNU-General Public License [33]. Extensive validation efforts have been made to guarantee the correctness of the macros.

5. Applications

In previous work, both cohort and complete analyses have been applied to derive population-based cancer survival rates. Pure cohort analysis has been very popular. For example, the previous report of the EUROCARE project, an international collaborative study of European cancer registries, has included cohort estimates of 5-year survival of patients diagnosed in 1985–1989 and followed until 1994 [2]. Pure forms of complete analysis have been rare (e.g. [34]), but 'close to complete analysis' has been more commonly applied, in which all patients have been included who had been followed for at least some minimum time interval, such as 1 or 2 years, at the closing date of follow-up. Recent examples include analyses of long-term survival rates of cancer patients in Finland [35], Sweden [36,37], Italy [38] and the United States [39].

Very recently, period analysis has been applied to derive up-to-date estimates of cancer patient survival in a number of countries, including Finland [20], Estonia [23], Germany [16–19,21], the United States [14,22] and the United Kingdom [24], and pertinent analyses are underway in a number of countries, including, among others, Denmark, Sweden and the Netherlands. Furthermore, application of period analysis is foreseen in a number of international collaborative studies, including the EUROCARE study, in the future. Some cancer registries, such as the nationwide Finnish Cancer Registry and the nationwide German Childhood Cancer Registry, have already implemented period analysis as the standard tool for their annual reports [40,41].

In all of the previous applications, use of period analysis has shown that long-term survival rates for many forms of cancer have meanwhile become much higher than previously available survival statistics, which were based on traditional survival analysis, had disclosed. The differences have been particularly pronounced for cancers with rapid improvements over time, such as childhood cancers, breast cancer or ovarian cancer at relatively young ages [14,16–19,21–22].

In Fig. 5, the most recent estimates of 5-, 10-, 15-, and 20-year relative survival curves for all cancers combined, derived from the database of the nationwide Finnish Cancer Registry by traditional cohort analysis and by period analysis as shown in Fig. 2, are given according to age at diagnosis. The most recent 5-, 10-, 15-, and 20-year period survival estimates for the 1995–1999 period are given on a single 20-year survival curve (grey line). In the cohort analysis, different survival curves for the most recent 5-, 10-, 15-, and 20-year survival rates were obtained. With the database up to and including the year 1999, the most recent 5-, 10-, 15-, and 20-year cohort survival curves (black lines) pertain to cohorts of patients diagnosed in 1990–1994, 1985–1989, 1980–1984, and 1975–1979, respectively.

6. Discussion

Since the first publication suggesting the use of period analysis for cancer patient survival appeared in the literature in 1996, a thorough empirical evaluation has disclosed that

- this method provides more 'up-to-date' estimates of long-term cancer patient survival than tradi-

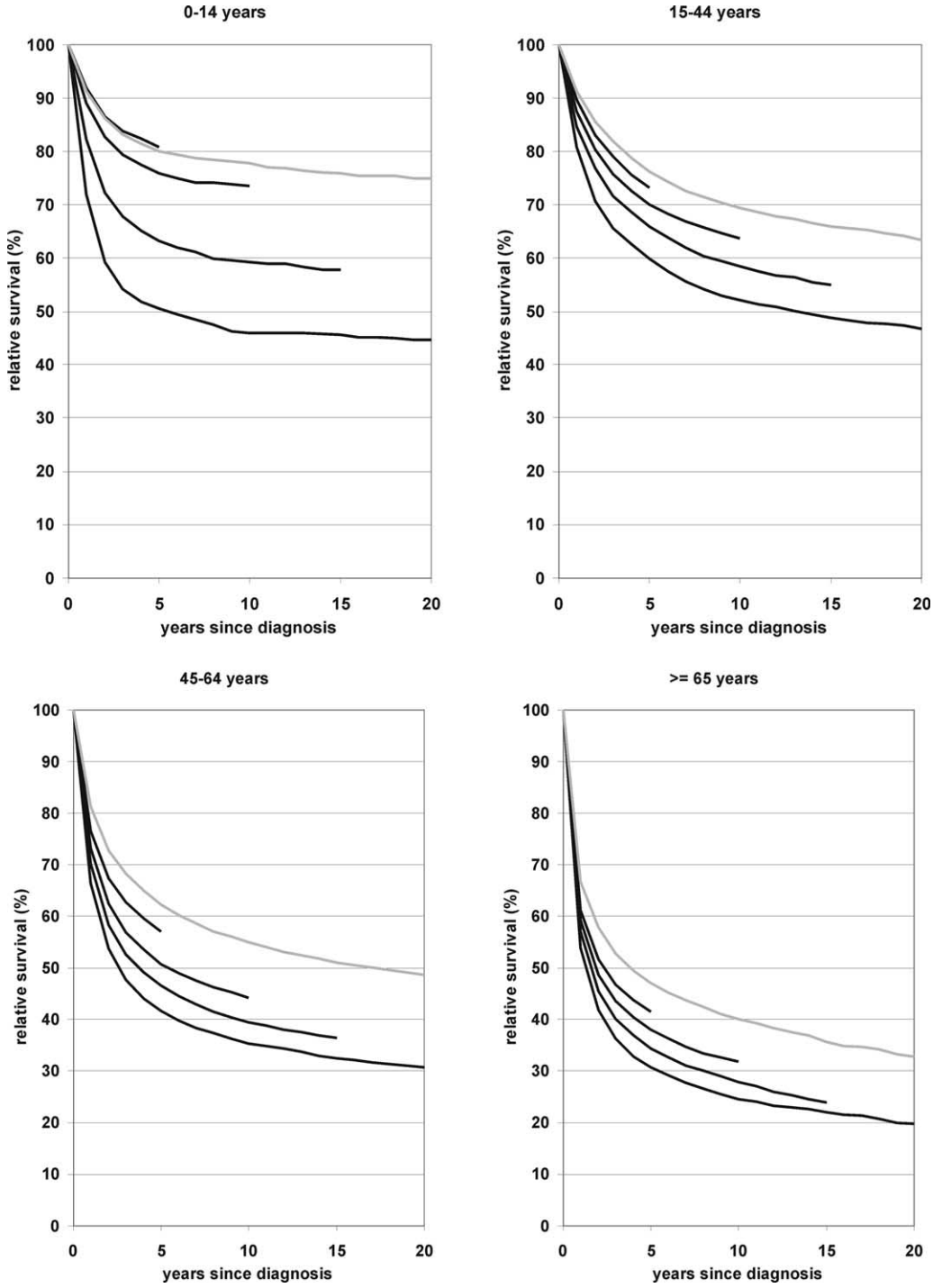

Fig. 5. Recent 5-, 10-, 15- and 20-year relative survival curves for patients with all forms of cancer in Finland derived by period analysis (pertaining to the 1995–1999 period, grey curve) or by cohort analysis (pertaining to patients diagnosed in 1990–1994, 1985–1989, 1980–1984 and 1975–1979, respectively; black curves).

tional methods of survival analysis

- period estimates of long-term cancer patient survival within some recent time period quite closely predict long-term survival rates observed later for patients diagnosed in that period
- period analysis advances the detection of time trends in 5-, 10-, 15-, and 20 years by almost 5, 10, 15, and 20 years, respectively, compared with traditional cohort-based survival analysis.

Although differences are somewhat less pronounced compared with previous applications of (close to) 'complete' analysis [11,12], these results imply that period analysis should be very useful for both the clinical

setting and public health applications. Nevertheless, it has only been adopted very recently and very slowly by the research community and the public health community.

An obvious question in this context is why the period method was only introduced for cancer patient survival estimates in 1996, as the period method has been around for many decades for constructing life tables and estimating current life expectancy in the field of demography. By contrast, it is only 35 to 70 years after the early landmark papers on cohort-based survival analysis approaches (e.g. [5–7,25,32,42]) that the period approach has been introduced for analysis of cancer patient survival. While we cannot offer an explanation for this phenomenon, we consider this to be another excellent example of the benefits of crossing disciplinary boundaries (here: between demography and epidemiology) in the development and application of statistical methodology.

Even after the method has been proposed, its adoption by the scientific community has been slow. Obvious obstacles against its more rapid adoption may have been the lack of pertinent training and software, as the method has not been taught in textbooks or specific courses in the past and period estimates are not provided in the software packages that are commonly used by cancer registries. Availability of an easy-to-use, publicly accessable computer program since early 2002 should enhance the possibilities of computational realisation. We also hope that the comprehensive presentation in this paper may help to disseminate knowledge of this methodology.

However, there has also been some scepticism against the use of the methodology among people who were aware of it for several years. The argument most often put forward against its use has been the theoretical possibility that period estimates of long-term survival may become (transiently) overly optimistic in certain situations, where advances in early detection or therapy do not increase the chance of cure, but merely postpone cancer deaths. While this concern is theoretically valid, the thorough empirical evaluations that have been carried out in the meantime [10–14] have clearly shown that this point is irrelevant in practice. By contrast, even period estimates for some recent calendar periods can be too pessimistic compared with the long-term survival rates later observed by patients diagnosed in that period (at least if the improvements in prognosis are ongoing). However, this underestimation is typically much less than that observed in estimates of long-term survival rates from traditional cohort-based analyses.

Further development of period analysis, e.g. by including modelling of recent time trends might be considered to reduce or overcome the prevailing tendency of the method to underestimate survival expectations of newly-diagnosed patients in cases of ongoing improvements in prognosis. However, the potential benefits of such modelling strategies would have to be weighed against the increased complexity and less straightforward interpretation of survival statistics that this approach would involve.

Fortunately, prognosis is now improving for many forms of cancer in many countries, and this improvement is more timely detected by use of period analysis. For other forms of cancer, such as lung and pancreatic cancers, prognosis has hardly changed over time and continues to be very poor. Under such conditions, survival rates derived from period analysis are essentially the same as those derived from traditional cohort-based survival analysis. In the (fortunately less common) situation of deterioration of survival rates over time, such alarming trends would likewise be more timely detected by period analysis rather than by traditional cohort-based analysis.

In summary, period analysis should be incorporated as a standard tool in the analysis of cancer registry data. It is a powerful tool to provide more 'up-to-date' cancer survival rates which should help to increase the value of cancer survival statistics for patients, clinicians and public health authorities. Notwithstanding the advantages of period analysis compared with traditional cohort-based survival analysis in providing 'up-to-date' survival estimates, the latter method remains the method of choice for specific applications, such as retrospective analyses of the survival experience of specific cohorts of patients, e.g. patients with specific forms of initial treatment. Period analyses should therefore supplement, not replace the traditional methods of survival analysis.

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