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# Hybrid analysis for up-to-date long-term survival rates in cancer registries with delayed recording of incident cases

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**Abstract**

Up-to-date monitoring of long-term survival is an important task of population-based and clinical cancer registries. A few years ago, a new method of survival analysis, denoted period analysis, was introduced to provide more up-to-date estimates of long-term survival. However, a prototypical period analysis may not be applicable in situations with delayed recording of incident cases. We introduce herein a hybrid type of analysis that combines elements of both traditional and period analyses which may still be feasible in such settings. The performance of the hybrid type of analysis compared with other design options is empirically evaluated and illustrated for children diagnosed with cancer in the United States. The empirical evaluation indicates that hybrid analysis may be useful to derive more up-to-date estimates of long-term survival compared with traditional design options if there is a strong improvement of survival over time, even in situations with a substantial delay in recording of incident cases.


*Keywords:* Children; Cancer registries; Statistical methods; Survival

## 1. Introduction

Long-term survival rates, such as 5- and 10-year survival rates, are the most widely used and most commonly reported outcome measures of patients with cancer [1]. In the past, the most recent long-term survival rates have mostly been derived from patients who have been under long-term observation since their diagnosis. As a result, patient survival figures have often been quite outdated at the time they were derived and published where there were major recent improvements in survival, e.g., due to treatment advances. A few years ago, a new method of survival analysis, denoted period analysis, was introduced to provide more up-to-date estimates of long-term survival rates [2]. This is achieved by exclusive consideration of the survival experience of patients (diagnosed in various calendar years) during some recent calendar period. After careful empirical evaluation [3,4], this method has meanwhile been employed to derive more up-to-date cancer survival rates in a number of countries (e.g. [5–8]). However, application of this approach requires that both incidence and follow-up data of cancer patients are available for this recent period.

However, the recording of incident cases, which continues to be a time-consuming and labour-intensive process in many cancer registries, is often delayed by a couple of years, whereas mortality follow-up of registered cases, which can ideally be done by routine record linkage with national death indices, is often more up-to date. For example, a recent analysis of cancer survival in England and Wales was based on incident cases up to 1999 (the most recent data available at the time of the analysis), while mortality follow-up (of patients diagnosed in 1999 or earlier years) was complete until

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the end of 2001 [9]. In other instances, databases for survival studies were collected in such a way that only patients with a minimum potential follow-up time were included. For example, in the EUROCARE study, a collaborative study on survival of cancer patients in Europe, the most recently collected data included patients diagnosed up to the year 1994 only, who were followed-up to 1999 [10].

In such situations, a prototypical period analysis for the most recent calendar years (such as the years 2000–2001 in the British study, or the years 1995–1999 in the EUROCARE study) may not be done. In this paper, we outline and illustrate the application of a hybrid type of analysis which combines elements of both traditional and period survival analyses and which may still be feasible and useful in such situations.

## 2. Patients and methods

To illustrate our approach, we consider the following example: We assume that, by the end of 1989, an up-to-date estimate of 10-year survival of patients with cancer was to be derived in a population-based cancer registry. We further assume that the cancer registry has been in operation since at least 1975. Fig. 1 shows the database available for estimating 10-year survival from this registry if both registration and mortality follow-up of patients were performed without any delay. In that case, an up-to-date estimate of 10-year survival might have been obtained for the year 1989 and possibly preceding years by period analysis. To come up with reasonably precise estimates, one might have considered including the combination of several years, say 1985–1989 in the analysis. Hence, a period estimate of 10-year survival in 1985–1989 may have been obtained from proportions B, D and E of the database as previously described. By contrast, traditional "cohort-wise" 10-year survival analysis would typically have reflected survival experience of patients who have been followed for 10 years, i.e., patients diagnosed in 1975–1979 who completed 10-year survival in 1985–1989 (proportions A and B of the database). Other traditional analyses would also have included patients diagnosed in later years, who did not have the opportunity to be observed over the entire 10-year follow-up, but who would have been censored at the closing date of follow-up (unless they died or were lost to follow-up before). This so-called "complete analysis" would have included portions A, B, C, D and E of the database.

In situations where there was a delay in the recording of incident cases by, say, 5 years, portion E of the database would not have been available by the end of 1989. In those situations, a prototypical period analysis for the 1985–1989 period would not have been possible. However, one might still have used key elements of

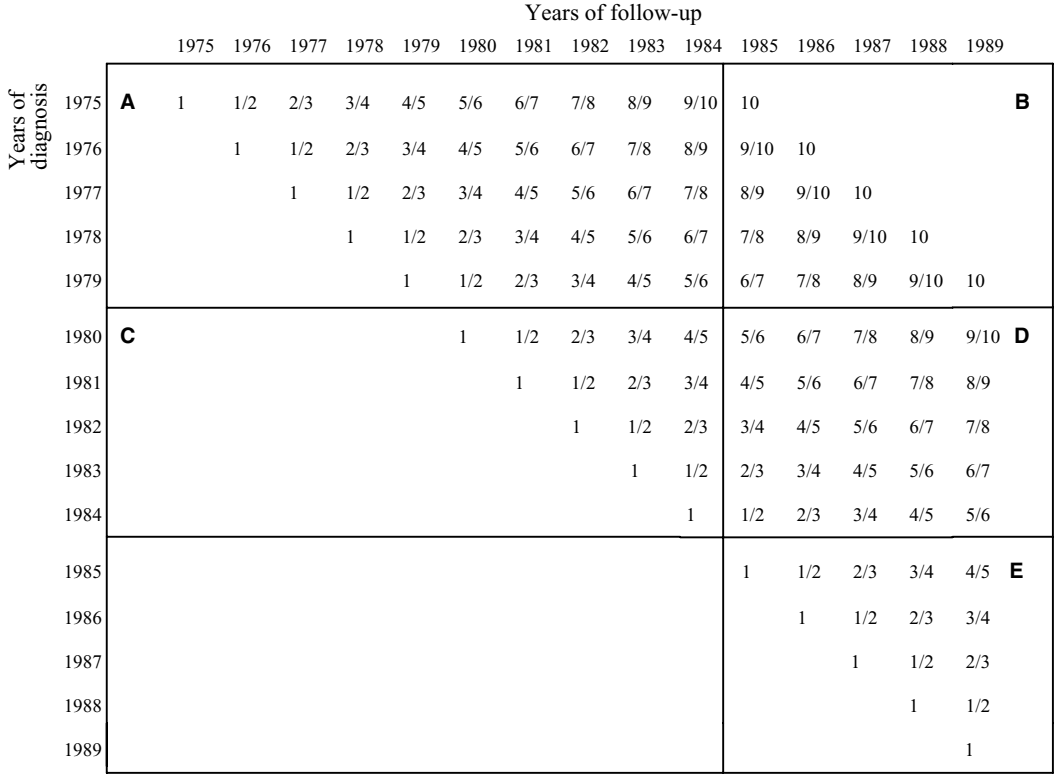


Fig. 1. Different proportions of the database used in the various design options of survival analyses. The numbers within the cells indicate the years of follow-up since diagnosis.

period analysis by combining the portions B and D of the database with portion C rather than E for the analysis in a ''hybrid'' type of analysis. The cohort analysis for the 1975–1979 cohort combining portions A and B of the database would not have been affected by the delayed recording of incident cases, whereas the complete analysis would have been restricted to portions A, B, C and D (rather than A, B, C, D, and E). An overview of the different design options in situations with and without delayed recording of incident cases is given in Table 1.

We carried out an empirical evaluation of the performance of the hybrid type of analysis compared with traditional cohort and complete analyses by comparing 10-year survival curves later observed for patients diagnosed in 1985–1989 with 10-year survival curves that might have been obtained by the end of 1989 using the different options of survival analysis. Because up-to-date monitoring of long-term survival rates is of particular relevance in situations where there are large increases in survival rates over time, we chose childhood cancer survival for illustration, given the major progress achieved in this field in recent decades [11,12]. In addition long-term survival rates are of particular relevance for this group of cancer patients.

All analyses were carried out using the 1973–2000 public use database of the Surveillance, Epidemiology, and End-Results (SEER) Program of the United States National Cancer Institute [13]. Data included in the 1973–2000 SEER database are from population-based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland, which together cover a population of approximately 30 million people. Our analysis is based on patients with a first diagnosis of cancer below age 15 years between 1975 and 1989 ($n = 9565$). Patients with missing information on the month of diagnosis (0.3%), or survival time (0.6%) were excluded, as were patients whose cancer was reported by death certificate only (0.2%) or autopsy only (0.4%), leaving a final number of 9476 children for the analysis. Data are presented for all races and both genders combined. In addition to analyses for all forms of cancer combined, specific analyses were carried out according to three major age groups (0–4, 5–9 and 10–14 years) and by common diagnostic groups. Specific survival curves are shown for leukaemias and lymphomas, i.e., common diagnostic groups for which particularly large progress in treatment has been achieved during the past decades [14–16]. Since mortality from competing causes of death is almost negligible for children, and relative survival rates are essentially the same as absolute survival rates for this age group, only absolute survival rates are presented in this paper. All analyses were performed with the SAS software package, using a publicly available macro for both cohort and period analyses [17], which was slightly extended to carry out the hybrid analysis.

Table 1
Design options for deriving 10-year survival at the end of 1989 in situations with and without delay of incidence recording

| | | Proportions of database included (see figure 1) | | | | |
|---|---|---|---|---|---|---|
| Incidence recording | Design option | A | B | C | D | E |
| Not delayed | Period analysis | | ■ | | ■ | ■ |
| | Complete analysis | ■ | ■ | ■ | ■ | ■ |
| | Cohort analysis | ■ | ■ | | | |
| | | | | | | |
| Delayed | Hybrid analysis | | ■ | ■ | ■ | |
| | Complete analysis | ■ | ■ | ■ | ■ | |
| | Cohort analysis | ■ | ■ | | | |

## 3. Results

Fig. 2 shows the performance of the various design options of survival analysis following immediate

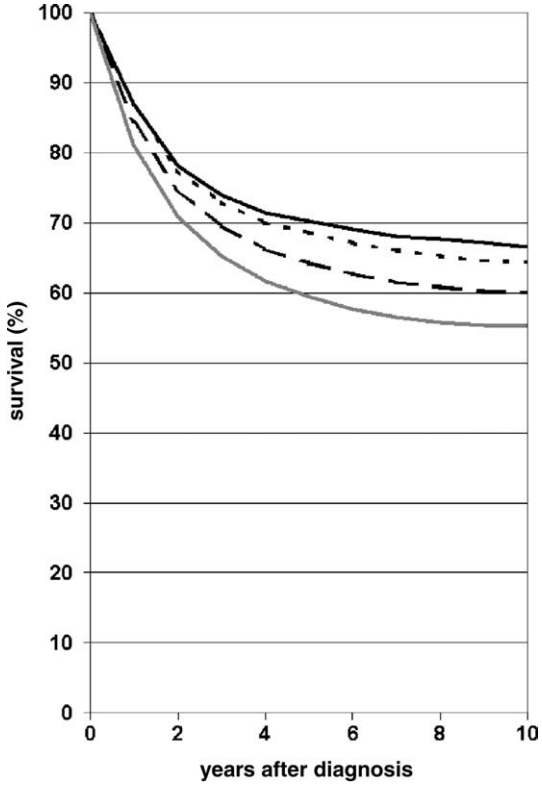


Fig. 2. Observed 10-year survival of children diagnosed with cancer in 1985–1989 (black solid curve) and 10-year survival estimates potentially available at the end of 1989 using period analysis (black short-dashed curve), complete analysis (black long-dashed curve) and cohort analysis (grey solid curve). All forms of childhood cancer combined, Surveillance, Epidemiology, and End-Results (SEER) 1973–2000 database.

recording of incident cases. All survival curves fall throughout the 10 years following diagnosis, which underlines the necessity of long-term follow-up to evaluate the prognosis of children with cancer. The general shape of the survival curves is quite similar for all types of survival analysis, but their slope, and hence the estimates of surviving children vary widely. The 10-year survival actually observed for children diagnosed with any form of cancer in 1985–1989 ($n = 3437$) was 66.5% (black solid curve). Period analysis for the 1985–1989 period would quite closely have predicted this result (64.3%, black short-dashed curve), whereas complete analysis (black long-dashed curve) and particularly cohort analysis (grey solid curve) would have provided much lower 10-year survival estimates (59.9% and 55.1%, respectively). Standard errors were below 1% for all of the 10-year survival estimates.

In situations with delayed recording of incident cases (Fig. 3), a prototypical period analysis would not have been feasible and the 10-year survival curve later observed for children diagnosed with any form of cancer in 1985–1989 could not have been predicted as closely. However, a hybrid type of analysis could have been carried out, which would still have provided a more up-to-date survival curve than the other techniques of analysis. The general shape of the survival curve obtained by hybrid analysis is again very similar to the shape of conventional survival curves, but the hybrid analysis would have yielded an estimate of 61.3% for 10-year survival (black short-dashed curve) in this situation, compared with estimates of 58.1% or 55.1% obtained by complete analysis (black long-dashed curve) or by cohort analysis (grey solid curve), respectively. Again, the standard errors were below 1% for all of the 10-year survival estimates. The same patterns were seen for each of the age groups 0–4 years, 5–9 years, and 10–14 years in additional, age-specific analyses (data not shown).

Obviously, all design options would yield identical point estimates of survival in the absence of any changes over time. As the results for all forms of childhood cancer include those cancers with no or little improvement over time, we carried out additional specific analyses for common forms of childhood cancer where major progress in treatments has been made over time, namely the childhood leukaemias and lymphomas. For these cancers, application of alternative designs of survival analysis might be particularly relevant.

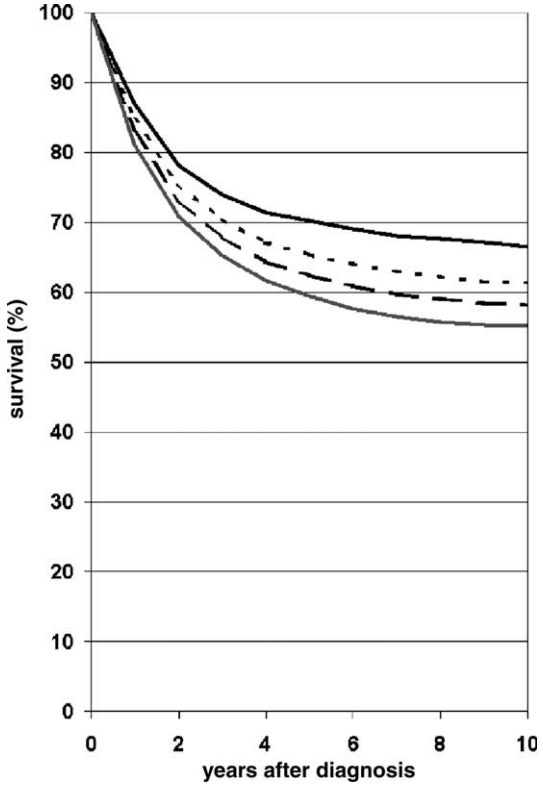


Fig. 3. Observed 10-year survival of children diagnosed with cancer in 1985–1989 (black solid curve) and 10-year survival estimates potentially available at the end of 1989 with delayed recording of incident cases using hybrid analysis (black short-dashed curve), complete analysis (black long-dashed curve) and cohort analysis (grey solid curve). All forms of childhood cancer combined, SEER 1973–2000 database.

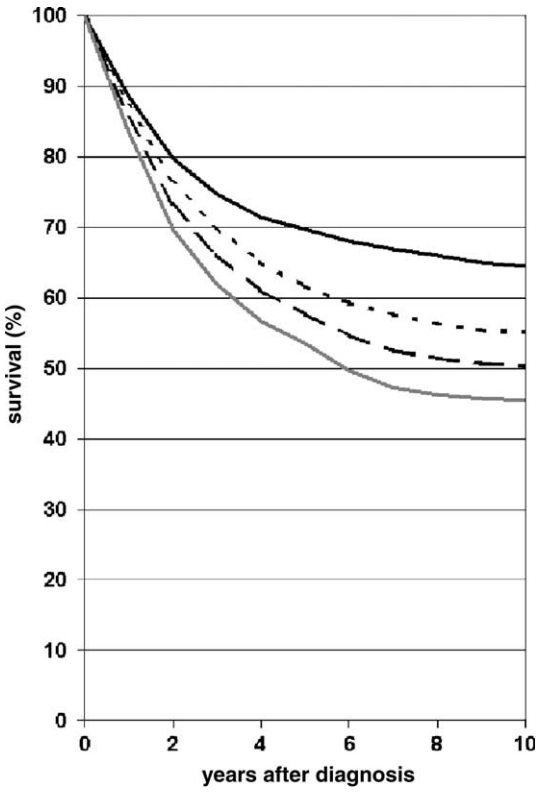


Fig. 4. Observed 10-year survival of children diagnosed with cancer in 1985–1989 (black solid curve) and 10-year survival estimates potentially available at the end of 1989 with delayed recording of incident cases using hybrid analysis (black short-dashed curve), complete analysis (black long-dashed curve) and cohort analysis (grey solid curve). Leukaemias, SEER 1973–2000 database.

As Fig. 4 shows, there has been tremendous improvements in prognosis for children with leukaemias, with a rise of 10-year survival from 45.4% for children diagnosed in 1975–1979 (grey solid curve) to 64.3% for children diagnosed in 1985–1989 (black solid curve). The hybrid estimate of 10-year survival that could have been obtained by the end of 1989 even with delayed recording of incident cases would have been 55.1% (standard error, SE, 1.6%, black short-dashed curve). Although substantially lower than the 10-year survival later observed for children diagnosed in 1985–1989, this estimate would have been approximately 5 and 10 percent units higher (and hence closer to the survival experience of the 1985–1989 cohort) than the 10-year survival estimates that could have been obtained by either complete analysis (50.3%, SE 1.2%, black long-dashed curve) or cohort analysis (45.4%, SE 1.7%, grey solid curve), respectively. If recording of incident cases was not delayed, a 10-year survival estimate for the 1985–1989 period of 58.7% could have been obtained.

The advantage of the hybrid design over the complete and cohort analyses would have been even more pronounced for the lymphomas (see Fig. 5), for which 10-year survival was also almost 20% higher for children diagnosed in 1985–1989 (75.8%, black solid curve) than for children diagnosed in 1975–1979 (57.1%, grey solid curve). Most of this increase could have been disclosed by hybrid analysis at the end of 1989 already (10-year survival estimate 69.2%, SE 2.6%, black short-dashed curve) even if the recording of incident cases was delayed by 5 years, whereas complete and cohort estimates available at that time would still have been much lower (62.5%, SE 1.9%, and 57.1%, SE 2.6%, respectively). If the recording of incident cases was not delayed, a 10-year survival estimate for the 1985–1989 period of 70.3% could have been obtained.

By contrast, hybrid, complete and cohort analyses yielded almost identical estimates of 10-year survival for children with malignancies of the central nervous system (53.3–53.8%) and the sympathetic nervous system (52.2–52.7%), reflecting the lack of improvement in prognosis in the 1980s for children with these malignancies. For all other forms of childhood malignancies combined, the 10-year hybrid, complete, and cohort estimates were 72.3%, 69.3% and 66.2%, respectively, i.e., the hybrid estimate was again closest to the 10-year survival later observed for the 1985–1989 cohort (75.4%; survival curves not shown).

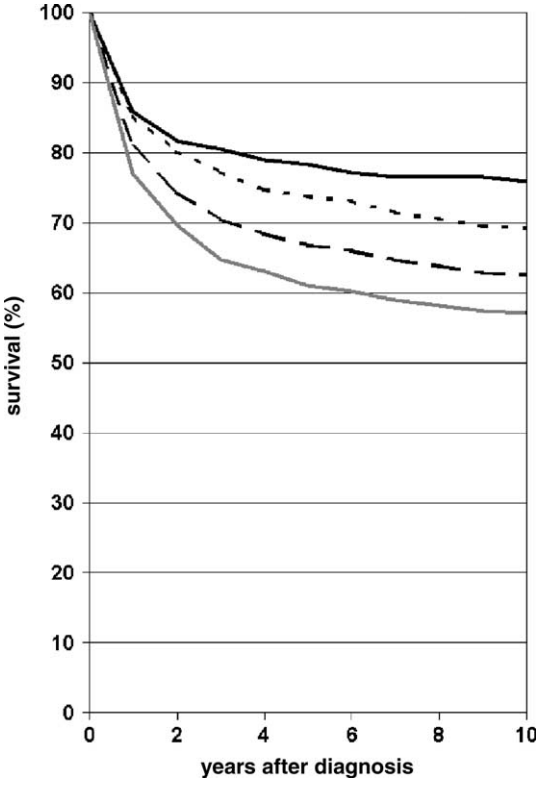


Fig. 5. Observed 10-year survival of children diagnosed with cancer in 1985–1989 (black solid curve) and 10-year survival estimates potentially available at the end of 1989 with delayed recording of incident cases using hybrid analysis (black short-dashed curve), complete analysis (black long-dashed curve) and cohort analysis (grey solid curve). Lymphomas, SEER 1973–2000 database.

## 4. Discussion

In this manuscript, a hybrid type of analysis was introduced to provide more up-to-date long-term survival estimates of patients with cancer, even in situations in which a prototypical period analysis, the primary method to achieve this goal, is not feasible due to the delayed recording of incident cases. Our empirical evaluation indicates that hybrid analysis may be a useful alternative under these conditions. This particularly applies in situations with large improvements in prognosis over time, which have been observed, for example, for some forms of childhood cancer during recent decades.

Delayed recording of incidence is very common, and, to some degree inevitable, in cancer registration. The delay can be considered as a cumulative process, resulting from many sources, including delayed case reporting to the registries, as well as a delay in data entry, processing, clean-up and analysis, often caused by the inadequate resources of cancer registries. There is also some trade-off between timeliness and completeness of incidence data regarding the cut-off-date up to which a cancer registry considers its data sufficiently complete for release: earlier release will provide more timely data, but may come at the price of less complete data in case of a non-negligible proportion of late notifications. Although there may also be some delay in the registration of deaths, vital statistics tend to be available in a quite timely manner in many countries, and mortality follow-up of registered cancer cases may also be performed within quite short

time-limits, at least for those cancer registries in which routine record linkage of their database with vital statistics is possible. As a result, the cut-off date for mortality follow-up is commonly more recent than the cut-off date for the recording of incident cases.

However, the time difference between both dates often varies between registries. For example, it was 1 year (31 December 1994 versus 31 December 1995) in a nationwide analysis of cancer survival in Finland carried out a couple of years ago [18], 2 years (31 December 2001 versus 31 December 1999) in a recent survival analysis for England and Wales [9], and typically in the range from 3 to 5 years in analyses of cancer patient survival in developing countries [19].

In other instances, a major lag between the closing date for inclusion of incident cases and for mortality follow-up has been introduced by the study design. This particularly applies to studies designed for carrying out traditional cohort analyses of survival. For example, the recently published EUROCARE III study was designed to estimate and compare 5-year cancer survival of patients diagnosed in 1990–1994 in various countries of Europe. The closing date of mortality follow-up was 31 December 1999. Although more recent incidence data would have been available for many European registries, only cases diagnosed in the 1990–1994 period were added to the EUROCARE database (which had already included cases diagnosed in earlier years) [20]. While this data structure served perfectly the primary goal of the EUROCARE III study, it limits the possibilities to derive additional recent period estimates of long-term survival, such as 10-year survival, for, say, the 1995–1999 period. Nevertheless, as suggested by our work, useful hybrid estimates of 10-year survival for the 1995–1999 period could still be obtained by combining elements of a period analysis for 1995–1999 (which would reflect the survival experience in various years following diagnosis of patients diagnosed in 1985–1994, but which on its own would suffer from sparseness of data for the early years of follow-up as well as potential bias, as further described below), and elements of a cohort analysis for the 1990–1994 cohort (which by itself would suffer from sparseness of data for the later years of follow-up).

In our analysis, we focused on prototypes of the various design options (period, complete, cohort and hybrid) to illustrate the main methodological issues as clearly as possible. The list of design options addressed in our analysis is as yet by no means exhaustive, and still other design options might be considered in various settings. For example, many studies have used designs that are somewhere between pure cohort analysis and pure complete analysis, in that only patients with some minimum potential follow-up time, such as 1, 2 or 3 years, which was shorter than the survival period of main interest (typically 5 or 10 years) were included (e.g. [18,21]).

In situations with delayed recording of incident cases, one might also consider carrying out a pure period analysis rather than a hybrid analysis despite the restrictions of the database. For example, in the setting introduced in Fig. 1, such an analysis could have been based on proportions B and D (rather than B, C and D) of the database. Although this type of analysis could provide more up-to-date estimates than the hybrid design, these estimates may be biased in the case of uneven distribution of hazards within the first year following diagnosis, as estimates of the first year survival would predominantly rely on the survival experience during the second half of this year. In addition, as shown in Fig. 1, fewer cells would contribute to the survival estimates compared with the other approaches. Therefore, these estimates would also be less precise.

In the examples given in our paper, pure period estimates were also derived for the sake of completeness (data not shown). However, they were not generally closer to the 10-year survival later observed for patients diagnosed in 1985–1989 than the other estimates, and their standard errors were, on average, approximately two to three times larger than those of the other estimates. We therefore recommend that hybrid analysis should be given preference over pure period analysis when the recording of incident cases is delayed.

When the delay in the recording of incident cases is short, such as one or two years, one might also consider a pure period analysis for the most recent years for which incident cases were recorded (i.e., by simply ignoring the most recent year(s) for which recording of incident cases is not available). However, it appears questionable, why one would want to accept a delay in the disclosure of potential recent improvements in survival even by just one or two years, if there are straightforward ways to overcome or at least reduce such a delay in the analysis. For example, the prognosis of patients with colorectal cancer in England and Wales has greatly improved in recent years. Using the aforementioned database from England and Wales [9], a hybrid analysis of 10-year relative survival combining a 2000–2001 period analysis with a 1998–1999 cohort analysis would yield 10-year relative survival estimates of 45.2% and 43.4% for male patients with colon cancer and rectum cancer, respectively. These are approximately 3 percent units higher than the corresponding estimates obtained by a period analysis for the 1998–1999 period (42.4% and 40.0%, respectively).

Period analysis and, in situations with delayed recording of incidence, hybrid analysis, may be the designs of choice if up-to-date estimates are the primary focus of the analysis. However, preferences may differ, if other criteria are of primary concern, such as the precision of the estimates (which is typically highest in a complete analysis), or the survival experience of defined cohorts of patients diagnosed in specific years, who

might also be more homogeneous with respect to the standard treatment used during those years. Hence, the type of survival analysis used in a specific study should be chosen in such a way that it best matches both the data available and the specific purpose of the study. In this sense, the hybrid design may be a useful addition to the variety of available options, allowing for yet more flexible analytical strategies. However, besides enhanced chances of carrying out survival analyses that best meet the specific aims of a given study, the variety of design options also carries the danger of reducing the comparability of results between studies. An unequivocal description of the methodology used in the analyses (for which a graphical presentation such as the one shown in Fig. 1 could serve as model) is therefore of the utmost importance.

As for the other design options, availability of appropriate and user-friendly software is a prerequisite for the application of the hybrid design in routine analyses. Hybrid analysis can be carried out with minor modifications of existing, publicly available SAS macros, which have been primarily developed for period analyses, but which may also be used for cohort and complete analyses. A detailed description of these macros has been given elsewhere [17,22,23]. The only modification needed to carry out hybrid rather than period analyses is that variable specifications (rather than a single overall specification) for the beginning and the end of the period to be included in the analysis have to be made for patients diagnosed in the various calendar years. The SAS macros may be used to derive both absolute survival rates (as in the examples shown in this paper) and relative survival rates [24]. In addition, a STATA macro, likewise able to perform survival analysis according to all of the above described strategies, is available on request from the authors.

In summary, the hybrid design may be a useful supplement to existing design options for the analysis of up-to-date long-term survival rates by cancer registries. It extends the applicability of the period approach in survival analysis to commonly encountered situations with different cut-off dates for inclusion of incident cases and for mortality follow-up.

## Conflict of interest statement

None declared.

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