

The EURO CARE Study: strengths, limitations and perspectives of population-based, comparative survival studies

Cancer registries have provided population-based, comparative survival statistics for cancer patients since 1960 [1]. However, the largest co-ordinated effort of this kind has been the EURO CARE project—a European, co-operative, cancer registry-based study on cancer patient survival and care [2–5], which includes data from 67 population-based cancer registries operating in 22 European countries. EURO CARE has been promoted by the European Community under the Health Service Research (EURO CARE-1, patients diagnosed from 1978 to 1984 in 12 European countries), BIOMED (EURO CARE-2, patients diagnosed from 1985 to 1989 in 17 European countries), Fourth Framework programmes (the present EURO CARE-3, patients diagnosed from 1990 to 1994 in 22 European countries), and is currently being funded by an Italian Foundation (Compagnia di San Paolo), as well as, in the case of several registries, by local funds. Recently, an agreement was reached with the cancer registries of the USA, Canada, Australia and Japan to expand survival comparisons to other populations in developed countries (the CONCORD project).

However, of the many studies that cancer epidemiologists carry out, comparing cancer patient survival between populations is amongst the most controversial [6–8]. In fact, survival differences are intrinsically difficult to interpret, as longer survival may depend on either later death or earlier diagnosis; the latter of which may not be of benefit to the patient. In turn, death postponement may derive from more effective conventional treatment either due to earlier diagnosis, or from the availability of better treatment facilities. In order to disentangle these different reasons for survival differences requires standardised information on disease stage at diagnosis, on the actual diagnostic procedures used for staging, and on treatment; information that is not usually available to population-based cancer registries in a standardised format. This has been the object of special studies nested within the EURO CARE project, for which cancer registries collect further clinical and pathological information according to an agreed protocol on a representative sample of incident cancer cases, the so-called ‘high resolution’ studies. Such studies are presently being carried out for breast [9, 10], colon [11], prostate and testicular cancer by several cancer registries in France, Italy, Spain, The Netherlands, the UK, Estonia, Poland, Slovakia, Slovenia and the Nordic countries. Whatever the explanation for the survival differences is, the basic aims of EURO CARE are to describe cancer patient survival in Europe, to disclose whether there are any differences between populations, and if so, how large they are, how they evolve and how reliable the survival estimates are. The

present monograph describes these basic survival aspects for European patients diagnosed from 1990 to 1994.

Besides the intrinsic difficulties in interpreting survival data, several methodological difficulties must be taken into account that may bias survival comparisons. These can be classified into the following major categories [12]:

- the different statistical methodology used to control for mortality from other causes and for different age structures in the patient populations;
- completeness of case ascertainment;
- completeness of follow-up; and
- the different nature or definition of the illness, which may depend on the availability of diagnostic means and on registration procedures.

Other points to be considered in this introductory note concern the perspectives to improve:

- the timeliness of survival statistics; and
- the interpretation of survival differences, through further ‘high resolution’ studies.

We are confident that the development of survival studies will provide a stimulus for further improvements in the quality of cancer registration and the development of cancer registries in countries that still lack them.

Statistical methodology

The basic statistical method used throughout the EURO CARE project is the computation of relative survival, i.e. the ratio of the survival observed in cancer patients to the survival that would be expected in the general population of the same age, sex and residence [13]. Relative survival can be interpreted as an estimate of the proportion of patients who survive, after correction for background mortality. Before international comparisons, relative survival ratios are then adjusted for age, using as standard the distribution of age at diagnosis of the pool of European patients included in the study. To allow comparisons between genders, the same age standard was used for both males and females, but the standard distributions are specific for cancer sites.

Completeness of case ascertainment

The validity of population-based survival comparisons is clearly dependent on the validity of cancer incidence data. In principle, a cancer registry should be notified of all cancer diagnoses occur-

ring in a defined population. In practice several registries may suffer from underreporting. Cases known to the registry on the basis of death certificate only (DCO) are not included in survival statistics (because the date of diagnosis is not known). Therefore, a high proportion of DCO cases, besides indicating that the registration is not exhaustive, may indicate that survival is overestimated [14–16]. Registries that do not have access to, or do not use, death certificates in their routine activity—as in France, The Netherlands or Sweden—are also likely to overestimate survival. On the contrary, the practice followed by several registries to systematically trace back all DCO cases to find some clinical information (in particular the date of diagnosis) may result in lower survival estimates. In fact, fatal cases whose diagnosis was not notified will eventually be included in the analysis, while long-term survivors that were not notified will be missed. This bias may specially affect survival estimates of cancer registries where the proportion of death certificate initiated cases is relatively high but the proportion of those who remain DCO is very low. For instance, in Denmark this procedure of tracing back DCO may have caused an underestimation of survival by a small percentage. Underascertainment of non-fatal cases might also partly explain the poor outcome registered by some UK cancer registries [16,17].

In central and southern Europe, cancer registration does not cover the whole country—as is the case in Nordic countries and some Eastern countries—but only a few towns or provinces. The comparison between populations may still be perfectly valid but these regional populations are not necessarily representative of the country as a whole. Nevertheless, in the absence of more representative data, these regional survival proportions have been used to estimate European survival proportions, using weightings proportional to the reciprocal of the cancer registry's coverage in each country. The European cancer survival tables included in this monograph always indicate what proportion of the different national populations is covered by the cancer registries providing the survival figures.

Completeness of follow-up

Procedures for follow-up of cancer patients in order to establish whether they are still alive also vary a lot between registries, from active clinical follow-up, to record linkage with population files, to linkage with death certificates. Registries may miss cancer deaths because patients are lost to follow-up, because of errors in patient identification and linkage, or because only death certificates mentioning cancer are obtained, while those patients who die from other causes are omitted. Missing information that the patient died has a disproportionate effect on survival estimates for patients with highly lethal cancers, over those that have cancers with good prognosis. Let us suppose, for instance, that 10% of cancer deaths were missed. Survival of patients with lung cancer will be overestimated by about 90% (e.g. a 10% 5-year survival would become 19%). Survival of patients with Hodgkin's disease, however, will be only slightly overestimated (from 90% to 91%). Survival of breast cancer patients would change from 80% to 82%, and so on. To check the completeness of follow-up, several cancer registries carried out a survey on lung cancer patients that

apparently survived beyond 5 years in EURO CARE [18]: 1.4% of them were actually dead, the proportion ranging from 0.5% to 3%. If a 3% error were applied to a cancer site whose 5-year survival is above 70%, the error would be confined to <1%. Incomplete follow-up, therefore, may not heavily bias survival comparisons for most cancer sites.

To provide some hints on the existence of systematic biases due to incomplete follow-up, one may compare countries for the survival of all the most lethal cancers, such as oesophagus, liver and biliary duct, pancreas, lung or acute myeloid leukaemia, as well as for patients with metastatic disease when first diagnosed (see Capocaccia et al., this issue, tables 6 and 7). Spanish registries, for instance, showed higher than average survival for most of these sites, thus suggesting a follow-up bias. However, two recent quality control studies of long-term survivors carried out in Spain showed that the proportion of dead patients erroneously classified as alive was only 1.5% and 2.4%, respectively, in the cancer registries of Navarra [19] and Mallorca [20].

Description of tumours

The biological nature of diseases coded under the same rubric of the International Classification of Diseases (ICD) may vary in different populations. Cancer registries systematically collect information on tumour diagnosis in terms of site of occurrence and morphological diagnosis. However, most publications of adult cancer incidence and survival have only been able to provide data by cancer site, because morphological diagnoses are not systematically available and, above all, are far from being standardised. To facilitate survival analysis by histological diagnosis, the EURO CARE database managing system only accepts morphological codes officially foreseen in the ICD for Oncology (ICD-O). Data providers are requested to translate any locally used codes into existing codes. Unlikely site–morphology combinations are also systematically checked. Therefore, the EURO CARE database allows analyses by morphology and a working group has been set up to systematically analyse rare cancer entities. However, the present monograph still confines the analysis to survival by organ site, as defined by the ICD-9, without attempting to distinguish between different histopathological entities, with the exception of melanomas, lymphomas and leukaemias.

Problems in comparing survival between populations may also arise within the same site–morphology entity, e.g. for head and neck, bladder, ovary and myeloma [21]. Head and neck cancers should be properly classified according to fourth digit subsites, e.g. glottic and supraglottic larynx cancers, which have different prognoses and different geographical distributions; only a few cancer registries have recognised the importance of properly classifying the site of origin of the tumour within head and neck organs [22]. Urothelial tumours of the bladder may be very difficult to classify in terms of degree of malignancy and invasiveness, and cancer registries do not have standard rules for the inclusion or exclusion of lesions whose invasiveness could not be histologically proven. EURO CARE followed the rule of including all urothelial tumours, independent of the documentation of

malignant behaviour, and thus overestimating survival, possibly in some registries more than in others. Some ovarian cystoadenocarcinomas are labelled as of ‘borderline malignancy’; the ICD-O behaviour code of these lesions changed from /1 (uncertain malignancy) in the first edition, to /3 (malignant) in the second edition, and again to /1 in the third edition of the manual; they were excluded in the previous EURO CARE monographs but are included in the present one, as well as in the data set available for time trend analysis. However, these cases represent <1% of all ovarian cancers in the EURO CARE database. Multiple myeloma provides another example of a syndrome with somewhat arbitrary definition. The diagnosis requires a serum electrophoretic peak of monoclonal immunoglobulins above predefined levels, a biopsy showing bone marrow colonisation by plasma cells greater than a predefined percentage, and/or multiple lytic bone lesions, but there are not universally accepted diagnostic standards. Frequently, moreover, the illness is diagnosed as ‘indolent’ or ‘smouldering’ myeloma in the course of the clinical follow-up of an asymptomatic monoclonal gammopathy that may be incidentally discovered during a routine blood examination. Therefore, the inclusion of borderline lesions and the date of diagnosis may vary a lot depending on the diagnostic and surveillance protocols. Country-specific survival estimates for all these cancer sites are made available in the present monograph, but the differences between populations should be considered with great caution.

Timeliness of survival statistics

EURO CARE analyses of population-based survival data were only carried out when all registries had provided 5-year survival data for a given incidence period. Considering the time needed for data collection, checking, analysis and publication, it is understandable that the reports appeared after a considerable delay. Reducing the delay in which information on survival is provided to policy makers, to medical doctors, and to the public is important in order to increase their usefulness and to optimise their use. In fact, by definition, cumulative 5-year survival probability reflects past diagnostic and treatment procedures, which may be no longer relevant today. The present EURO CARE monograph, for instance, concerns patients that have been treated, on average, 10 years ago. In the future, it is planned to invite cancer registries to freely send in new releases of their complete database whenever they perform any substantial update, particularly with regard to more recent life status checks, or the inclusion of cases diagnosed in more recent periods, or both. No minimum length of follow-up will be required, and the reception, updating, quality control and correction of data will be speeded up. The availability, at least for a subset of contributing registries, of data on patients diagnosed very recently (2 or 3 years earlier) will allow the monitoring of patient short-term survival probabilities, which are the most sensitive to improvements in patient management. Also, in order to take into account recent cases for estimating long-term survival, a method has been proposed that multiplies the probability of 1-year survival of patients diagnosed 1 year ago times the 2-year survival probability conditional to having survived the first year for patients diagnosed 2 years ago, times the 3-year survival con-

ditional to having survived 2 years for patients diagnosed 3 years ago, and so on [23]. Such a method has been tested on the long-term series of the Finnish cancer registry data and proved to be highly accurate in predicting long-term survival of more recently diagnosed cases [24].

High resolution studies

The basic EURO CARE strategy for understanding whether the increases in survival observed in some populations were due to better therapy or to earlier diagnosis has been to collect standardised information on disease stage at diagnosis. If survival differences disappear once they are stratified or adjusted for stage, they can be assumed to be mainly due to earlier diagnosis. On the other hand, differences in stage-specific survival comparisons strongly suggest an important effect of treatment. Understanding the role of these two components in determining survival differences between populations over time is important for evaluating and planning cancer control strategies.

Unfortunately, this simple picture is complicated by several artefacts that affect survival analysis and can flaw its interpretation. The first one derives from the so-called ‘stage migration’ phenomenon. The evolution of diagnostic technology has increased the sensitivity of detecting loco-regional extension of tumours and silent distant metastasis. Stage-specific survival, therefore, may increase just because a fraction of tumours that previously would have been labelled as localised can now be recognised as advanced, thus increasing the survival of both the localised set (because they are more localised) and the advanced stage set (because they also include the less advanced cases that in the absence of modern staging procedures would have been diagnosed as localised). The availability of information on relevant staging procedures allows the control of the stage migration phenomenon in statistical analysis. For instance, the analysis of high resolution studies on colorectal cancer and on breast cancer showed that a large part of the survival differences between European populations was due to differing stage distribution. It also allowed the identification of cases in which the difference could not be explained by stage, suggesting that treatment was not adequate [10, 11].

Another potential artefact is that of lead-time bias. Diagnosis at an earlier stage can increase survival by simply anticipating the date of diagnosis without postponing the date of death. In this case, longer survival associated to a more favourable stage distribution is not an advantage for the considered population. High resolution analysis does not help in separating a real advantage due to earlier diagnosis from lead-time bias. However, one may expect that, with earlier diagnosis, a higher proportion of patients will be diagnosed early enough to be successfully treated, and we will observe a higher proportion of cured. On the other hand, lead-time bias can just result in a longer survival time of fatal cases. The proportion of patients that are cured from their disease, defined as those whose survival does not differ from the survival of the general population of the same age, can be estimated modelling relative survival as a function of follow-up time. When the relative survival curve becomes parallel to the abscissa the corres-

Table 1. Rationale of EUROCARE methodologies for interpreting survival trends

Problem	Methodology	Interpretation
Is the increasing survival trend due to better treatment (or increased access to the appropriate treatment) or to earlier diagnosis?	High resolution survival analyses adjusted by disease stage at diagnosis and stage migration (i.e. adjusted also for staging procedures).	If stage-adjusted survival does not increase any more, one may conclude that the overall survival improvement is due to a more favourable stage distribution at diagnosis. If stage-adjusted survival increases, one may conclude that treatment has improved.
If increasing survival depends on earlier diagnosis, how much is it due to lead-time bias (earlier diagnosis without later death) and how much to increased probability of cure?	Cure models, describing survival in terms of the proportion of patients that are cured, and the survival time of fatal cases.	Lead-time bias would only increase the survival time of fatal cases. More effective treatment also increases the proportion of cured patients.
Does the increased proportion of cured patients reflect increased effectiveness of treatment (due to better treatment or more favourable stage distribution) or also the overdiagnosis of ‘pseudo-cancers’?	Cure models applied to each specific disease stage at diagnosis.	If the proportion of cured does not increase in stage-specific models, the overall survival increase is due to more favourable stage distribution. If the proportion of cured increases only or mostly in localised stage, overdiagnosis is to be hypothesised. If it increases also in advanced stages, one may conclude that (access to) treatment improved.

ponding value describes the proportion of cured. The application of the cure survival model can therefore help discriminate between mere diagnostic anticipation and true survival advantage [25]. An increased proportion of cured may also be accompanied by a shorter survival of fatal cases, indicating that the patients that have been rescued were the less advanced.

A further bias may derive from the possible inclusion in the patient population of a number of ‘pseudo-cancers’, i.e. of incidentally found cancers that would never have progressed to give clinical signs. A certain proportion of cancers detected during screening fall into this category. If the frequency of these pseudo-cancers is variable between populations, or is increasing over time, the consequent difference in survival will be entirely reflected on the proportion of cured. Cure survival models are therefore not able to detect this bias, unless they are applied to stage-specific subgroups of patients. It is reasonable to assume that pseudo-cancers will all belong to the lowest stage category. Differences in the proportion of cured in stage-specific subgroups other than the earliest one can be therefore interpreted as genuine survival gain. In conclusion, the application of cure models to high resolution studies can theoretically provide a complete conceptual framework for a meaningful interpretation of survival differences. Table 1 summarises the rationale for interpreting survival differences detected in conventional descriptive analyses. However, the interpretation of survival trends should always take into account the contemporary trends in incidence and mortality rates, as well as in care practices.

F. Berrino*

Department of Preventive and Predictive Medicine,
Epidemiology Unit, Istituto Nazionale per lo Studio e la Cura
dei Tumori, Milano, Italy
(*E-mail: berrino@istitutotumori.mi.it)

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