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Editorial Comment

Comparative cancer survival information in Europe

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1. The need for population-based survival studies

Accurate population-based information on cancer patient survival is indispensable for effective cancer control, and cancer registries have the essential task of collecting that information.[1] While clinicians need survival from clinical series to evaluate the efficacy of their treatments, only population-based survival comparisons can provide information on the effectiveness of healthcare systems.[2,3] Population-based cancer registration is also necessary for monitoring cancer incidence and for estimating cancer prevalence (the proportion of people living with a diagnosis of cancer) which are required for healthcare planning and resource allocation. Cancer mortality also provides important information for cancer control but, as discussed subsequently, it is not sufficient on its own.

In the early 1990s the European Community sponsored EUROCARE (European cancer registry-based study of cancer patients' survival and care), a Europe-wide concerted action to comparatively analyse survival data from European population-based cancer registries. The first analyses became available in 1995 with the publication of EUROCARE-1 on 30 cancer registry populations from 12 countries.[4] EUROCARE-1 revealed dramatic between-country differences in cancer survival, with low rates in eastern European populations, intermediate rates in Denmark and the UK, and high rates in the other western European populations surveyed. Subsequent pan-European studies (EUROCARE-2, cases diagnosed between 1985 and 1989[5–8]; EUROCARE-3, cases diagnosed between 1990 and 1995[9]) which included more cancer registry populations and many more European patients, and the ACCIS study on childhood cancer,[10] broadly confirmed the EUROCARE-1 findings, but also suggested that across Europe survival differences might be widening.[11] However, time trend analyses presented in the present EUROCARE-4 monograph, which include cases diagnosed up to 1999, clearly

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indicate a narrowing of survival differences, with absolute improvements greater for countries with low survival in the past, than for countries where survival was already high.[12]

The EUROCARE findings are now widely recognised as reflecting real differences in cancer survival across Europe,[13] and the European Commission has included cancer patient survival in the priority list of health indicators.[2] However, after the publication of EUROCARE-2, the European Community stopped supporting EUROCARE and the project continues thanks to financial support from the Italian *Compagnia di San Paolo* Foundation. It is unfortunate that European governments are reluctant to finance studies that assess the comparative effectiveness and efficiency of their health systems.

Analyses of EUROCARE data have also revealed considerable within-country variations in cancer survival. In Italy survival is significantly better in the wealthy north than the poorer south.[14] In the small and affluent, but culturally varied country of Switzerland, cancer survival varies quite surprisingly with geography,[15] suggesting that access to early diagnosis and care or quality of treatment also vary. Studies in the UK have shown that cancer survival is lower in socially deprived areas.[16,17] Among the Nordic countries of Europe, Iceland, Norway, Sweden and Finland on one hand are characterised by excellent overall cancer survival, while Denmark has much worse survival, and the difference can only be partly explained by differences in case mix.[18]

2. Publication delay

Population-based survival studies may be criticised because too much time elapses between the latest diagnosis year and the presentation of results. During the intervening years, more effective treatments are introduced, and the picture presented may no longer be current and hence of limited relevance. However, progress in cancer treatment is seldom followed by rapid changes in population-based long-term survival estimates. More often, survival improves gradually as the new protocols become available and accessible to an increasing proportion of patients. There have been exceptions however, such as the introduction of cisplatin for testicular cancer. Nevertheless, it is important to monitor how quickly progress in clinical research is transferred into everyday clinical practice. One of the objectives of EUROCARE-4 is to shorten the gap between the introduction of new treatments and the statistical demonstration of their effect (or lack of effect) on survival. The first EUROCARE study published its main results 11 years after the latest diagnosis year (1984), and efforts have been made since then to reduce publication delay. The present monograph of the main EUROCARE-4 results includes, for over half of participating cancer registries, cases diagnosed up to the end of 2002[19]; so the delay has been reduced to 6 years. This acceleration was made possible by improvements in data collection and processing, and by using period survival analysis techniques. Summary EUROCARE-4 results were published even earlier in 2007.[20]

Nevertheless, there has been some delay in publication of main EUROCARE-4 results due to residual errors and problems that emerged concerning vital status follow-up in a small number of cancer registries, and the definition of multiple tumours, which have now been resolved. The error corrections imply that the present EUROCARE-4 dataset differs slightly[21] from that on which the summary EUROCARE-4 publications were based, and that the already published results are not completely consistent with those in this monograph. Our policy of correcting and updating the database will continue into the third phase of EUROCARE-4, concerned with in-depth cancer site-specific analyses.

3. What is new in EUROCARE-4

As noted above, the new technique of period survival has been applied for the first time in this EUROCARE round. Other important novelties have also been introduced. Extensive estimates of the proportions of patients cured of their disease are now presented for selected major cancer sites by country. These estimates were obtained using cure or mixture models.[22] The main indicator presented by EUROCARE is 5-year relative survival which is perceived as approximating to the probability of being cured of a cancer. However, for several cancers, most notably breast cancer and prostate cancer, excess mortality persists for many years after diagnosis, so that a considerable fraction of those surviving 5 years after diagnosis eventually die of their cancer. This is the main reason for the introduction of cure models to estimate cure rates.

Another important novelty of the current EUROCARE round is that we addressed the issue of multiple tumours occurring in the same patient. The standard EUROCARE approach – and the only one permitting comparison with other survival studies – is to exclude consideration of any subsequent primary tumours. Here we show that including subsequent tumours does not dramatically change survival estimates, but improves the comparability of results between recently established registries and those with a long history of registration activity.[23]

The quality of survival data has improved considerably and progressively since EUROCARE-1. The proportions of cases lost to follow-up and known only by death certificate have decreased. However, between-country (and registry) variation in survival for rapidly fatal cancers, like those of oesophagus, liver, pancreas, and lung, still suggests incomplete follow-up for several registries with improbably high survival.[21] Also, the longer observation period available in EUROCARE-4 is providing more definite evidence on the quality of follow-up. Failures in death ascertainment tend in the long run to select a group of false survivors that is clearly detected by relative survival analysis methods. Datasets from several registries have been removed from specific analyses on this ground, either for 5-year[24] or long-term[20,21] survival analysis.

4. How representative are EUROCARE data?

A persistent problem with EUROCARE is that for several European countries cancer registration covers only a small fraction of the total national population. Summary results for these countries may not therefore represent the situation in the country as a whole; and for EUROCARE-4 this is likely to be the case for Czech Republic, Germany, Italy, Poland and

Spain. In Italy, for example, the richer northern part of the country is better covered by cancer registration than the south of the country, where cancer survival is poor.[25] Some epidemiologists therefore prefer to restrict survival comparisons to entire national populations.[26] Nevertheless, cancer registries cover well-defined geographic areas and populations, and when robust estimates indicate population-based differences in survival (between countries or between regions), then the health service of the area with poorer survival is potentially improvable – if not to the level of the area with best survival, then at least to the level of an area with better survival but similar wealth (see below).

Five-year relative survival for all cancers combined, adjusted for age distribution and case mix, is one of the main EUROCARE-4 indicators: it is the 5-year survival one would observe if cancer incidence were the same in all countries considered, and the age structure were also the same; it is the most succinct indicator of cancer control performance.[25] Table 1 shows this indicator for each participating country, for men and women separately, with 95% confidence intervals (CIs). The estimated value of this indicator for Europe as a whole was 49.6% (95% CI 49.5–49.7) for both sexes, 44.8% (95% CI 44.6–45.0) for men, and 54.6% (95% CI 54.4–54.8) for women.[25] The countries in Table 1 are ranked by decreasing per capita total national expenditure for health (TNEH) adjusted for per capita purchasing power.[27] There was a moderate correlation between TNEH and 5-year age- and case mix-adjusted relative survival for all cancers combined (r^2 = 0.56 for women, r^2 =0.43 for men). There were notable exceptions, however: Denmark and the UK had lower survival than countries with similar TNEH; Finland had better survival than expected from its moderate health expenditure, suggesting effective health management; Spain, Italy and Portugal also had better survival than countries with comparable TNEH, but do not have complete cancer registration, and survival in the areas covered may not reflect that of the whole nation. It is noteworthy that Switzerland had very similar survival levels to Sweden, but at much higher TNEH, suggesting that cost-effectiveness could be improved in Switzerland.

5. Mortality versus survival

Some authorities argue that mortality statistics are preferable to survival statistics for comparing cancer outcomes between nations, because mortality data are generally available for entire national populations, and because length or lead time bias due to screening can have a major impact on cancer survival differences.[28,29] We have repeatedly stressed that survival is a complex indicator: longer survival may reflect earlier diagnosis, over-diagnosis or later death. However, all these components depend on the resources a country allocates to cancer control, thus explaining the relationship between TNEH and age- and case-mix-adjusted 5-year relative survival for all cancers combined. Unfortunately, it is impossible to disentangle these contributors to improved survival from the data routinely available to cancer registries. EUROCARE therefore carries out 'high resolution' studies, collecting detailed information on disease stage at diagnosis and the procedures used to establish disease stage from representative samples of patients, and analysing survival in relation to these factors, which can suggest reasons for improved survival.

Note, however, that mortality statistics are also unable, usually, to distinguish effects due to primary prevention,

Table 1 – Five-year relative survival (with standard error, SE) adjusted for age and case-mix by country, for all cancers combined[24] estimated from the EUROCARE-4 dataset.

Country (coverage[a])	Average TNEH/year (US$) 1994 to 2002	Women		Men	
		Five-year RS	SE	Five-year RS	SE
Switzerland (17%)	4251	56.6	0.4	48.3	0.5
Germany (1%)	3958	55.5	0.6	47.4	0.6
Norway (100%)	3063	55.8	0.3	43.2	0.4
France (17%)	3039	56.6	0.3	45.5	0.4
Iceland (100%)	2906	58.2	1.3	48.5	1.2
Denmark (100%)	2861	53.5	0.3	36.7	0.5
Belgium (58%)	2706	56.3	0.3	48.1	0.4
Netherlands (34%)	2705	54.8	0.3	45.7	0.4
Sweden (100%)	2693	57.9	0.2	46.4	0.3
Austria (100%)	2665	55.7	0.2	47.6	0.3
Italy (28%)	2557	57.5	0.1	47.6	0.2
UK (100%)	2542	51.4	0.1	41.4	0.2
Finland (100%)	2198	56.9	0.3	46.2	0.4
Ireland (100%)	1804	51.4	0.4	42.0	0.5
Spain (16%)	1197	55.3	0.3	44.9	0.4
Portugal (43%)	1088	54.9	0.5	45.6	0.6
Czech Rep. (8%)	597	49.7	0.8	37.2	0.8
Slovenia (100%)	529	49.4	0.5	36.5	0.6
Poland (9%)	427	49.8	0.4	39.4	0.5
European mean	Not applicable	54.6	0.1	44.8	0.1

Countries are ranked according to per capita total national expenditure on health (TNEH).
a Proportion of national population covered by cancer registration in 1998.

earlier diagnosis and better treatment.[30] Furthermore, they provide a blurred and delayed indication of trends, since people who die of cancer in a given year will have been diagnosed in any of several previous years. Changes in death certification practices over time, and coding differences between and within countries,[31] also complicate the interpretation of mortality data. Thus, difficulties inherent in interpreting survival statistics do not imply that mortality statistics are superior: both can help to interpret trends and between-country differences in cancer control.[30]

6. Relevance of population-based survival to clinicians

In general, clinicians tend to under-use the results from population-based survival studies. They more often rely on data from randomised clinical trials or outcome studies from hospitals or groups of hospitals, with the data broken down by disease stage, age, and performance status. Nevertheless, oncologists are often disconcerted to learn that population-based survival is lower than in clinical series, particularly for adult cancer patients. The reasons are not difficult to find: patients included in clinical studies are highly selected and typically treated in specialised cancer centres, and hence not representative of cancer patients in general. In hospital-based studies, disease stage at diagnosis is usually carefully determined (most of the available information on prognosis by stage derives from such sources), yet the determination of stage depends crucially on the staging procedures used, which vary markedly between centres and, of course, over time[32]; for these reasons survival comparisons in clinical series (between hospitals or over time) are not reliable.

In contrast to the situation with adults, population-based survival for childhood cancers is fairly similar to that observed in the clinical setting.[33] This is probably due to the inclusion of most patients in clinical trials, and also the good response to appropriate treatment that characterises many childhood cancers.[8,34]

Population-based survival data are therefore relevant to clinicians because they can be used as a standard against which their own outcomes can be compared. If the survival of their patients is well above average, perhaps it is due to geographic, demographic, social or economic selection of patients, rather than better treatment. On the other hand, if survival is worse than average, perhaps it is because their centre tends to treat more advanced cases than other centres. Reliable answers to these questions can only be obtained if the standard of reference (the local or national cancer registry) has access to reliable information on stage at diagnosis, and this in turn depends on the accuracy and completeness of the data that hospitals (clinicians) furnish to cancer registries.

A limitation of cancer registry-based survival data is that they are rarely available by disease stage at diagnosis, and this is mainly because data on stage and staging procedures are not systematically available to cancer registries. Better appreciation of the role of cancer registries and better communication between clinicians and cancer registries may help to improve this situation.

7. Relevance of population-based survival to administrators and policy makers

Although some countries have used cancer survival statistics to set priorities for the provision of cancer care, the economic and social implications[2] of changes in cancer incidence and survival are not widely appreciated. Cancer incidence is increasing – mainly because life expectancy is increasing – and this is being accompanied by a steady increase in survival for many major cancers. The resulting increase in prevalence implies the need to devote more resources to the clinical surveillance and care of surviving cancer patients.

Major advances have been and are being made in cancer treatment. Diagnostic imaging modalities are becoming ever more sensitive and sophisticated, but are hugely expensive. There is a marked trend towards less invasive treatments,[35] which is reducing treatment-related morbidity and probably contributing to improved cancer survival. Advances in the molecular characterisation of cancers have led to the development of a new generation of drugs that specifically target cancer-related mechanisms, such as angiogenesis, inflammation, cellular signalling systems, and cell-cycle control mechanisms. Over 300 new 'targeted' drugs are currently being tested.[36] There will be strong commercial pressure to introduce these expensive agents into clinical practice, particularly because many existing high-cost cytotoxic drugs will lose patent protection in 2009. Some of these new drugs will add just a few months to life, but several are expected to prolong life considerably.[36] Intensive research on the genetic characterisation of tumour and host is being carried out to make it possible to identify patients who will benefit from particular targeted therapies. This 'personalisation' of treatment will reduce the market for individual drugs, and push up prices. The trend is therefore firmly toward more costly treatments and this is likely to increase, not reduce, inequities in treatment access. Major marketed targeted therapies include monoclonal antibodies against growth factors or growth factor receptors and small molecules interfering with signal transmission pathways. Their use increased dramatically in recent years and their effect is likely to become apparent in the next EUROCARE runs. Their cost per annum of treatment range between 50,000 and 100,000 Euros and their indication is still on the rise.[36] Just to give a few examples on the most effective new drugs, the indication of trastuzumab, originally approved for metastatic HER-2 positive breast cancer, has been extended to the adjuvant setting, thereby dramatically increasing the market; the antiangiogenic drug bevacizumab is presently approved for metastatic colon, breast, kidney, and non small cell lung cancer but its indications are likely to expand soon and results of trials on its use for adjuvant treatment for colon cancer are expected in a few years. Studies on the adjuvant setting are also ongoing for cetuximab, presently approved only for metastatic colon cancers positive for epidermal growth factor receptor. For those concerned with the allocation of resources for control cancer, it is essential to have reliable methods of monitoring, at the population level, the impact of these new treatments. Cancer registries are well placed to perform this task but to do so effectively they need to collect more detailed and stand-

ardised information.[37–40] More extensive record linkage with clinical, diagnostic and drug prescription databases is likely to become possible in several countries and will greatly facilitate information gathering.

It would also be useful to expand cancer registration to collect information on co-morbidity,[41] disease recurrence,[42] and quality of life, thereby making it possible to analyse the likely impact of increasing cancer prevalence on individuals and society.

To be able to do their job effectively cancer registries must be adequately financed. But full support of co-ordinated Europe-wide cancer registry-based research is also required to better document geographic and social inequalities in access to diagnostic facilities, primary treatment and palliative care.

Following the revelation of unexpectedly poor cancer survival in Denmark and the UK by EUROCARE, in 2000 cancer action plans were implemented in these countries with the aim of improving cancer treatment and outcomes. The Danish plan[43] focused on the organisation of surgery, monitoring indicators, better interplay between primary and secondary sectors, education of health professionals, and improvement of diagnostic, oncological and radiotherapy capacity. Population-based studies were launched to monitor the effect of these changes on survival and mortality.[44] The NHS plans for the UK made new commitments in several areas, including inequality, speed of access, screening, staffing, and multi-disciplinary working in cancer centres, and also set up means to monitor progress.[45]

8. Relevance of population-based survival to cancer survivors and the public

Highlighting international survival differences in the media may convey the wrong message. Inflammatory newspaper headlines, such as those reporting that cancer survival is worse than a lottery (Daily Mail, April 23, 1999) or that only miracles can save cancer patients in southern Italy (L'Espresso, June 22, 2000), or politicians declaring that it is better to be treated in the US than in the UK (The New York Times, October 31, 2007) suggest that scientists need to communicate more effectively with the media. Cancer survival is clearly an important subject for public debate, but the public must be adequately informed. For example, breast cancer survival has been reported as being significantly higher in the US than Europe; however, a comparative study found that differences in age, stage at diagnosis, and number of lymph nodes evaluated explained most of the excess risk of European patients,[46] indicating that the problem is later diagnosis rather than less effective treatments. Pilot high resolution studies[47,48] in Europe on breast and colon cancer also suggest that survival differences across western European countries are largely attributable to diagnostic delay, although larger scale high resolution studies are necessary to address these issues more rigorously. For all cancers combined, 5-year period survival estimates for 2000–2002 were much higher for the American patients monitored by the 14 cancer registries in the SEER programme (66.3% for men and 62.9% for women) than in the 47 European cancer registries included in the EUROCARE period survival analysis (47.3% for men and 55.8% for women).[20] The huge difference for men was largely due to the lower incidence of rapidly fatal cancers (mainly lung and stomach) and the exceptionally high incidence and survival for prostate cancers in the US – largely attributable to overdiagnosis.[49] After excluding prostate cancer, the survival difference between American and European men decreased by about half (46.9% in the US; 38.1% in Europe). Nevertheless, with a few exceptions (stomach, testes, Hodgkin's disease and acute myeloid leukaemias), average survival for specific cancer sites was higher in the US than in Europe. For most of these cancer sites (not for prostate or large bowel cancer), however, US survival was within the range of European countries. European patients need to know that there is no particular reason to think that cancer treatment in the US is better than can be obtained in Europe. It is also important to stress that in both Europe and the US there are large survival differences between the rich and poor.[17,50] Also, the survival differences between European populations for all cancers combined would decrease after exclusion of prostate cancer, and, to a lesser extent, breast cancer, whose survival is artificially increased by lead time due to screening, but the overall geographical pattern highlighted by EUROCARE would not change.

Table 2 – Relative excess risks of death (RER) with 95% confidence intervals for all cancers combined[a].

	RER highest risk
European region[b] (eastern Europe versus central Europe)	1.29 (1.27–1.30)
Age at diagnosis[c] (55–99 years versus 15–54 years)	1.60 (1.57–1.61)
Sex[d] (men versus women)	1.05 (1.04–1.05)

For European region, age at diagnosis, and sex, the category at highest risk is compared with the category at lowest risk.

a All cancer sites in 9th revision of International Classification of Diseases (ICD-9) except non-melanoma skin.

b Eastern Europe comprises populations in the Czech Republic and Poland. Central Europe (reference category) comprises populations in Austria, Belgium, France, Germany, the Netherlands, and Switzerland. RER is adjusted by case-mix, age at diagnosis and sex. RERs for other European regions compared to central Europe were: UK and Ireland 1.26 (1.25–1.27); Nordic countries 1.07 (1.06–1.08); and populations in southern European countries (Italy, Malta, Portugal, Slovenia, and Spain) 1.01 (1.00–1.02)

c RER adjusted by case-mix, and sex. RERs relative to age 15–54 years were 1.29 (1.28–1.29) for patients aged 55–64 years; 1.54 (1.53–1.55) for patients aged 65–74, and 2.15 (2.14–2.16) for patients aged 75–99.

d All sites in ICD-9 except non-melanoma skin, breast, cervix uteri, corpus uteri, ovary, vagina and vulva, prostate, testes, and penis. RER adjusted by case-mix and age at diagnosis.

9. What Europe has learned from the EUROCARE studies

The main lesson is that the survival of European cancer patients varies markedly by country, region, age and sex. Table 2 summarises these differences, as determined by EUROCARE-4, in terms of relative excess risks of death for all cancers combined, after adjustment for case mix. The relative excess risk of death is 28% higher in Eastern Europe than central Europe; the relative excess risk of death is much higher for patients of age 55–99 years than those of age 15–54 years, and male cancer patients have a significantly higher risk of dying than women. Europe faces a major challenge in reducing these inequalities.

Conflict of interest statement

None declared.

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