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The EUROCARE study of survival of cancer patients in Europe: aims, current status, strengths and weaknesses

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Survival is the most thoroughly researched of the indicators of the effectiveness of cancer treatment and, together with cancer incidence, prevalence and mortality, a major indicator of cancer burden. Only recently, however, highly comparable population-based data on European cancer patients survival have become available to researchers and health care planners [1–3]. These estimates are, in fact, being used as a valid source for health policy throughout Europe. At present, the EUROCARE database includes approximately four million cancer cases from 65 populations covered by cancer registries in 20 European countries (Appendix A).

The main results of the analysis of this database showed that when highly effective treatment is available, for adult cancers such as testicular cancer and Hodgkin's disease, intercountry differences are not very large, at least in western Europe. On the contrary, when the disease stage at diagnosis matters the most, such as for stomach, colon, rectum and breast cancer, the analysis showed large survival differences between populations [1–3]. For adult cancers, the worst results were from eastern European countries. Also in western Europe, however, significant differences were observed. For instance, survival for many cancer sites was somewhat lower in the United Kingdom and Denmark with respect to the other countries of northern Europe and some populations in central and southern Europe. Survival trends over time increased everywhere but, with a few exceptions, differences between populations persisted across the time period studied so far (cases diagnosed between 1978 and 1989).

Several ancillary analyses were carried out to check the validity of the survival comparison, namely on the comparability of disease definition, on the definition of the date of diagnosis and on the completeness of follow-up [4,5]. In most cases, the effect of errors and biases proved to be much smaller than the actual survival differences between populations and the validity of comparisons within Europe proved to be robust. For a few tumour sites, however, the different case mix of histological types or anatomical subsites within the same three digit code of the International Classification of diseases made it difficult to interpret between population differences. It was the case, for instance, for pharynx and larynx cancers, which comprise mostly tonsil and glottic cancers in northern Europe and mostly hypopharynx and supraglottic cancers, characterised by a poor prognosis, in southern Europe [6]. Problems exist also for the diagnostic definition of several highly lethal cancers, such as pancreatic, liver and lung cancers for which the differential diagnosis with other non-tumour diseases can be difficult, thus cancer registries may include some false-positive diagnoses that inflate to some extent the measured survival. These problems have been thoroughly considered in the EUROCARE monographs [1–3], but they are still poorly understood by readers, who may not realise that, for instance, a small difference in survival of breast cancer patients is much more reliable than a several-fold difference in survival after pancreatic cancer [7]. In addition, the comparisons of EUROCARE data with North American, Australian and Japanese data, which frequently show higher rates than in Europe, still require a lot of attentive scrutiny, and more formal studies [8].

Several arguments have been marshalled by those who wish to downplay the role of survival comparisons between countries and over time. The first has been that comparing national survival data as provided by Nordic countries, Scotland and some eastern countries, with regional or provincial data as those provided by central

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and southern European countries is unfair, because the first ones truly reflect cancer patients survival in the country, while the latter may just show the performance of special regions where perhaps oncological services are especially well developed. This point is difficult to defend when within country comparisons are also available. For most cancer sites, for instance, survival variability within England and Wales shows a smaller range than variability between the EUROCARE countries [9]. When countries are compared with regions, national pride should not be an issue. Whenever a population, whether national or regional, fares better than another, it means that the latter may improve its performance. A second argument is that the quality and exaustiveness of the information in regional southern European registries may not be as good as in the UK and Nordic countries. Follow-up may be incomplete and the exclusion of cases known to the registries on the basis of the death certificate only may bias the case series towards a better prognosis. This is a widespread prejudice rooted in the history of epidemiology, which actually developed much later in central and southern Europe than in the north. Presently, however, several southern registries have quality indicators as good as the best cancer registries of northern Europe. The third popular argument is that survival figures are not suitable for geographical and temporal trend analyses because of the underlying trends in registration practices, diagnostic equipment and screening, which make the date of diagnosis and, therefore, survival time almost impossible to interpret [10]. According to this criticism, the only reliable end-point would be mortality. In a similar vein of caution, we should also be careful not to assume that death certification is comparable across countries and is not affected by diagnostic performances and changes in coding rules and practices. Actually, a proper interpretation of cancer trends requires considering mortality, incidence and survival. A fourth nihilistic view is that, whatever their reliability, survival comparisons are useless, because the only relevant information is whether patients are properly treated according to standard protocols issued from randomised trials and consensus conferences [11]. This is a respectable point of view which, however, is not evidence-based. What would be the interpretation if a high standard of diagnostic and treatment practice were not accompanied by the expected outcome? How could we assess such an expectancy if outcome were not measured?

None of these arguments undermines the conclusion that serious survival differences between European counties do exist and need to be explained. The first reaction of lay people in the face of these differences is that the reason must be treatment, and representatives of drug companies are ready to endorse this view notwithstanding the lack of evidence [12]. Anyone working in this field will admit that part of the explanation of the poor performance recorded in some populations is likely to be due to poor equipment and poor professional skill, but for several differences highlighted by EUROCARE this is unlikely to be the main reason [13]. Actually, the most ambitious aim of the EUROCARE project is to understand the reasons for survival differences: whether they are due to different disease stages at diagnosis (i.e. early diagnosis versus late diagnosis) or to different treatments, or to lead time or other biases. For several adult cancers, this aim is being pursued through three different strategies.

1. Multivariate analysis of survival at different follow-up intervals. Considering colon cancer [14], for instance, most of the survival differences between countries proved to be confined to the first 6-month period following diagnosis, suggesting that the most important determinant of survival differences is the proportion of advanced cases at the time of diagnosis. A similar analysis for breast cancer suggests that both early diagnosis and treatment may be of importance [15].
2. Mixed model analysis of the two major components of survival: the proportion of cured patients and the survival distribution of the patients that are going to die of the disease. If only the latter improved, without a corresponding increase of the proportion of cured, it would suggest that the overall increase is just due to early diagnosis without major advantages for the patients. The model has been tested for colon cancer on Finnish data (data not shown), where the availability of survival data for several decades (1953–1992) allows a direct observation of the cure rate, and now can be applied to the whole EUROCARE database [17]. The analysis showed that both components of survival had increased over time, suggesting a real improvement.
3. High Resolution Studies. Stage-specific or stage-adjusted comparisons on samples of incident cases for which participating registries collect standardised information on stage at diagnosis, staging procedures actually performed, such as number of nodes histologically examined to search for nodal metastasis or imaging techniques for distant metastasis, and treatment. Adjusting for diagnostic and staging procedures is essential for unbiased stage-specific comparisons. When survival increases both in localised and advanced stages, in fact, one would be tempted to conclude that treatment is improving, but the same effect could be due just to an improvement of diagnostic procedures, which may shift the classification of cases from the localised to the advanced stage category, thus apparently improving the prognosis of both.

Analyses of the most frequent adult cancers — lung, breast and colon — show that important international differences do actually exist in both diagnostic and treatment attitudes [18,19]. Analysis of the 3-year survival data of the High Resolution EUROCARE study on colorectal cancer shows that international differences tend to decrease when properly adjusted for stage, suggesting that precocity of diagnosis explains more survival variation than treatment [19]. In addition, for breast cancer, the EUROCARE High Resolution Study suggests that early or late diagnosis is the major determinant of the survival differences observed between western European countries for cases diagnosed in the early nineties.

Evaluating the quality of health care is a notoriously difficult problem with no standard solutions. Survival rates are by no means a simple and straightforward indicator and it is hardly surprising that complementary methods for evaluating the performance of health systems are being sought. The low incidence of childhood cancer makes survival differences even more difficult to evaluate for those who have the responsibility for planning health services. The present volume shows that major differences between eastern and western European countries do exist for most childhood cancers. Most likely these differences, which mirror those observed for adult patients, reflect huge economical and social inequalities within former socialist countries, but within western Europe it seems difficult to recognise a general pattern that could help in identifying the need for specific action plans. To increase the power of geographical comparison, we have computed an overall survival score for all childhood cancers together, adjusted for age and cancer type, according to the ICCC [20], through a direct standardisation using the distribution of cases from the whole EUROCARE-2 childhood database (cases diagnosed between 1985 and 1989) as a standard (Table 1). This may help to compare the overall performance of the paediatric oncology of different countries. The national registries of England and Wales and of Scotland were grouped into a single area because their survival figures were generally similar. The registries for Finland, Southern Sweden and Iceland were also grouped but, however, they were kept separate from Denmark because of the quite different rates that had already been noted for adult cancers. Germany is presented alone because of its national registry. As for the other central and southern European registries, only Italy had a sufficient number of cases to be examined separately. All the other registries were grouped into a single broad geographical category. Adjustment was made for age (three strata) and for diagnostic category (15 categories). These include the 14 most frequent cancers, accounting for 85% of all cancers, and a last category including all the other cancers. Adjusted survival rates of all cancers combined slightly reduced variability

Table 1
Survival after childhood cancer in Europe: 5-year survival rates of patients diagnosed in 1985–1989, adjusted by age and cancer type

European country or area[a]	(*n*)	5-year survival (%)	
		Standardised	Crude
Nordic countries	(904)	75	77
Germany	(5364)	72	72
Italy	(833)	71	69
Other Western countries	(1187)	67	69
UK	(5880)	66	66
Denmark	(640)	65	66
Eastern countries	(1340)	55	55

[a] Nordic countries include Finland, Iceland and south Sweden. Other western countries include Austria, The Netherlands, France, Spain and Switzerland. Eastern countries include Estonia, Poland, Slovakia and Slovenia.

with respect to crude comparisons. The Nordic (Finland, Iceland and Sweden) survival figure was higher than the other European survival figures (75% versus values between 55 and 72%). The difference was remarkable with respect to Eastern countries (55%), whereas for the other western populations survival ranged between 72 in Germany, 69 in the other central and southern European countries and 66 in Denmark and the UK. Survival in Finland, Iceland and Sweden, therefore, seems to represent a gold standard to which all countries who devote similar resources and have comparable health systems can reasonably aspire. Further studies are needed, however, to check this geographical pattern on larger and more recent series, to understand how much the differences could be overcome through health care planning, and to disentangle which aspects of cancer care require priority investment.

There is no doubt that the dramatic reduction of childhood cancer mortality in the last few decades has been due to the increasing availability of effective treatments. This has been a triumph of modern medicine and a formidable challenge to understand why childhood cancers are more curable than adult cancer, and why some still escape conventional therapy. Beside continuing monitoring survival, therefore, the priority for further population-based studies is to quantify the proportion of patients that are treated according to agreed protocols, possibly by geographical and financial access to care and by cultural indicators. Such studies could stimulate the improvement of health services and would also improve the quality of cancer registration systems and their comparability throughout Europe. A further priority, that we are presently addressing in the frame of the EUROPREVAL project (a concerted action between European cancer registries largely overlapping with the EUROCARE working group), is to estimate the prevalence of patients who survived childhood cancer, which should then be qualified with the prevalence of the side-effects of treatment.

Appendix A. The EUROCARE-3 Working Group

Austria: W. Oberaigner (Cancer Registry of Tirol). *Denmark*: H. Storm (Danish Cancer Society 'Institute of Cancer Epidemiology'). *Estonia*: T. Aareleid (Estonian Cancer Registry). *Finland*: T. Hakulinen (Finnish Cancer Registry). *France:* G. Hédelin, P. Schaffer (Bas-Rhin Cancer Registry), H. Lefevre (Calvados Digestive Cancer Registry), J. Mace-Lesec'h (Calvados General Cancer Registry), J. Faivre (Côte d'Or Digestive Cancer Registry), G. Chaplain (Côte d'Or Gynaecologic Cancer Registry), P.M. Carli (Côte d'Or Malignant Haemopathies Registry), P. Arveux (Doubs Cancer Registry), H. Mathieu-Daudé (Herault Cancer Registry), J. Estève (International Agency for Research on Cancer), C. Exbrayat (Isère Cancer Registry), N. Raverdy (Somme Cancer Registry), P. Grosclaude (Tarn Cancer Registry) *Germany:* P. Kaatsch, J. Michaelis (German Registry of Childhood Malignancies), H. Ziegler (Saarland Cancer Registry). *Iceland*: L. Tryggvadottir, H. Tulinius (Icelandic Cancer Registry). *Italy*: P. Crosignani (Project Leader), P. Crosignani, G. Gatta, A. Micheli, M. Sant, (Lombardy Cancer Registry), S. Ferretti (Ferrara Cancer Registry), E. Conti (Latina Cancer Registry), M. Vercelli, A. Quaglia (Liguria Cancer Registry — NCI, Genova), F. Pannelli, S. Vitarelli (Macerata Cancer Registry), M. Federico, L. Mangone (Modena Cancer Registry), M. Ponz De Leon (Modena Colorectal Cancer Registry), V. De Lisi, L. Serventi (Parma Cancer Registry), R. Zanetti (Piedmont Cancer Registry), C. Magnani (Piedmont Childhood Cancer Registry), L. Gafà, R. Tumino (Ragusa Cancer Registry), F. Falcini (Romagna Cancer Registry), M. Budroni (Sassari Cancer Registry), G. Stanta (Trieste Cancer Registry), E. Paci, E. Crocetti (Tuscan Cancer Registry), L. Simonato (Venetian Cancer Registry) R. Capocaccia, G. De Angelis, F. Valente, A. Verdecchia, (National Institute of Health, Rome). *Malta*: M. Dalmas, (Malta National Cancer Registry) *Norway*: F. Langmark, (Cancer Registry of Norway) *Poland*: J. Rachtan, (Cracow Cancer Registry), M. Bielska-Lasota, Z. Wronkowski (Warsaw Cancer Registry). *Slovakia:* I. Plesko, (National Cancer Registry of Slovakia). *Slovenia:* V. Pompe-Kirn (Cancer Registry of Slovenia). *Spain:* I. Izarzugaza (Basque Country Cancer Registry), C. Martinez-Garcia (Granada Cancer Registry), I. Garau (Mallorca Cancer Registry), C. Navarro (Murcia Cancer Registry) E. Ardanaz, C. Moreno (Navarra Cancer Registry), J. Borràs, J. Galceran (Tarragona Cancer Registry), A.R. Ramos (Registry Tumours of Valencia). *Sweden:* T. Möller (Southern Swedish Regional Tumour Registry). *Switzerland*: J. Torhorst, (Basel Cancer Registry), C. Bouchardy, M. Obradovic, L. Raymond, (Geneva Cancer Registry). *The Czech Republic*: J. Jechova (Institute on Health Information of Czech Republic). *The Netherlands*: J.W.W. Coebergh (Eindhoven Cancer Registry), A. Van Der Does-van der Berg, (DCLSG), O. Visser (Amsterdam Cancer Registry). *Scotland:* R. Black, (Scottish Cancer Intelligence Unit). *England*: T.W. Davies, S. Godward (East Anglian Cancer Registry), M.P. Coleman (London School of Hygiene and Tropical Medicine), E.M.I. Williams (The Merseyside and Cheshire Cancer Registry), D. Forman (Northern and Yorkshire Cancer Registry and Information Service & Centre for Cancer Research), M.J. Quinn (Office for National Statistics), M. Roche, S. Edwards (Oxford Cancer Intelligence Unit), C. Stiller (Childhood Cancer Research Group) J. Smith (South and West Cancer Intelligence Unit), J. Bell (Thames Cancer Registry), H. Botha (Trent Cancer Registry), G. Lawrence (West Midlands Cancer Intelligence Unit), J. Steward (Welsh Cancer Intelligence and Surveillance Unit).

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