

Not credible: a subversion of science by the pharmaceutical industry. Commentary on A global comparison regarding patient access to cancer drugs (Ann Oncol 2007; 18 Suppl 3: pp 1–75)

In 2005, Sweden’s famous Karolinska Institute allowed its name to become associated with the *Karolinska Report*, which concluded that the more cancer drugs there are on the market in a country, and the more quickly they are licensed for the market, the higher is that country’s cancer survival rate [1].

The standard of evidence used in the first *Karolinska Report* to link cancer survival and the availability of cancer drugs was far below that used by the drug industry and licensing authorities to assess whether a drug is effective [2]. When asked “If they pushed that evidence forward to the regulatory bodies, it wouldn’t be accepted?”, I confidently said it wouldn’t stand up in peer-reviewed publication, never mind with a licensing authority [3].

I was wrong. *Karolinska Report 2* has now been published [4], no longer European but global in scope, and this time as a peer-reviewed supplement in the *Annals of Oncology*, the official journal of the European Society for Medical Oncology, read by most of the European cancer specialists who prescribe cancer drugs.

the new Karolinska report

The new report examines the uptake of new cancer drugs and cancer survival or mortality in 19 European countries, plus Australia, Canada, Japan, New Zealand, South Africa and the USA. The analysis starts: “Economists believe that the development of new products is the main reason why people are better off today”, and sets out to test the hypothesis that “treating patients with newer drugs increases cancer survival rates”. It shows wide variation in the speed of licensing cancer drugs and in cancer drug expenditure around 2003. It then examines survival trends in the USA, survival patterns in five countries in Europe, and mortality trends in 20 countries, each as a function of drug ‘vintage’ (the year a drug was first launched). Space precludes discussion of all three analyses, and I will focus on the European analysis of cancer survival and drug ‘vintage’. Like the first report, it concludes there is a relationship between the uptake of new cancer drugs and cancer survival. The UK receives special attention as having ‘low and slow’ uptake of new cancer drugs, together with relatively low cancer survival.

But the European ‘survival rates’ in the Karolinska report are not survival rates at all: “We estimated survival rates by

dividing 1-year or 5-year prevalence by incidence.”. In other words, the ‘survival rates’ in the report are not even calculated from the cancer patients’ actual duration of survival, which has been standard practice for over 50 years [5]. Dividing the total number of (say) 5-year survivors by the total number of cancer patients diagnosed each year—a tactic which ignores both year-to-year changes in those numbers and the wide differences in cancer survival by age, sex and cancer type—also amounts to assuming that all cancer patients have the *same* risk of death, and that the risk is *constant*, from diagnosis up to the fifth anniversary. For most cancers, that is simply not true [6], as every clinician and cancer patient knows.

The Karolinska ‘survival rates’ are thus, in effect, poor approximations to ‘crude’ or all-causes survival, instead of relative survival [7], the standard approach to international survival comparison for decades [8]. Relative survival is adjusted for mortality from other causes of death (background mortality), which varies widely by age, sex and country, and has a big impact on international survival comparisons [9].

The cancer survival estimates in the Karolinska report are wrong. For France, the report gives 5-year survival for all cancers combined as 71% for women and 53% for men, the highest of the EU countries examined. Cancer survival specialists in France recently estimated 5-year *relative* survival for all cancers combined at 63% for women and 44% for men [10]—some 8–9% below the values in the Karolinska report. The *crude* survival rates against which the figures in the Karolinska report should more properly be compared were 55 and 36%, respectively, some 16 to 17% below the values in the report. Yet the authors appear to conclude that their novel approach to the estimation of cancer survival is reliable on the basis of just one comparison between their (crude) survival figure for the USA and a (relative) survival estimate from the US SEER program. They use the same example for both reports.

Drug usage data for some 77 000 patients were taken from IMS Oncology Analyzer, a market-oriented database supplied by about 1200 doctors, who collect complete cancer patient treatment histories for about 12 000 patients a year in each of France, Germany, Spain, Italy and the UK. Curiously, the authors argue that since data on individual patients are not available to test their hypothesis that treating cancer patients with newer drugs increases survival, they were forced to use grouped data from countries. Yet studies of the survival of all cancer patients in a defined population as a function of the treatment actually received by each patient are not new [11, 12], and IMS Oncology [13] claims to offer “the most comprehensive patient case history information available on

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the market, enabling study of patient treatment from diagnosis to current day ... by stage and line of therapy". Why not analyse the survival of those patients? IMS also records hormonal therapy, radiotherapy, surgery and supportive therapies, but the Karolinska report only examines the drug data. No information is provided on the sampling structure of the IMS database or its representativeness as a guide to drug usage.

The cancer prevalence data used in the report were taken from GLOBOCAN [14], the International Agency for Research on Cancer database. The underlying survival data came from the EURO CARE-3 study, which relates to patients diagnosed during 1990–1994 [15]. So the data on drug usage, around 2003, refer to patients diagnosed some 10 years *after* the cancer patients with whose survival those data are modelled. When challenged over this issue on the first Karolinska report [2], the authors responded that they could have chosen to use drug availability for 1995 or 1997 instead of 2000, but "since availability (and vintage) in different years is strongly correlated, that will not make the results misleading" [16]. The authors do at least acknowledge this problem in the latest report, but more recent data on survival in Europe are not yet available (EURO CARE-4 will be published later in 2007). Yet, despite noting that cancer drug expenditure quadrupled during the period 1995–2005, and half the cancer drug expenditure in 2005 was for drugs launched during that period, the authors again sidestep this issue by claiming that national cancer drug uptake in 2003 is still likely to be representative of uptake in or around 1993.

Such a speculative assumption cannot reliably underpin the conclusion that low usage or expenditure on cancer drugs today is the cause of low survival for patients diagnosed 10 years ago. It is all the more surprising because the report focuses on anti-cancer drugs licensed after 1995, such as rituximab (Mabthera, 1997), trastuzumab (Herceptin, 1998) and imatinib (Glivec, 2001), which were not even available to treat patients diagnosed during 1990–1994 [17]. Strong conclusions about cause and effect normally require a longitudinal approach in which the exposure (drug usage) precedes the outcome (cancer survival), preferably in the same patients.

In short, the new Karolinska report uses flawed methods to reach flawed conclusions about the link between cancer drug 'vintage' and cancer survival in European countries.

the impact of chemotherapy on cancer survival

Chemotherapy has contributed to improving the outcomes from many of the malignancies of childhood, and from testicular cancer, Hodgkin's disease and breast cancer in adults, among other cancers. But early diagnosis and prompt access to optimal surgery and/or radiotherapy are the mainstay of treatment for these and most other adult cancers, and the Karolinska report does not assess these. An assessment of the impact of cancer drugs on survival in Australia and the USA [18], derived from clinical trials that reported a benefit attributable solely to chemotherapy for one of 22 different adult

malignancies, suggests that the overall contribution of chemotherapy to survival up to 5 years after diagnosis may be about 2%. Even that estimate is based on assuming that the benefits observed in each clinical trial were actually achieved by all cancer patients in the population who would be eligible for the chemotherapy in question. The authors conclude that chemotherapy only makes a minor contribution to adult cancer survival.

Given the coverage of these issues in the media, however, cancer patients and the wider public could be forgiven for imagining the overall impact of chemotherapy to be very different. That may be due to the lack of a profitable, world-wide industry focussed on improving surgical or radiotherapeutic technique, or on optimizing staffing levels, training and access to health care.

strategy

The first *Karolinska Report* concluded that more drugs and faster licensing boost a country's cancer survival figures. The report was funded by Hoffmann-La Roche, a leading manufacturer of cancer drugs. In July 2006, a press officer for Hoffmann-La Roche wrote to my institution: "we are looking for an independent, academic review of available data on cancer care in Europe to be used at the launch [of] *Cancer United*, a new campaign launching in Brussels on 19 October 2006 to call for a pan-European cancer strategy. The review might include data from the Organisation for Economic Co-operation and Development (OECD) on health expenditure and the Karolinska Institutet pan-European comparison on patient access to cancer drugs". The suggestion is illuminating. She went on: "Would the London School of Hygiene and Tropical Medicine have an academic, who would be an authority in this field and available to supervise the work? This would be a funded project and we would be looking to the School to advise on an appropriate budget.". There would also be substantial PR for the School and the scientist concerned.

One of the launch documents said: "*Cancer United* is the first pan-European campaign driven by an interdisciplinary coalition to improve access to cancer care for patients across Europe. [Cancer] is the second main cause of death in Europe after cardiovascular disease. Yet inequalities in access to cancer care still exist [citing only the *Karolinska Report*], and that must change.". Strong stuff. The *Cancer United* campaign, and its launch in Brussels, were both funded by Hoffmann-La Roche.

An industry seeking to purchase 'independent' academic corroboration of an industry-funded study on drug access and cancer outcome, in order to support the launch of an industry-funded campaign in which wider use of the industry's products would be expected to figure highly, might expect to be viewed with some concern, if not by marketing executives, then at least by scientists. Especially since the European Union is now considering a proposal to spend up to one billion euros under the 7th Framework Programme on a 7-year public-private research programme (Innovative Medicines Initiative) to develop new therapeutic drugs [19].

Unsurprisingly, *Karolinska Report 2* also had a big impact in the media. Under the front-page headline "Cancer survival

rates worst in western Europe”, the *Daily Telegraph*, a major UK newspaper, wrote [20]: “British cancer patients are substantially more likely to die of the disease than those in other western European countries because of poor access to the latest drugs, according to an authoritative report.”. It quoted one of the authors: “Our report highlights that in many countries new drugs are not reaching patients quickly enough and that this is having an adverse impact on patient survival.”. Both conclusions are unequivocal; neither is supported by the report. The Karolinska report’s emphasis on the cancer survival contrast between France and Britain was also a focus for the BBC [21]: “... and that brings us to perhaps the starkest difference in treatment between France and the UK: access to new cancer medicines”.

An editorial in the *Lancet* [22] also accepted the survival results at face value, commenting: “... to dismiss this very detailed report that looks beyond pure [cancer drug] usage data and tries to assess outcomes in three different ways is premature and petulant”.

It is neither premature nor petulant to criticize a 75-page report that invents an incorrect method of estimating cancer survival in a single short sentence, gets the wrong answer, models the incorrect results with drug data for a period some 10 years *after* the patients were diagnosed, and then concludes that low national survival rates are due to poor access to cancer drugs and slow national drug licensing.

summary

No-one wants cancer patients to be denied access to drugs (or any other treatment) that may save or prolong their lives. Research to identify survival deficits that may be due to inadequate access to cancer drugs (or any other treatment) is obviously desirable.

The key question addressed in the two Karolinska reports—whether national cancer survival is associated with national cancer drug licensing—is not a disinterested question. Since both reports were funded by an industry which actively seeks to extend the market for its products, we should not be surprised. But then very particular care is required in evaluating the methods, the results and the conclusions [23, 24]: and here, they do not stand up to scrutiny.

The wider concern is that a drug industry-funded report based on incorrect science can still achieve wide and uncritical publicity, with the serious attendant risk of misleading oncologists, policy-makers, and the public.

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acknowledgements

Declaration of interest: I have no conflict of interest to declare.

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A response to this editorial from B Jönsson, F Lichtenberg, and N. Wilkins can be found on pages 1585—1587 of this issue.