New drugs and survival: does the Karolinska report make sense?

Michel Coleman

Is it possible to demonstrate that access to new drugs impacts on a country's survival rates? Last September, the Karolinska report claimed to have done just that. Here, **Michel Coleman** argues that its conclusions were misleading and unsupported by the data and analysis. In the Debate that follows, the authors respond and health economists and policy advisors offer their views.

IN a recent cancer debate in the British House of Commons, the opening statement by John Baron MP included the following: "The Opposition recognise that there have been improvements in outcomes, but they have not outstripped comparable improvements in continental survival rates. **According to last year's report from the Karolinska Institute, the UK still lags behind other European countries** when it comes to survival rates over periods of one year and five years. In fact, Britain has one of the worst survival rates in all of western Europe: whereas 81 per cent of cancer patients in France survive for one year, the equivalent UK figure is only 67 per cent. Even Albania and Lithuania have better one-year and five-year survival rates than we do." (Bold text throughout indicates emphasis added.)

These remarks are seriously misleading, but Mr Baron is not to blame. The report from the Karolinska Institute has gained wide currency since its publication in September 2005. But the report is seriously flawed: the cancer survival data in the report, the statistical models of survival as a function of the availability of chemotherapy drugs, the authors' conclusions from those models – they are all wrong. It seems important to set the record straight, since the faulty data and conclusions may lead to inappropriate decisions by politicians, or undue frustration among cancer patients.

The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials, and it is no part of my intention here to challenge that evidence.

But I do challenge the nature and scope of the cancer survival data presented in the Karolinska report, and the way in which those data have been modelled with data on the national availability of cancer drugs. If my critique of the Karolinska report is correct, those analyses cannot be used to support its policy-related conclusions about the impact of the availability of cancer drugs in a given country on cancer survival rates in that country.

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"It is important to set the record straight, as faulty data and conclusions may lead to faulty decisions"

What the report says

The executive summary and the conclusion show that the potential policy i mpact of linking cancer survival with the availability of drugs in Europe is clearly understood. The report says: "These results [on the speed of uptake of drugs throughout Europe] underscore the reality that cancer patients in Europe do not have equal or rapid access to cancer drug therapies, but what is the real-life impact of this imbalance? Dr Frank Lichtenberg of Columbia University highlights that **access to more cancer drugs means improved survival rates for patients.** His analysis of the situation in the US demonstrated that the increase in the stock of cancer drugs accounted for 50–60% of the increase in survival rates in the first 6 years post diagnosis.

"In addition, his examination of the USA and selected European countries indicates that an increase in the number of available drugs is associated with an increase in both the one-year and five-year survival rates. Therefore, with the importance of new drug therapies in the battle against cancer, it is clearly in the best interest of cancer patients that new, innovative drug therapies are made available to them as soon as possible. **Reduced or delayed access to cancer drugs has a very real impact on patient survival."**

The evidence for this assertion is based on chapter 7 of the report, "Pharmaceutical innovation and cancer survival", which is described as a 'commentary' prepared by Frank Lichtenberg at Columbia in August 2005. He examines cancer survival trends in the US in relation to drug availability, and carries out a similar exercise with European data. This is described as an investigation of "the effect of availability of new drugs on survival from 17 types of cancer in more than 35 countries." The data sources and the description of the methods are reprinted here in the box on p 28. No other detail is provided on either data sources or methods. No reference for the method is given.

Results are shown for 38 European countries (Table 7.2, p89 of the report) in the form of one-year and five-year survival rates (%), for all cancers combined in both sexes, along with the annual number of cases and the number of new drugs launched since 1982. No survival data are shown for 17 different cancers. No results are given from the modelling of cancer survival as a function of the availability of drugs. Instead, these results are summarised as follows:

"The estimates indicated that an increase in the number of available drugs is associated with an increase in both the 1-year and the 5-year survival rates. The sample includes both European and non-European countries. Two additional analyses related to this distinction have been performed:

1. We estimated survival models using the full sample of countries but allowed the ln(N_DRUG) coefficient to be different in the European and non-European sectors. We saw no evidence of a difference. Availability of drugs seems to have the same effect on cancer survival within Europe as it does in the rest of the world.
2. We tried estimating survival models using data for European countries only. This reduces the sample size by

THE KAROLINSKA REPORT

A pan-European Comparison Regarding Patient Access to Cancer Drugs, generally known as 'the Karolinska report', was written by Nils Wilking of the Karolinska Institute in Stockholm, Sweden, and Bengt Jönsson of the Stockholm School of Economics. The data modelling and analysis was carried out by Frank Lichtenberg of Columbia University in the US. The report was funded by Roche and was published by the Karolinska Institute in collaboration with the Stockholm School of Economics in September 2005. It can be accessed at http://ki.se/content/1/c4/33/52/Cancer_Report.pdf.

60%. We did not obtain statistically significant results. However, one might well obtain statistically significant results based on European data only using time-series incidence, mortality and drug utilisation data."

Interpretation

Several serious problems complicate the interpretation of this material.

First, the report says of the GLOBOCAN data (used for survival, see box below): "These incidence data are collated from national cancer registries". This is not so. The GLOBOCAN website (http://www-dep.iarc.fr/globocan/database.htm) makes it clear that "Incidence data are available from cancer registries. They cover entire national populations, **or samples of such populations from selected regions.**" This leads the authors into modelling what are often regional cancer survival rates with national drug marketing data.

Second, the International Agency for Research on Cancer (IARC), which compiles the GLOBOCAN database, does not itself collect or produce cancer survival data. As the website clearly states, survival data in GLOBOCAN 2002 were taken directly from the EU-sponsored EUROCARE study into cancer survival in Europe, in this case EUROCARE-3 (Berrino et al. *Ann Oncol* 14:v1–v155). They relate to patients who were diagnosed during 1990–94 and followed up to 1999. Yet those survival data have been deployed in the model in the Karolinska report in relation to the number of drugs available in 2000, as if they were for patients who had been diagnosed in the year 2000 or later.

Third, five-year survival data for cancer patients diagnosed in 2000 could not have been published at the time of these analyses (August 2005). Only so-called 'period estimates' (Brenner et al. *Int J Epidemiol* 31:456–462) could have been used to 'predict' such survival rates, but period survival estimates were not included in the GLOBOCAN database that was the source of the data.

Fourth, in 12 of the 38 countries (Albania, Bosnia-Herzegovina, Bulgaria, Cyprus, Greece, Hungary, Luxembourg, Macedonia, Moldova,

KAROLINSKA REPORT: DATA SOURCES AND METHODS

The data used to model drug availability against survival in the Karolinska report came from three different sources.

- The *survival* data were taken from the GLOBOCAN 2002 database (though in the Karolinska report this was given as GLOBOCAN 2000)
- Data on drugs approved by tumour type were taken from the Cancer Care Ontario (CCO) Formulary
- Data on *drug availability* were taken from the IMS Lifecycle New Product Focus

The model to which these data were applied is described in the report as follows:

"These data are used for estimating a model that included both fixed cancer-type effects and fixed country effects, which control for all determinants of cancer survival that are invariant across cancer types within a given country and that are invariant across countries for a given cancer type.

$$SURVij = , \ln(N\_DRUGij) + \bullet i + \%_{o}j + \hat{A}ij\ 1$$

Where:

SURVij = the (1-year or 5-year) survival rate for cancer type i in country j

N_DRUGij = the number of drugs for cancer type i available in country j

ai = a fixed effect for cancer type i

dj = a fixed effect for country j

eij = a disturbance

"Due to inclusion of fixed cancer-type and country effects in the model, , [sic: i.e. the comma ","] represents the effect of relative drug availability within a country on relative survival rates within the country. Suppose that, on average (across all countries), the survival rate of cancer type A is 25% higher than the survival rate of cancer type B, and the number of drugs for cancer type A is 35% higher than the number of drugs for cancer type B.

"Then one would expect that if, in a particular country, the number of drugs for cancer type A is only 20% higher than the number of drugs for cancer type B, the survival rate of cancer type A is less than 25% higher than the survival rate of cancer type B. Indeed, estimation of the model requires that the relative availability of drugs for different cancer types varies across countries."

"It treats the number of drugs on the market as the sole explanation for differences in cancer survival"

Romania, Serbia-Montenegro, Ukraine) for which the authors purport to give national survival rates for patients diagnosed in 2000, no cancer registry was in operation in those countries in that year, and in most cases there is still no such registry. In fact, the 'survival rates' for those countries, reproduced in the Karolinska report, were taken in GLOBOCAN to be a weighted average of survival rates in other countries in the same region of Europe for which national or pooled multi-registry estimates of survival *were* available from EUROCARE-3. For example, for Albania, in Southern Europe, survival rates in GLOBOCAN were taken to be a weighted average of the cancer-specific survival rates reported from EUROCARE-3 for Italy, Malta, Portugal, Slovenia and Spain, weighted by the cancer-specific mortality rates in Albania. Equivalent procedures were adopted for other countries from which no survival data were available. This was done in order to estimate cancer prevalence[1], *not* as the basis for an international comparison of survival, and *certainly not* as the basis for modelling international variation in survival as a function of the availability of cancer drugs.

Fifth, almost no information is given on the methods or the results of the modelling. The results are simply summarised in the form of the conclusion "that an **increase** in the number of available drugs is associated with an **increase** in both the 1-year and the 1-year survival rates. The sample includes both European and non-European countries."

Sixth, the survival data from Europe that are used in the model represent a single time point (supposedly in the year 2000). No data on survival trends are presented that could support a conclusion of any *increase* in survival over time as a function of drug availability.

Lastly, the model is extremely simplistic. It treats the number of drugs available on the market, regardless of their availability to patients, or their actual use in individual patients included in the survival analyses, as the sole explanatory factor for international differences in cancer survival. Most of the Karolinska report deals in detail with the marketing of cancer drugs in Europe over the last 20 years. I have no comment on the analysis of the availability of cancer drugs per se, except that the report seems to be pervaded by an assumption that the market availability of a licensed cancer drug is the chief factor influencing the national survival rate for that cancer, whereas surgery and radiotherapy remain the mainstay of treatment for most of the common malignancies.

Conclusion

The analysis of cancer survival in relation to the availability of cancer drugs in the Karolinska report is very misleading. It purports to show cancer survival data from several countries for which no such data are available: those incorrect data have already been cited in a parliamentary debate in the UK, and quite possibly elsewhere. The report provides no data on cancer survival beyond those published in 2003 for EUROCARE-3. Real survival data from some countries are then used alongside imaginary data for other countries in a crude statistical model designed to estimate the 'effect' of the number of cancer drugs on the market in 2000 on cancer survival (all cancers, both sexes combined). Worse, the survival data used to model the impact of cancer drugs available in 2000 are for patients who were diagnosed in 1990–1994 – some *six to ten years before the currency of the drug data*. For 12 of the 38 countries, the 'survival data' are actually the average survival rates from four or five completely different countries from the same broad geographic region of Europe. The conclusion that an *increase* in the availability of cancer drugs is associated with an *increase* in cancer survival rates is also completely unsupported by the data presented in the report.

Neither the cancer survival data nor the analyses of them can support the policy conclusions in the Karolinska report.

1. Methods of estimating prevalence: "Partial prevalence (1-, 3- and 5-year prevalent cases) were obtained by combining the annual number of new cases and the corresponding probability of survival by time. ... Several sources of site-specific survival were used. ... Europe: The EUROCARE-3 project provid[ed] figures from several European cancer registries for [patients diagnosed during] the period 1990–1994. Where possible, country-specific survival estimates were used, based on regional cancer registries, and **four regional estimates were prepared for countries where no local survival data were available.**" (Ferlay J et al. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. IARC 1 May 2006; http://www-dep.iarc.fr).

THE DEBATE

CancerWorld asked the authors of the Karolinska report to respond to the points raised in Coleman's critique, and European health economists and policy advisors were asked to comment on the report, and more generally on whether it is possible to draw out the impact one particular aspect of cancer therapy has on survival rates, and if so, how this can be done in the most meaningful way.

In their response, the authors said that the report's findings show significant differences in access to new drugs and the implications of these differences merit discussion. "The Karolinska report provides for the first time comprehensive information on the use of new cancer drugs in different countries, and it documents substantial variation in the uptake of new drugs, and systematic differences between countries. The UK, for example, is slower than other European countries in the uptake and use of new cancer drugs." The report goes further, they said, and investigated different reasons for the observed differences. While it concluded that economic factors play a role, "countries with lower GDP and health-care expenditures per capita, such as Poland, the Czech Republic and Hungary, tend to have slower uptake of new cancer drugs," most of the variation, said the authors, "seems to be explained by factors related to how cancer care is funded and paid for, and by attitudes towards innovation."

"We think that it is important to point out these differences and to discuss the factors behind them, and to consider what can be done to achieve a more rational allocation of resources to cancer care in Europe. This is of interest not only for oncologists and other health-care professionals, but for patients and the general public as well."

Coleman's criticisms related both to the quality of the data and to the methodology used to model survival data against access to new drugs. On the question of the data, the authors agreed that Coleman's criticisms regarding the use of drug availability rather than actual use in the models was fair comment. "The point is well taken, and in the follow-up report to be published later this year, we will have a new set of estimates based on the vintage of drugs actually used. This may strengthen the relation, but probably not lead to a different conclusion since availability and use are correlated."

However, they rejected the other charges relating to the quality of data, arguing that, though "the data available for assessing the relation across countries between actual use of new cancer drugs and improvements in survival over time are far from perfect", the limitations are by no means sufficiently serious to invalidate the findings of the report.

Taking Coleman's points in turn, they stated, "First, we do not see any problem modelling regional cancer survival rates with national data on drug availability. If a drug has not been launched in a given country, then it is not available for use in any region of the country. So regional drug availability = national drug availability.

"Second, the estimated survival rates were obtained by dividing one-year or five-year prevalence by incidence. The results of this procedure appear to be consistent with other estimates of survival rates. For example, the method used implies that the five-year survival rate for all sites other than non-melanoma skin for males in the US is 63.8% [=2431746/ (5*762399)]. According to the US National Cancer Institute, the five-year survival rate for all sites for males in the US during 1995–2000 was 64.0%.

"Third, the fact that the incidence and prevalence data may refer to different time periods would, of course, introduce errors of measurement in the estimates of survival rates. However, these errors are likely to be random, i.e., uncorrelated with the drug availability measure. Random errors of measurement in the dependent variable do not cause any statistical bias."

Regarding Coleman's point about

the GLOBOCAN/EUROCARE 3 data having been compiled to estimate cancer prevalence and not as a basis for modelling survival as a function of the availability of cancer drugs, the authors said "The argument that [these data] can only be used for the specific purpose for which they were collected is absurd."

As for the criticism that changes in survival as a function of access to new drugs cannot be explored using survival data from a single time point, the authors commented, "We did not use international data on survival trends since such data are not available. The analysis on changes in survival over time is done for the US survival alone."

CancerWorld asked European experts from a variety of fields to what extent they felt that Coleman's criticisms of the quality of the data were valid.

Renée Otter is a director and medical oncologist at the Comprehensive Cancer Centre North-Netherlands, who sits on the board of the Netherlands' National Comprehensive Cancer Plan and is involved in many European projects relating to registries, benchmarking of cancer care and guidelines.

She agreed with Coleman's analysis and said the flaws he pointed to effectively invalidated the claim of the Karolinksa report to demonstrate an impact of drug availability on survival.

"If you don't have other data, the only report you can make is about two different things. One part is the survival analysis, the other one is the availability of drugs." These results, she said, could be used as the basis to propose a project that could use both data but in a different way. "You should try to get these data over the same period, and only use data that are not an expectation, but are actually observed in the different countries."

Isabelle Durant-Zaleski is a health economist based at the Hôpital Henri Mondor in Paris, and has a long history of working with epidemiological data to investigate disparities in health outcomes. She says that international comparisons in healthcare are difficult, but can be useful. "What these very large macro-economic comparisons do is draw your attention to something strange. And to me that is exactly what the Karolinska report does.

"It is very good academic practice to challenge the methods and challenge the results, and this is what Michel Coleman is doing, but it is also useful to do some perhaps imperfect comparisons and difficult comparisons, as the authors of the Karolinska report do, because it puts access to cancer care on the political agenda."

Her views are echoed to an extent by Mattias Neyt, a pharmaco-economist who works for the Belgian health technology assessment agency, the KCE, and has recently been involved in assessing the cost-benefits of Herceptin [trastuzumab] in an adjuvant setting. He argues that you have to work with the data you have. "What is best? To do no research or to research with the best available data? I would choose the second. You can find interesting results. How robust they are is another question, but if they don't have more recent figures, that doesn't mean they shouldn't do research at all."

Mike Richards, the UK's National Cancer Director, in contrast, thinks that modeling survival rates from one period against the number of drugs available in another is very likely to come up with misleading results. "The only accurate measure we have of survival rates between countries come from EUROCARE 3, and they relate to patients diagnosed between 1990 and 1994. None of the new drugs we are now talking about, except for Taxol [paclitaxel], had even been licensed at that point. Everything people are talking about now, like Herceptin or Glivec [imatinib] or Rituximab [mabthera], weren't even available so they could not possibly have affected survival rates for people diagnosed in 1990–1994."

The authors counter 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."

Methodology

In addition to the issues relating to the data used, Coleman also criticised the methodology of the Karolinska report. He argued that the methods used to analyse access to drugs as a function of survival did not provide any basis for the assertion made in the executive summary that "Reduced or delayed access to cancer drugs has a very real impact on patient survival." Firstly, says Coleman, no information was given on the methods or results of the modelling, and secondly, the number of drugs available on the market was treated as the sole explanatory factor for differences in survival.

The authors say they were surprised by these criticisms, particularly as Coleman himself acknowledges that "The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials." Information from clinical trials needs to be supplemented with studies based on drug availability and use in actual clinical

"How can our results be misleading if they support the results from clinical studies?"

practice, said the authors, particularly given the fact that of the 57 cancer drugs approved by the US Food and Drug Administration through the regular process since 1994, only 18 were approved on the basis of a survival endpoint, and in none of the 14 granted accelerated approval was a survival endpoint used (see *J Clin Oncol* 21:1404–11).

"Observational studies enable investigation of the impact of innovation in cancer management on costs as well as outcomes… How can our conclusions be misleading if they support the results from the clinical studies?"

While welcoming serious discussion and comments on the methods and data used for these sorts of observational studies, the authors argued that it would have been better if Coleman had read the original research papers before concluding that the models were all wrong. "A number of misunderstandings could have been avoided." The full paper to the similar study conducted by Lichtenberg in the US can be accessed at www.nber.org/papers/w10328, and a revised version taking into account the European data will be posted there soon, say the authors.

They also point out that Coleman fails to provide any alternative explanation or interpretation of the results, and merely implies that the results obtained should not have been obtained.

On the question of the methodology, Zaleski said, "In my view the method is not appropriate for the causal relationship, but it is appropriate to attract attention to discrepancies. It showed there might be a correlation, but establishing causal relationships between a treatment and an outcome – in this case new drugs and survival – is very difficult outside of randomised controlled trials."

She mentions, however, a similar piece of research carried out by the OECD health policy unit, which looked at the use of mammography and survival of breast cancer. "It is not quite the same exercise, but it is not very different. In the case of the OECD report, they identified the fact that, for example, France has 10 times as many mammographs as Canada, standardised by women over the age of 40, yet the survival in Canada from breast cancer is exactly the same as in France. So this means that for people who are interested in public health, you have to look more in-depth."

The Karolinska report, she says, "is a good attempt to have comparisons that would enable you to go further. It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report. The OECD is extremely prudent."

Zaleski suggests one possible explanation for the correlation found between survival and access to new drugs could be that the latter is a "surrogate marker" for something else. "Countries which have speedy access to new drugs may also have better coordination of care and better access to specialised oncologists. It also means access to research protocols, possibly access to multidisciplinary teams, or even access to other innovative or state-of-the-art cancer treatments." This, she stresses, can only be conjecture, which can only be validated by more detailed research, "which is what the Karolinska report and Michel Coleman's piece urge us to do."

Otter also questions whether the methodology used could ever demonstrate a causal relationship between new drugs and survival. "I don't think that in the way they have put their project together you can make any relationship – even if it was in the same time period. It sounds like the story I was told in my first course on epidemiology about there being an increasing number of births because we have an increasing number of storks."

The issue, she suggests, should be whether patients are getting the drugs recommended in evidence-based guidelines. "The drugs you give are dependent on the stage of the tumour. So in some countries you routinely give adjuvant chemotherapy, and in others you will rarely give adjuvant chemotherapy, because there are no stage I patients in these countries. They come too late to the doctor."

She also argues that the role of drugs in cancer management makes it unlikely that they are a big factor in explaining differences in survival. "Very good surgery and very good radiotherapy are more relevant for survival than drugs. The exceptions are all haematological diseases, children's cancer and testicular cancer. For all the others we know that the

additional drugs influence your survival chances less than surgery with or without radiotherapy. Drugs have more influence on survival in the palliative phase of the tumour than in the curative setting."

More fundamental still, says Otter, is getting the diagnosis right so you can plan the most appropriate treatment. "Everything starts with a very accurate diagnosis and staging. Then you need people who are very specialised for the surgery, people who are very specialised for the radiotherapy with access to state-of-the-art radiotherapy equipment. Third comes the medical oncology."

Back in 2000, Richards called in a team of international experts to look at exactly the same survival data as was used in the Karolinska report, with the brief that they were to establish whether the data that showed the UK bumping along the bottom of the European cancer survival league table were an actual reflection of reality, and if so, what could explain the poor results.

"The overwhelming view from that meeting was that we did have to accept the UK had worse survival rates than comparable Western countries. But we also found that the main reason for that was due to patients presenting with more advanced disease in the UK than in those other countries. What that tells me is that it matters as much what goes on before diagnosis as what goes on after diagnosis, if not more."

This finding was reached by looking at the patient data on stage of diagnosis that was available from a number of high-resolution studies that were included in EUROCARE-3. "But that's all the registry studies can tell us – they can't tell us more because they have insufficient data on treatment."

Richards speculates that drug expenditure may be a proxy for overall cancer expenditure.

Future studies

As a policy maker whose job is to use the resources available in the most effective way to improve Britain's cancer services, Richards warmly welcomes studies that throw light on the relative contribution of different aspects of cancer care to the overall outcome. He says, however, that to be of practical value they need to look at a range of input variables. He points to the growing body of evidence that in certain cancers, such as colorectal cancer, the quality of surgery is decisive in reducing local recurrence rates, and is therefore likely to be important in explaining differential survival rates.

"You would need data on stage at presentation, then compare that with a whole load of different things like what treatments are actually being given, what training is being given, what is the quality of surgery and the radiotherapy."

He accepts that such studies are not easy, because it is difficult to get comparable measurements across countries. The best way, he suggests, would be to get countries that are prepared to do this well to work together. "I think you need to engage with people from the individual countries who know what is going on and can advise as to what the data might mean and what is a realistic and reasonable comparison to make."

Zaleski points to a study recently carried out by Stanford University, which posed the question: Has the introduction of new technologies for heart treatment changed the outcome in heart attack? It also looked at how variations in the speed at which these new technologies were introduced into routine practice impacted on survival. "Heart attacks is a much easier topic, because people die quickly, so survival data are easy to get. They have been able to show correlations between the introduction of new technology, the use of health care, and survival. But that is a multicountry endeavour with a very large database and a lot of work to have comparable data."

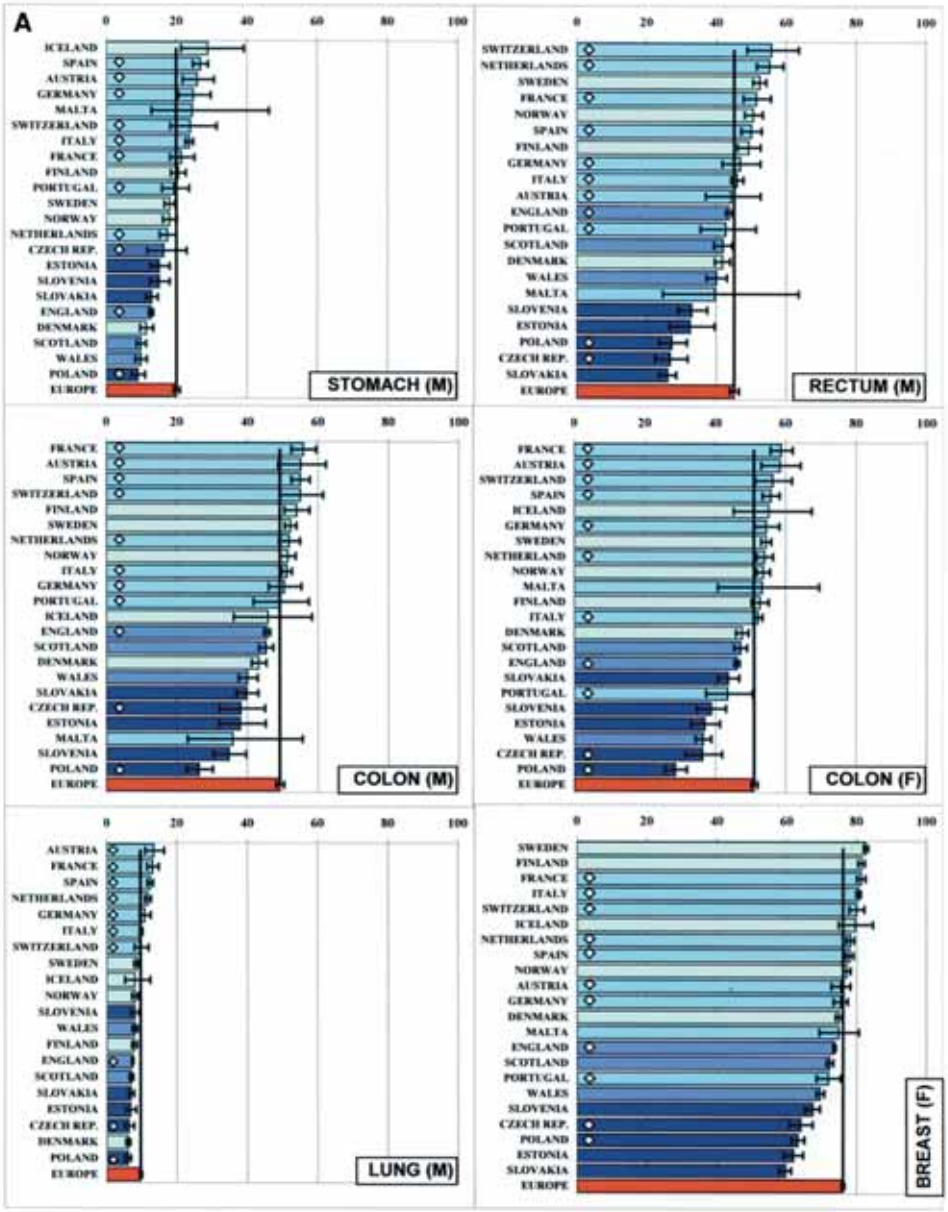
It should in principle be feasible to apply a similar methodology to cancer, says Zaleski. "The idea there would probably be to look at one type of cancer and begin with a case study. This would have to be done with multicountry comparisons. You would need to have a large number of countries, because there are so many treatment variables. You want to have more countries than variables, and you need longitudinal data of good quality."

Longitudinal data are needed to track the treatments a single patient has throughout their cancer journey. Getting hold of this data, says Zaleski,

"It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report"

Why the disparity? The EUROCARE results showed that in some countries cancer patients stand a better chance of survival than in others. The reasons will vary from cancer to cancer. In colorectal cancers, good quality surgery is known to be critical in avoiding recurrences. In breast cancer, expert surgery, radiotherapy and appropriate drugs all play a role. Catching the cancer early and getting the diagnostic work-up right are enormously important. Evidence showing the relative contribution made by each factor on survival rates would be very helpful for policy makers deciding where to concentrate their resources

CANCER SURVIVAL ACROSS EUROPE



Source: MP Coleman et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol* 14 (Suppl 5):v137. Reprinted with permission from Oxford University Press

"It would be worth looking in detail at what accounts for survival differences"

Access to drugs may be a proxy for general expenditure on cancer or state-of-the-art innovations

could prove a problem. "In many countries, like France, you do not have linkage of discharge data. When a patient has had several treatments, there is no national database where those treatments can be linked to the same patient. That is why they looked at heart attacks, because most of the treatments are done on the first admission."

She also mentions the need to look at how reimbursement systems determine which patients actually have access to drugs that are on the market – something also highlighted in the Karolinska report.

Otter suggests that it would be worthwhile comparing some regions in Eastern Europe with some in Western Europe and looking in detail at what accounts for survival differences. Incidence and survival data would have to come from well-documented regional-based cancer registries, but the study would have to be hospital-based, using 'cancer centres of excellence', to get good data on diagnosis and treatment. It should look at one cancer at a time, focusing on high-incidence cancers in order to have enough patients to be able to identify small differences. The variables she would like examined include the use of good diagnostic procedures and good staging procedures, the education of surgeons, the volume of surgeons, multidisciplinary discussions, radiotherapy equipment and the availability of drugs.

"First we should identify some countries which are able to get drugs or not able to get drugs, able to give adequate radiotherapy or not, and high-quality surgery or not. And this is what we should try to compare between countries."

She feels there is potential for making better use of existing networks and data. She mentions in particular the EUROCHIP project – a Europe-wide study to compare different indicators of diagnostics and treatment in different countries.

"I think by combining high-resolution studies, EUROCHIP and some additional data, at least we can try a pilot study. It won't be easy, but I think it should be possible, and it is a much better approach than the Karolinska one.

Otter believes that working to coordinate European guidelines and find ways to ensure that guidelines are followed is the way forward, not just for drugs, but also for diagnostics, radiotherapy, surgical procedures and so on. The availability of a given therapy is not the issue, she says, because if that therapy is not in the guidelines, it won't be paid for and it won't be used.

She mentions the European project CoCanCPG, which is bringing together all the bodies responsible for drawing up guidelines in countries and institutions. It aims firstly to identify the level of evidence in relevant publications to reach conclusions for international guidelines, and, secondly, to gain insight into the problems and processes of translating the evidence into national guidelines that are regularly revised and applied in practice.

Better research needed

The Karolinska report flagged up some significant differences in the rate at which cancer drugs hit the market across Europe. There seems to be general agreement that the suggested correlation with survival merits further examination. Though the experts *CancerWorld* spoke to do not believe the evidence in the report substantiates the claim that "Reduced or delayed access to cancer drugs has a very real impact on patient survival," they do believe access to drugs may be a proxy for general expenditure on cancer, or access to research protocols or state-of-the-art innovations in general – a point also made in the report.

The authors themselves are committed to further refining the findings of the report, "We are well aware of limitations of methods and data, and will continue to work to improve on both, because questions about the relation between innovation, costs and outcome in cancer deserve answers."

The contributors to this discussion, however, clearly believe that modelling drug availability alone against survival cannot guide policy makers in deciding where to concentrate resources and efforts to get the best impact on survival.

This can only be done through more in-depth studies that can look at the contribution of a variety of aspects of stage of detection, diagnostics and treatments.

The Debate was compiled by Anna Wagstaff