

EUROCARE 4 delivers its verdict

→ Anna Wagstaff

The EUROCARE 4 report has delivered an implicit merit mark to eastern European countries, whose relatively poor survival figures are now improving faster than those in the rest of Europe. But older patients are still far less likely to survive a cancer diagnosis than younger patients, and the gap is getting wider. The verdict? Must do better.

The results of the latest EUROCARE study were published in March in a supplement of the *European Journal of Cancer*, packed with tables, graphs, bar charts, scatter plots and other statistical wizardry.

It's not a riveting read – statisticians by their nature resist drawing all but the most qualified conclusions and stand ready to pounce on anyone caught treating their findings in a cavalier fashion. Yet the data presented in the 200-page report represent a goldmine for policy makers, practitioners, researchers and public health professionals working to reduce the suffering and death from cancer in Europe.

Drawing together the individual experiences of around three million adult

cancer patients, diagnosed between 1995 and 1999, and using data – all quality controlled with common parameters – taken from 82 cancer registries in 23 European countries, EUROCARE 4, presents the 'big picture' with a statistical robustness that randomised trial investigators can only dream of.

For shock value, it would be hard to match the findings of the early EUROCARE studies, which first revealed the dramatic East–West gap in both incidence and mortality, and threw the spotlight on the importance of prevention (particularly anti-smoking measures) and early detection. It may even be hard to match the impact of EUROCARE 3, whose league tables of shame prompted the UK and Denmark to formulate the first comprehensive cancer plans, which are now being recommended for the

whole of Europe (though it won't be until EUROCARE 5 that we get to see whether the plans have lived up to expectations).

Yet EUROCARE 4 has its own important stories to tell about the social, biological and geographical issues that need to be tackled if we are to make progress against cancer.

THE BIG PICTURE

How do you sum up the picture painted by millions of bits of data on survival, gathered by age, sex, cancer site, region and date of diagnosis – and calculated in absolute terms, or relative to the survival expected of people of a similar sex/age/region, or adjusted for differences in case mix, or conditional on surviving the first year after diagnosis, or even separating the

The Eurocare 4 report card

Eurocare 4 found marked variations in survival within the European population:

- Cancer patients in eastern Europe are still 28% more likely to die from the disease than patients in central Europe, even after accounting for differences in case mix, age at diagnosis and sex.
- Patients who are aged between 55 and 99 years when diagnosed with cancer are 60% more likely to die of cancer than those aged 15–54 years old at diagnosis (adjusted by case mix and sex).
- Male cancer patients are 5% more likely to die from their disease than female patients (leaving aside the sex-specific cancers and non-melanoma skin cancer).

chronic survival cases from the cured?

“Marked variations” is the characterisation used by the authors of the EURO-CARE 4 supplement, who highlight, in particular, the continuing survival gap between East and West, between older and younger patients, and between men and women. In other words, your chances of surviving cancer still depend in part on where you live and who you are. “Europe faces a major challenge in reducing these inequalities,” conclude the authors.

At first sight, this is a rather dispiriting conclusion, given that it echoes so closely the main findings of EURO-CARE 3, published six years ago, which stated that “generating an appropriate level of concern” when addressing



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regional inequalities, in particular, would be “an important outcome” of the EURO-CARE project.

A closer look, however, tells a different story. Though cancer patients in eastern Europe still have a 28% ‘relative excess risk of death’, this was calculated by comparing the data from countries in eastern Europe with those from the region showing the best survival figures – central Europe. By contrast, a comparison with the UK and Ireland, or with southern Europe, would reveal a far smaller gap. More importantly, the data from the EURO-CARE 3 study showed

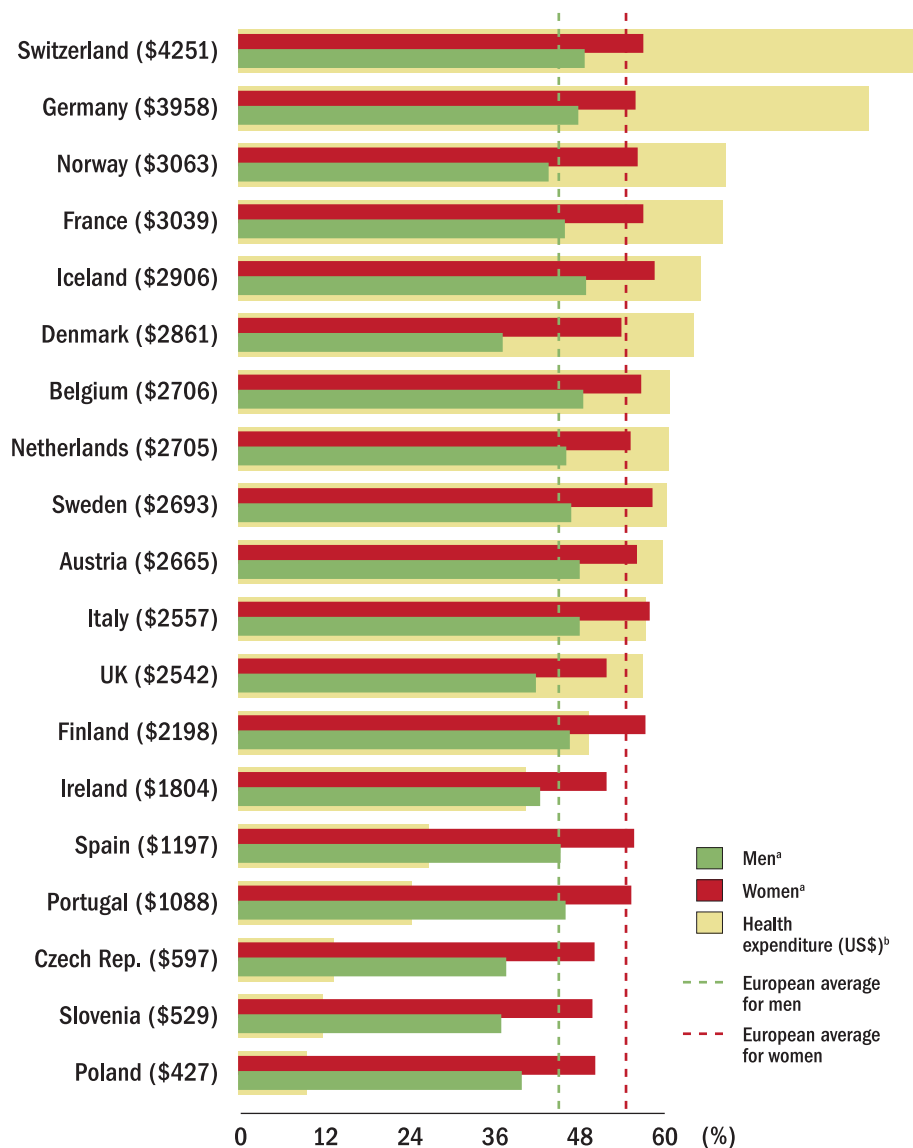
that survival and mortality were improving at a slower rate in eastern European countries than in the rest of Europe, and that the inequality was therefore getting worse. EURO-CARE 4, by contrast, tells a tale of a closing gap, as the countries with the worst survival rate make the fastest progress – childhood cancers being a particular success story.

THE EAST-WEST GAP

Although situated on the East–West border and categorised as a part of southern Europe within the EURO-CARE studies, Slovenia has

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Five-year survival ranked by health spend



Despite progress towards closing the East–West gap, considerable variation still exists between the countries with the best survival and those with the worst. Per capita health spend strongly influences cancer outcomes, but some countries achieve more for their expenditure (eg Finland) than others (eg UK and Denmark)

become a champion for eastern European efforts to improve their cancer control, and typifies many of the problems of the region. Not least among these is a per capita health spend that is significantly below the European average – half that of Portugal, one fifth that of Sweden and one eighth that of Switzerland.

Maja Primic Žakelj, Head of Epidemiology and Cancer Registries at the Slovenia Institute of Oncology, says a report, shortly to be published, on survival trends in Slovenia 1991–2005 chimes strongly with the EURO CARE findings of above-average progress in the region. Comparing survival for patients diagnosed between 1991 and 1995 against those diagnosed between 2001 and 2005 reveals that the proportion of cancer patients alive five years on from their diagnosis rose 12 percentage points over the 10-year period, from 40% to 52%. It’s encouraging, she says, but this rate of improvement needs to be maintained – while prostate cancer was among those showing the greatest survival gain, EURO CARE 4 showed survival for patients diagnosed in the period 2000–2002 still 16 percentage points lower than the European average. On the plus side, Slovenia now equals or out-

^a Five-year relative survival of patients diagnosed between 1995 and 1999

^b Average per capita yearly expenditure on all health care 1994–2002

Source: Modified from Franco Berrino et al, Comparative cancer survival information in Europe. EJC 45:903 © Elsevier 2009

“Resources must be spent carefully, on the basis of evidence-based data and a reliable cost-benefit analysis”

performs the European average for some rare cancers, for instance in testicular and thyroid cancer and Hodgkin's disease "where patients are now treated in specialised centres."

Primic broadly agrees with the assessment in the EUROCARE 4 report which suggests that the survival improvements in eastern Europe "may indicate that these countries have made efforts to adopt new diagnostic procedures and standard protocols," but she adds that greater awareness among primary physicians and increased levels of screening have been important in getting cancers diagnosed earlier. Looking to the future, she believes the biggest survival gains will come from organisational measures – in particular, concentrating cancer treatments in fewer hospitals that can offer specialist, quality-controlled, multidisciplinary treatment. "Currently cancer patients are treated in practically all general hospitals in Slovenia," she says.

Will the increasing use of very expensive targeted drugs – in both adjuvant and advanced settings – pose a threat to the continued narrowing of the East–West survival gap? EURO-CARE 4 can throw no light on this, as even Glivec (imatinib), one of the first such drugs, only came into use right at the very end of the period covered by EURO-CARE 4. Primic, however, does not see this as a major issue. "As far as very expensive therapies are concerned, the proportion of cancers where they are effective in major prolongation of survival is not so great."

Marek Nowacki, director of the Maria Skłodowska-Curie Institute of Oncology in Warsaw, Poland, speaks in a similar vein. "The incremental growth

of expenditure on new cancer medicines has not contributed to a proportional improvement in outcome," he notes, adding that Poland, which has the lowest per capita health expenditure of all the countries represented in EURO-CARE 4, showed the biggest improvement, "which shows that the very limited resources for oncology must be spent carefully, on the basis of evidence-based data, preceded by a reliable cost-benefit ratio analysis."

That said, Nowacki is very clear that further improvement will depend on securing additional funding. He believes that for all the hand-wringing by policy makers over the East–West survival gap, the European Commission (EC) is still failing to put its money where its mouth is. "One of the fundamental challenges for the European Health Commissioner is solving the issue of equal access to healthcare which, in the context of oncology, means equalising the chance of all Europeans in the area of prevention, treatment and terminal care. The European Commission allocates only symbolic funds to programmes of cancer control."

To be fair, thanks to the efforts of MEPs Against Cancer, the European Cancer Patient Coalition, the Slovenian and the Portuguese governments and others, backed by the evidence provided by the EURO-CARE project, cancer – and specifically the issues surrounding the East–West divide – has shot up the European agenda over the past few years, and the EC has finally agreed to set up a European Cancer Partnership, set to be launched around September this year, with responsibility in this area. But while funding proposals for poorer

countries remain largely restricted to exhorting governments to use their sorely needed structural fund money to invest in cancer control, the impact of all this on the ground remains to be seen – and it will be EURO-CAREs 5, 6 and 7 that will document that story.

THE AGE GAP

Meanwhile, EURO-CARE 4 has opened up a new front in its exposure of inequalities, providing the strongest evidence so far that elderly patients stand a far lower chance of surviving a cancer diagnosis than younger patients – and the gap between them is getting wider, because improvement in outcomes over time are benefiting younger patients more than older patients.

An analysis of the relative excess risk of death (RER) for cancer patients aged 70–84 compared to those aged 55–69 (which should be 1.00 if both age groups stood the same chance of survival) showed an RER of 1.39 for older women and 1.17 for older men in 1988, steadily increasing to reach 1.6 for women and 1.20 for men by 1999.

This has to be a major cause for concern, not least because the older age group accounts for a higher – and increasing – proportion of all cancer patients than the younger one, so it is not a marginal group that is suffering poorer outcomes.

Matti Aapro, executive director of the International Society of Geriatric Oncology (SIOG) says he is not surprised by the EURO-CARE 4 data. "It confirms at a European level what has already been documented by individual reports from researchers in North America and Europe." He hopes that the EURO-CARE

“The key now is to make sure doctors know about
[geriatric] assessment tools and that they use them”

data will help raise awareness of the size of the problem and stimulate greater research in this field and prompt policy makers to take action.

“GPs and patients should understand that there are many cancers for which adequate treatments can be provided that can either cure or decrease the morbidity, provided you start the treatment on time,” says Aapro. Sadly, he adds, it is clear that too many elderly patients are being let down by inadequate treatment on the misplaced assumption that their age rules out treatment with standard regimens.

Tools have now been developed to enable doctors to assess the health status of more elderly patients to help them distinguish between those who are healthy enough to be treated according to standard guidelines and those who may need a modified regimen – the key now is to make sure doctors know about them and that they use them, says Aapro. In an effort to help this process along, SIOG is currently a simplified version of the assessment tool.

Yet much still remains unknown about how common comorbidities impact on patient survival in various treatment settings, not least because

new drugs tend to be trialled only in the fittest patients, who are often unrepresentative of the population the drug is intended for.

For geriatric oncologists, an “important outcome” of EURO CARE 4 will be “generating an appropriate level of concern” to stimulate action to reverse the growing disadvantage of elderly patients, as happened when the East–West gap first came under the spotlight.

THE GENDER GAP

In the case of the survival gap between women and men, EURO CARE 4 has, in some ways, already achieved an important outcome. The unexplained survival advantage of approximately 5% that women cancer patients have over men has been the subject of speculation for some time. Some have suggested cultural factors are largely to blame – women are better at picking up symptoms, men don’t like going to the doctor – while others have put their money on biological differences as the primary explanation.

Thanks to the large quantity of survival data stratified by age at diagnosis, EURO CARE 4 has been able to shed some important new light on the debate. The data show that the marked survival gap

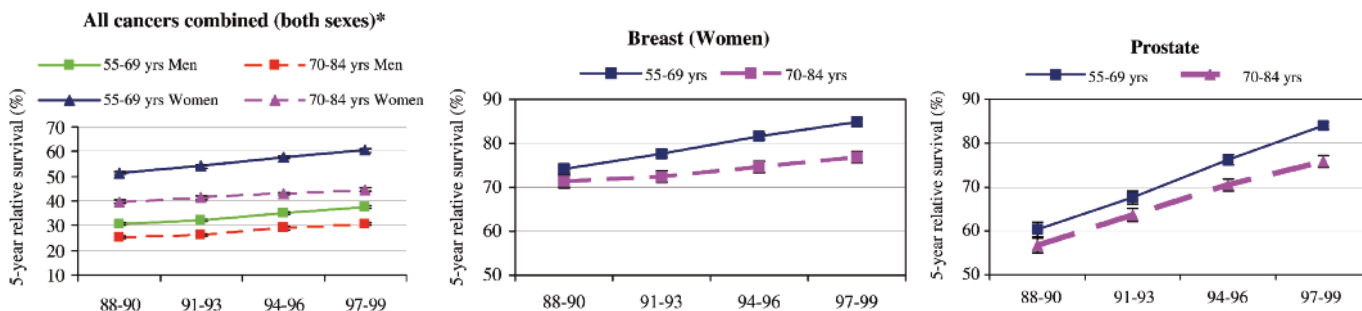
between the sexes reduces progressively with age, from an extraordinary 12 percentage points in the age group 15–44, to only 1.3 percentage points at 75–99 years.

In the absence of any obvious cultural factors that might explain this pattern, the report concludes that biology is at work here. “As women progress from mature fertility through peri-menopause, their sex hormone status changes profoundly, similar dramatic changes do not occur in men. It seems probable therefore the sex hormones are the prime mediators of the female survival advantage.”

Andrea Micheli of the Istituto Tumori in Milan, Italy, is lead author of the EURO CARE 4 report on the survival advantage of women and has been researching this story for many years. He believes the new epidemiological data point the way to a promising new area of research. “I think we need to study this phenomenon, as it could hypothetically have a future preventive and/or therapeutic relevance... Identifying which female sex hormone condition is responsible for the female survival advantage has to be the first step,” he says.

Micheli stresses, however, that the survival advantage is not all down to biology. “There is some evidence that

FIVE-YEAR RELATIVE SURVIVAL TREND (1988–1999) FOR ELDERLY AND MIDDLE-AGED CANCER PATIENTS



Improved detection and treatment is benefiting younger patients more than older patients, leading to a widening gap in survival

*All cancer sites except prostate and non-melanoma skin cancers

Source: Alberto Quaglia et al, The cancer survival gap between elderly and middle-aged patients in Europe is widening. *EJC* 45, p1009, © Elsevier 2009

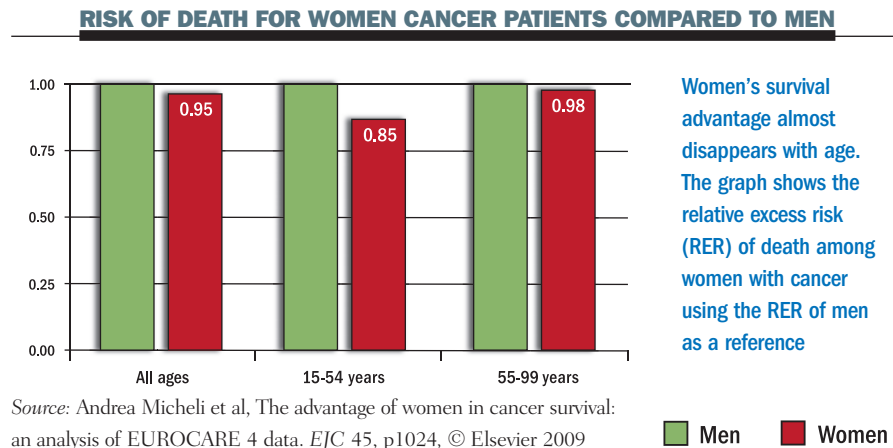
men are more reluctant to show up," he says. "We are currently involved in a European cancer registry study from which it will be possible to investigate gender differences in diagnosis delay." He estimates that social and cultural issues account for around 20% of the survival difference between men and women, indicating a need for health education targeted at men.

FUNDING FEARS

Like its predecessors, EUROCORE 4 really is one of the great triumphs of European coordination – all the more impressive for having found ways to keep going despite the withdrawal of funding from the European Commission, and constant threats from national data and privacy protection laws.

"It's been a struggle," says Roberto Capocaccia, coordinating author of the EUROCORE 4 supplement, based at the National Centre for Epidemiology, Surveillance and Health Promotion in Rome, Italy. While each country's cancer registry has its own base of funding (and registry coverage is still non-existent or very partial in many countries), there is a funding gap when it comes to paying for the European coordination. "We've had no money from the EC. There is some funding from the San Torino Foundation for EUROCORE, and some from the high-resolution studies in Italy. We use some of these funds to organise meetings with colleagues in different countries."

Representation from eastern Europe was actually lower for EUROCORE 4 than its predecessor, with only Poland, the Czech Republic and Slovenia contributing data (though the latter is categorised as southern Europe). Estonia and Slova-



kia, both present in the EUROCORE 3 study, had to drop out – the first because of laws preventing the linking of registry data with death certificates, the second for organisational reasons.

Capocaccia is optimistic, however, that cancer registries are spreading in Europe, and EUROCORE 5 will include a substantially greater number of cases. "For eastern Europe, we are sure to have data from Croatia, and there are a few more countries with emerging registries." Central European countries like Germany are also getting their act together. Germany's input into EUROCORE 4 was based on a data covering a paltry 1% of the total population; this is set to increase to near national coverage.

Funding, however, remains a worry. EUROCORE suffered a double whammy, says Capocaccia, because, when the EC stopped funding EUROCORE, it also ended the Europe Against Cancer programme, which had been supporting a variety of epidemiological projects. "We had a project which for the

first time provided prevalence data for Europe, but we have not been able to continue this work." Europe-wide 'high-resolution studies', which are able to look in much greater detail at factors that might influence survival, have also had to be stopped for lack of funding, says Capocaccia, adding that such studies had in the past generated essential information, including the fact that most of the survival difference within Europe, and between Europe and the US, results from later diagnosis rather than worse treatment. "This is important for policy."

Capocaccia hopes that Eurocourse, a new project aimed at coordinating funding priorities between the funding institutions of EU Member States, may help Europe-wide coordinated studies find the funding they need. Given the key role EUROCORE findings have already played in helping Europe develop appropriate cancer control policies, anyone who cares about reducing the suffering and death from cancer will surely be hoping the same.

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