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Cancer mortality: favourable trends continue

Cancer deaths in Europe have declined steadily from the period 1990–1994 to 2000–2004, new figures show. However, large variations remain between countries and according to gender.

Between the two periods, deaths from all cancers in the European Union fell by 9 percent in men (from 185.2 to 168 deaths per 100,000 population) and 8 percent in women (from 104.8 to 96.9 per 100,000). There was a large fall among the middle aged population.

The report (doi:10.1093/annonc/mdp530) contains mortality rates by country and by cancer.

Dr Cristina Bosetti (Mario Negri Institute, Milan, Italy) said: 'The key message of our paper is that the favourable trends in cancer mortality in Europe have continued over the most recent years. This is due mainly to the falls in lung and other tobacco-related cancers in men, the persistent decline in gastric cancer, but also appreciable falls in colorectal cancer.

'Screening and early diagnosis have contributed to the decline in cervical and breast cancer, although the fall in breast cancer mortality is mainly due to improved treatment. Therapeutic advancements have also played a role in the reduced mortality from testicular cancer, Hodgkin's lymphoma and leukaemias, although the declines have been delayed and are smaller in Eastern Europe.'

Notwithstanding the general favourable trends, the researchers found a two-fold difference in both cancer mortality and incidence across European countries. For men, the highest mortality rates in 2000–2004 were in Hungary (255/100,000), the Czech Republic (215/100,000) and Poland (209/100,000); the lowest were in Sweden (125/100,000), Finland (130/100,000), and Switzerland (136/100,000).

For women, the highest mortality rates were in Denmark (141/100,000), Hungary (131/100,000) and Scotland (123/100,000), and the lowest in Spain (78/100,000), Greece (79/100,000) and Portugal (80/100,000).

Where alcohol or tobacco consumption, or a combination of the two, has increased (particularly in women), there was a rise in deaths from cancers known to have these as risk factors, such as lung, mouth, pharynx and oesophagus.

'Further reduction of tobacco smoking remains the key priority for cancer control in Europe,' the authors wrote. 'Interventions in alcohol drinking, aspects of nutrition, including overweight and obesity, and more widespread adoption of screening, early diagnosis and therapeutic advancements for treatable cancers would contribute to further reduce the European cancer burden in the near future.'

New lung cancer staging classification discussed

Key recommendations in the 7th edition of the tumour, node, metastasis (TNM) classification for lung cancer were discussed at a virtual roundtable of experts in November, 2009.

The classification, which is jointly administered by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), was published in 2009, the first revision in 12 years.

The International Association for the Study of Lung Cancer (IASLC) had a central role in updating the classification; changes were based on the IASLC international data base which includes more than 100,000 cases, treated by all modalities of care. Dr Peter Goldstraw (London, UK), past chair of the IASLC staging project, said this allows 'intensive validation.'

The current N classification remains in the 7th edition, but M1 is reclassified as T4 where there are additional tumour nodules in other ipsilateral lobes. M1 becomes M1a where there are additional tumour nodules in the contralateral lung; and M1b where there are distant metastases.

Dr Frank Detterbeck (Yale Cancer Center) stressed that the new classification system is a nomenclature which cannot serve as a shortcut to treatment selection.

But it facilitates ongoing international collaboration. It 'provides a mechanism for discussion of ideas, issues, definitions as they come up relative to anatomic staging,' he said.

In future, genetic characterisation will open up a completely different approach to anatomic screening, which will create issues and challenges: 'The IASLSC staging effort provides the infrastructure to address these,' Dr Detterbeck said.

Staging Manual in Thoracic Oncology ISBN: 978-0-9799274-3-0.

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

doi:10.1016/j.ejca.2009.12.001

NICE says no to bevacizumab...

The UK's National Institute for Health and Clinical Excellence (NICE) has issued a preliminary negative decision on bevacizumab (Avastin) in combination with oxaliplatin-based therapy for the treatment of metastatic colorectal cancer (mCRC).

However, Roche has announced that it will continue to work with NICE with the aim of making the drug generally available in the UK. In conjunction with the UK's Department of Health, the company had developed a subsidised package of care at a cost per quality-adjusted life year (QALY) of UK £36,000. This is just above the commonly accepted NICE threshold of £30,000 per year.

Dr Rob Glynne Jones (Mount Vernon Hospital, Middlesex), chief medical advisor of the charity Bowel Cancer UK, said, We would encourage all the relevant parties – NICE, the manufacturers and the Department of Health – to continue to work on the details of a Patient Access Scheme that will meet the necessary criteria and ensure that NICE approves this drug for NHS use.'

John Melville, General Manager of Roche UK, said patients in Australia, Canada and most of Europe gain access, but patients in the UK, Latvia and Poland don't.

... yes to oral topotecan

NICE has recommended oral topotecan as an option for people with relapsed small-cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. It may be used only where the combination of cyclophosphamide, doxorubicin and vincristine is contraindicated.

Intravenous topotecan is not recommended by NICE for people with relapsed small-cell lung cancer.

NICE has said that people with relapsed SCLC currently receiving oral topotecan but who do not meet the specified criteria – and those receiving intravenous topotecan – 'should have the option to continue their treatment until they and their clinicians consider it appropriate to stop.'

Accelerated approval for ofatumumab

GlaxoSmithKline (GSK) and Genmab have announced the accelerated approval of ofatumumab (Arzerra) by the US' Food and Drug Administration (FDA) for use in patients with chronic lymphocytic leukaemia (CLL) that is refractory to fludarabine and alemtuzumab.

Ofatumumab is the first antibody from Danish company Genmab to reach the market.

The approval is based on results from a study in which 42% of CLL patients who were refractory to both fludarabine and alemtuzumab responded. The median duration of response was 6.5 months. The FDA's Oncologic Drugs Advisory Committee (ODAC) had met at ASCO in May, 2009. The panel voted 10–3 that the data 'were likely to predict clinical benefit' in these patients.

Ofatumumab is a monoclonal antibody that attaches to the small and large loop epitopes on the CD20 molecule on the surface of B-cells. It boosts the body's immune response to normal and cancerous B-cells.

The most common adverse reactions include neutropenia, pneumonia, pyrexia, fatigue, rash, nausea, bronchitis and upper respiratory tract infections.

'Thromboembolism risk' with erythropoiesis agents

Use of erythropoiesis-stimulating agents is associated with an increased risk of venous thromboembolism, US researchers say.

Agents such as erythropoietin and darbopoietin are approved to reduce the number of blood transfusions required during chemotherapy.

Dr Dawn Herschman (Columbia University, New York) and colleagues patients diagnosed with colon, non-small cell lung, or breast cancer, or with diffuse large B-cell lymphoma between 1991 and 2002. They were aged 65 years or older and were identified in the Surveillance, Epidemiology and End Results-Medicare database.

'FURTHER EFFORTS AT MONITORING LONG-TERM TOXICITY OF EXPENSIVE ONCOLOGY DRUGS ARE NEEDED'

Patients who received an erythropoiesis-stimulating agent were at increased risk of developing venous thromboembolism. Overall survival was similar in both groups, according to the paper, which was published in the Journal of the National Cancer Institute (doi: 10.1093/jnci/djp429).

The authors note that the number of patients receiving erythropoiesis-stimulating agents increased approximately 10-fold from 1991 to 2002. The rate of blood transfusions over the same time period, however, remained constant at 22%.

'Further efforts at monitoring use and long-term toxicity of expensive oncology drugs should be put in place to ensure that for any drug the benefits outweigh the risks in community practice,' the authors write.

Ambulight receives CE Mark

Ambicare has been given the go-ahead to market its product, Ambulight PDT, in Europe. It has received a CE Mark for the innovative treatment of non-melanoma skin cancer.

Ambulight PDT is small disposable light emitting sticking plaster, designed to deliver photodynamic therapy (PDT) directly to the site of skin lesions. Patients will be able to continue with their normal daily routine when undergoing PDT, the company says.

In Europe, PDT is recommended for non melanoma skin cancer. It is a 2-step process involving the application of a pharmaceutical cream, which creates a photosensitive daughter compound. Controlled exposure to a selective light source then activates the light-sensitive chemical which attacks the diseased cells.

Current treatment usually involves a day patient appointment at the hospital, where a large static PDT source is used to treat a limited number of patients. "This is inconvenient for the patient and costly for the healthcare provider as it ties up a hospital day bed, as well as restricting the number of patients who can be treated. Ambulight PDT would allow healthcare providers to shift treatment from hospitals to GP surgeries or office-based dermatologists, the company says.

EUROFILE

EU seeks research harmony through Joint Programming

By the spring of 2010, the European Union will have a new instrument in place to help countries co-ordinate their research funding, in order to spend it more effectively and reduce EU-wide duplication. Called *Joint Programming*, eleven countries have already signed up to take part in the pilot action on Alzheimer's disease, and discussions are underway to make cancer research one of the next areas in line.

At the behest of national research ministers, the European Commission has spent the last two years scrutinising national research programmes, where the bulk of public R&D (around 85%), is programmed, financed, monitored and evaluated. It concluded that a lack of cross-border collaboration in national programmes makes it difficult to address common challenges jointly, complicates the pooling of data and expertise that is scattered across Europe, hinders cross-border researcher mobility and training, and slows down the international dissemination of research results. In turn, it causes duplication of research, and delays breakthroughs.

Joint Programming will provide a platform for public authorities to come together voluntarily, and launch targeted research programmes in several pan-European research areas.

The onus of the approach is on joint decision-making. For countries choosing to take part, the first step will be developing a common vision for the research area: setting out long term objectives based on expert guidance, stakeholder consultation, and foresight activities. It could equally be based on a joint evaluation of existing programmes and capacities.

Participants would work on agreeing a number of framework conditions: the procedures for peer review, the rules for cross-border funding and measures to protect IPR.

Once a common vision is established, they will draw up a strategic research agenda with specific measurable objectives. Although the Commission's Framework programme could be used to part finance projects, no new funding will be available, and all participating public authorities are expected to fund the research through their own programmes. For it to work, 'they must be willing to pool a proportion of their national funding for the initiative from the outset,' explains one Commission official. Other countries would be able to join in at this stage without having contributed to the common vision or research agenda.

The Commission will provide a secretariat for each of the initiatives proposed, facilitate meetings and if asked, provide expert advice or statistical data.

'IDEAS COME FROM SMALL GROUPS AND THIS INITIATIVE WILL REDUCE THEIR NATIONAL FUNDING'

Potential broad themes for joint programming include agriculture, food security and climate change; health, food and prevention of diet related diseases; protecting cultural heritage; living independently and actively in old age; and water challenges. Only two or three of these will be taken forward in spring 2010, along with the pilot initiative on Alzheimer's, for which participating countries are already establishing framework conditions.

Cancer research has been discussed as an area for joint programming in health from the offset. One target of the Commission's Cancer Partnership plan launched in autumn 2009 is to co-ordinate one-third of cancer research from all funding sources, by 2013. 'That's around 1.5 billion euro of funding,' said Janez Potočnik, EU research commissioner at the time. 'There's no way we can co-ordinate that amount without Joint Programming. Currently we co-ordinate 0.25 billon euro.'

Proposed by Italy, the first cancer research area being discussed is the development and optimisation of diagnostic and therapeutic strategies for cancer patients with a poor prognosis. Although there is broad consensus on the topic throughout the cancer community, the use of Joint Programming has received mixed reactions.

Chair of the European Cancer Research Managers Forum, Richard Sullivan says, 'The administration and organisational cost of running something like this has always been a huge, huge administrative headache.'

'To get people to the table you need to be very specific about what you do,' he adds. 'There are specific pieces of research that need to be transnational because it's the only way to get the science done. This is what Joint Programming should focus on.'

Sullivan agrees that strategies for poor prognosis is one such area, along with prevention epidemiology, paediatric oncology, and rare cancers.

Liselotte Højgaard (Rigshospitalet Hospital Copenhagen), Chair of the European Medical Research Councils Committee supports Joint Programming for all areas of medical research. 'People are more committed and more engaged when they buy in,' she says. 'There'll be a lot of politics and negotiation involved in picking the right area, but it's also important that it's a large enough area. You need to have a high enough number of good researchers that can command billions of euros. Otherwise the area gets supersaturated – the money can't be absorbed by researchers and then it goes to second class research.'

'PEOPLE ARE MORE COMMITTED AND MORE ENGAGED WHEN THEY BUY IN'

Håkan Mellstedt (CancerCentreKarolinska), former president of ESMO, thinks joint programming should not be used to develop a vision and strategic research agenda. 'The ideas and direction of research is very difficult to manage with a large consortium, it's always ineffective,' he says. 'It will be very difficult to unite people. Unless it's for testing the validity of hypotheses, then you can proceed much faster with a grouping like this. Ideas and directions come from small groups and excellent individual researchers and this initiative will only take national funding away from them.'

Saffina Rana
Brussels

Call for 'two way' translational research

Core knowledge about the development of cancer needs to be translated both into better treatments but also back into population-based research and work in prevention, according to the head of IARC (International Agency for Research on Cancer), Professor Christopher Wild.

'My plea is really for a 2 way translation,' he told delegates at a special session on European partnership for action against cancer at the Joint ECCO 15–34th ESMO Multidisciplinary Congress (Berlin, 20–24 September, 2009). Translational cancer research should come to mean taking new knowledge of mechanisms both into the clinic but also back into the population.

'There is a huge opportunity at the moment to take understanding from basic science about mechanisms of carcinogenesis and the molecular genetics of tumours and not only to translate that into better treatments but also to go back into population-based research and work in prevention,' he said.

'WE'RE MISSING A BIG OPPORTUNITY'

Increasing knowledge about the development of cancer not only gives clues to the susceptibility of a tumour to treatment, but also to the aetiology of that cancer. 'Some of the tools that are being developed can be applied into the population to help improve our knowledge about the causes of cancer,' he said.

Speaking later to *EJC*, Professor Wild when large trials identify genes involved in cancer development, commercial interest drives research into novel diagnostics and treatments. But research into aspects of the environment that alter genetic activity is not backed in the same way. 'We're missing a big opportunity,' he said.

Diet, for example, is known to lead to epigenetic changes which alter cancer risk, he said. 'But what is it that diet does to a cell to predispose it to cancer? How these changes occur and whether they can be reversed have not been thoroughly explored. We have some insights into the pathways being modulated, but we need to make sure that we explore epigenetic changes in basic science, as well as in the clinic. We could profit in both directions.'

The European partnership document states that one in three cancers is preventable and states that this is the most cost effective response. 'At the same time we know that 80–90% cancers have an environmental cause. The potential for prevention is much higher than 30% and one of my concerns is that we're taking the prevention agenda forward but forgetting perhaps that there's still a lot unknown about the causes of cancer.

Professor Christopher Wild

'In any of the common cancers a large proportion are of unknown aetiology. Along with studies about how to implement prevention we must carry through continued research into the cases of cancer so we increase that proportion where we have practical action to recommend,' he said.

At the first Presidential session of the Congress, Health Commissioner Androulla Vassiliou had given an excellent presentation 'in terms of the balance between the focus on prevention and treatment in cancer research'. But throughout the rest of the session, the language drifted back towards a patient focus and translational research into the clinical setting Professor Wild said: 'There is still a lot of work to do to carry this balance through into future practice.'

Nobel Prize for telomere and telomerase research

Three US scientists were awarded the Nobel Prize in Physiology or Medicine 2009 for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.

Professor Elizabeth Blackburn (University of California, San Francisco) and Professor Jack Szostak (Massachusetts General Hospital, Boston) discovered that a unique DNA sequence in the structures at the end of chromosomes – the telomeres – protects the chromosomes from degradation. Professor Carol Greider (Johns Hopkins University School of Medicine, Baltimore) and Professor Blackburn identified telomerase, the enzyme that makes telomere DNA.

'These discoveries explained how the ends of the chromosomes are protected by the telomeres and that they are built by telomerase', a statement from the Nobel Assembly at Karolinska Institutet said.

'If the telomeres are shortened, cells age. Conversely, if telomerase activity is high, telomere length is maintained, and cellular senescence is delayed. This is the case in cancer cells, which can be considered to have eternal life,' the statement read. 'The award of the Nobel Prize recognises the discovery of a fundamental mechanism in the cell, a discovery that has stimulated the development of new therapeutic strategies.'

Following on from these discoveries, it was suggested that cancer could be treated by eradicating telomerase. 'Several studies are underway in this area, including clinical trials evaluating vaccines directed against cells with elevated telomerase activity.

'In conclusion, the discoveries by Blackburn, Greider and Szostak have added a new dimension to our understanding of the cell, shed light on disease mechanisms and stimulated the development of potential new therapies,' the Nobel Assembly said.

The scientists will share the prize of 10 million Swedish Kronor (almost 1 million Euros).

PODIUM

'The tide is turning' in the breast screening debate

Hazel Thornton was diagnosed with Ductal Carcinoma in Situ (DCIS) after attending population breast cancer screening in 1991. She declined an invitation to join the UK DCIS trial, concerned about aspects of trial design and the inadequacy of the information provided to potential participants. She has since published and presented widely and she is a Fellow of the UK's Royal Society of Medicine.

What do you see as the problem with the UK's Breast Screening Programme?
Its failure to provide balanced information to women being invited. It should provide leaflets that fairly set out evidence about the harms, risks, limitations and consequences of mammographic screening, as well as the potential benefit, so that women can make a proper informed decision on whether to attend.

What are the potential harms of screening?
Over detection, over treatment, exacerbation of fear, and lack of a sensible, evidence-based approach to early detection of disease. It stems from the general social trend to screen ever more intensively. The harder you look for anything the more you are going to find.

Breast cancer is a whole spectrum of disease and mammography screening is a very crude tool to use in an entire population-group of healthy women. Researchers have shown that the mortality rate from breast cancer is not hugely different across a range of countries including North America, Australasia, Europe, Asia and Africa *(The Breast 2008: 17; 217–9)*. The incidence rate, however, differs enormously, with North America topping the chart. Of course there are various factors at work but the overall message is that the more vigorously you screen a population, the more breast cancers you will find, but there will be a diminishingly small effect on mortality.

Screening programmes have done a lot of good in sharpening up diagnostic processes, but they have also done considerable harm.

How would better information for participants make a difference?
In the UK, we have had mammography screening for 20 years and women have never been given the information they would need to make a reasoned decision. You can't make a decision if you're not given all necessary facts. It doesn't treat women with dignity. Women's groups do the same thing when they purport to speak for women, which can be disrespectful and terribly patronising. Women are all different but they need access to good evidence-based facts and figures on potential benefits and harms. Many won't want the information; others will want every last statistic. But assumptions shouldn't be made about what 'all women' want.

Would this information encourage women to decline screening?
Not necessarily, but it is not wrong to say no. Each woman should be enabled to make her own decision according to her views and cultural attitudes. When screening was first established it was thought proper for doctors to be paternalistic but there's been a vast shift in the doctor-patient relationship since then.

It is still thought in some quarters that if women are told about all the harms and benefits, they won't go for screening. But it's not true. Some may decide not to but others will still go for screening and that's how it ought to be.

Is this a UK-specific debate?
No; it has certainly been taken up in the US and Australia. Discussion is becoming wider and more open and – even if it's sometimes heated – that is certainly a good thing. We'll only make progress by constantly exploring all evidence and viewpoints.

What progress is being made?
Following a letter written by 23 like-minded people to a national newspaper (*The Times, 19th February 2009*) the leaflet given to women invited for screening (*Breast Cancer: The Facts*) is now being rewritten. We're hoping that women will be informed about DCIS when invited. Further, we'd like to see all evidence sources referred to in the new leaflet, so that there's transparency about how figures have been arrived at. The UK *The Facts* leaflet claims 1,400 lives are saved per year but it doesn't say where the figure comes from. Transparency is essential to facilitate discussion. At the moment, it's belief versus reason, but the tide is turning.

Will new scanning methods alter the situation?
It isn't about modes of screening; it's about knowing what you are looking for. We understand more now about which DCIS are likely to progress and which are not. Invasive cancers don't necessarily kill women either. More basic research would clarify which cancers will progress, but we're not there yet.

What do you think needs to happen now?
We need a calmer, more measured debate, encouraging those with opposing views to collaborate. We also need more qualitative research to discover why people do what they do. There's such a lot we don't know. In the UK, the latest NHS Annual Review found a slight decline in acceptance among the women invited for the first time; the rate has dropped below 70% for the first time in 20 years. Women are not silly. They might not know all the statistics but they pick up on the vibes surrounding this debate. They're asking for better information now, to make up their own minds whether to attend.

Helen Saul