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Sharp Decline in US Breast Cancer Rates

The incidence of breast cancer among US women dropped significantly in 2003, following a marked reduction in use of hormone replacement therapy (HRT). Data presented at the 29th Annual San Antonio Breast Cancer Symposium (San Antonio, USA, 14th–17th December, 2006) backs the idea that women who discontinue HRT may reduce their chances of being diagnosed with breast cancer.

The analyses were based on the National Cancer Institute (NCI)'s Surveillance Epidemiology and End Results (SEER) data. Dr. Peter Ravdin (MD Anderson Cancer Center, Houston, Texas) said that breast cancer incidence in the US increased at 1.7% per year from 1990 to 1998. Between 1998 and 2002, incidence decreased at 1% per year. In 2003, there was a 7% decrease (6% in the first half of the year and 9% in the second half).

This drop in breast cancer incidence followed a steep reduction in HRT use prompted by publication of data from the Women's Health Initiative in 2002 (*JAMA* 2002;**288**:321–333). It linked long-term use of conjugated oestrogen-progesterone HRT to increased risk of invasive breast cancer.

Further subset analyses conducted by Dr. Ravdin and colleagues (*Proc 29th San Antonio Breast Cancer Symposium 2006 #5*) established that the decline in incidence in 2003 relative to 2000/2001 was most evident in women more than 50 years old (a 1%, 11%, 11% and 7% decline was seen for women in their 40s, 50s, 60s and 70s, respectively).

The decline in incidence in oestrogen receptor (ER)-positive invasive tumours was greater than for ER-negative tumours (8% versus 4%). When the analysis was restricted to patients 50–69 years of age, the difference in decline in incidence by ER status was more striking (12% versus 4%).

A similar study was published just before the San Antonio Symposium (*Jnl Clin Oncol doi:10.1200/JCO.2006.08.6504*). Scientists at the Northern California Cancer Center and at health insurer Kaiser Permanente used more recent data, up to 2004, from the California Cancer Registry. Dr. Christina A Clarke (Northern California Cancer Center) led the study and said that HRT use "dropped 68 percent between 2001 and 2003, and shortly thereafter we saw breast cancer rates drop by 10 to 11 percent. This drop was sustained in 2004, which tells us that the decline wasn't just a fluke."

"Based on what we know about the biology of hormone therapy [HRT], the declines make a lot of sense and we want to continue to track these parallel trends," she said.

Dr. Lisa Herrinton, from Kaiser Permanente's Division of Research said they could not conclude that HRT use caused the decline in breast cancer, because these data don't link HRT users directly to breast cancer diagnoses, "but they are certainly suggestive. If it holds up over time, a 10 percent decline in breast cancer incidence is really striking."

Rogue Gene linked to Breast and Childhood Cancers

Women who inherit one damaged copy of the DNA-repair gene PALB2 have double the normal risk of developing breast cancer, say UK researchers. When, rarely, children inherit 2 damaged copies, they develop a new subtype of Fanconi anaemia, which is characterised by a high risk of childhood solid tumours including medulloblastoma and Wilms' tumour.

Professor Nazneen Rahman (Institute of Cancer Research, Sutton, Surrey) and colleagues looked for faults in the PALB2 gene in 923 women with breast cancer and a family history of the disease which was not caused by the known breast cancer genes BRCA1 and BRCA2.

They found faults in PALB2 in 10 breast cancer patients, and in none of the 1084 healthy women controls. This difference, which is bigger than expected by chance, indicates that the PALB2 mutation is linked to some cases of breast cancer (*Nature Genetics 2006 doi: 10.1038/ng1959*).

In a second study (*Nature Genetics 2006 doi: 10.1038/ng1947*), researchers studied 82 children with Fanconi anaemia that was not due to any of the 11 genes previously known to be responsible. Seven children had inherited faults in both copies of PALB2 and belonged to this new subtype.

Professor Rahman: "Not only have we found that carrying a single faulty version of PALB2 leads to a small increased risk of breast cancer, but also that carrying two faulty copies of the gene is related to an aggressive form of the childhood disorder Fanconi anaemia."

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Clinical Trials Directive Slows Registration of Paediatric Studies

Registration of new non-commercial paediatric trials in Europe—essential for optimising paediatric treatments—has fallen since the Clinical Trials Directive 2001/20/EC was implemented, according to sarcoma experts meeting in Stuttgart, Germany (Nov 30–Dec 2, 2006). "Before implementation, 10–20 studies were opened per year in the UK, but this has now fallen to just a handful", says Kathy Pritchard-Jones (Royal Marsden Hospital, London, UK). "Treatment within a trial is associated with definite survival advantage and, with fewer trials available, we must fear cure rates in Europe will decline as a direct consequence of legislation which was originally intended to protect patients", Stefan Bielack (Olgahospital, Stuttgart, Germany) told *The Lancet Oncology (TLO)*.

Because the 2001 legislation was a directive it became mandatory for European Union member states to adopt the legislation by May 2004. The directive's aim was to simplify and harmonise administrative procedures governing trials and to provide patient protection by setting pan-European legal standards. However, although stakeholders were slow to react initially, there has been growing concern about how this legislation might hamper the running of non-commercial academic trials, particularly those in children. "Trials in children are particularly disadvantaged because these cancers are often complex heterogenous diseases requiring complex multimodal treatments, and are rare diseases requiring wider international collaboration", says Jeremy Whelan (University College Hospital, London, UK). Many trials in children try to optimise treatment rather than test new drugs. Bielack notes: "These treatments for children are not lucrative and nobody is willing to finance the extra costs or to assist in managing the exponentially increased bureaucratic workload". According to Herbert Jürgens, from the University Children's Hospital in Muenster, Germany, the Commission Directive 2005/28/EC set-out guidelines for good clinical practice and addressed some of these initial concerns, but this later directive did not exempt trials optimising treatments from full compliance with the 2001 directive.

Another issue, Bielack told delegates at the Stuttgart meeting, is that the directive requires a single sponsor to take overall responsibility for initiating and managing the trial, including all of the legal, ethical, and financial aspects, thereby taking on all the liability for no commercial benefit. Furthermore, Jürgens told *TLO* that 50–90% of medicines have never been evaluated in children and are classified as investigational medicinal products (IMPs) because they are often used outside their marketing indications. "The need for trials in children to develop paediatric medicines is gaining global recognition to avoid such off-label use, with its associated potential for inappropriate dosing and unforeseen adverse drug reactions."

In any trial, the sponsor has to report suspected unexpected serious adverse reactions (SUSARs) associated with IMPs to the competent authority, to the ethics committee, and to all investigators within 15 days of knowledge of a non-fatal event. But in Germany, Bielack commented, another level of bureaucracy has been added: "The same reporting requirements are mandatory for SUSARs from other studies investigating the same IMP." He cites as an example the use of interferon in the EURAMOS1 trial – a multinational collaborative study in children with osteosarcoma, launched under the new directive, of which he is the co-ordinator. "Interferon is used in a multitude of completely unrelated diseases and in adults [including] elderly patients with significant comorbidity. From the experience of the first 10 months of our trial, we have extrapolated that 180 000 pages of often irrelevant information on SUSARs will be distributed through-out Germany. This is like a polymerase chain reaction for waste paper and is bound to lead to a desensitisation for any real toxic-effects data."

Nonetheless, those at the Stuttgart meeting acknowledged the directive has resulted in a better structuring of multinational trials, and they highlighted the success of EURAMOS1. According to Mariana Resnicoff (co-ordinator of the European Science Foundation's European Collaborative Research Programme on pan-European Clinical Trials that provided funding for EURAMOS), "The experience gathered by the EURAMOS investigators could serve to pave the way for future pan-European academic clinical trials". Bielack agrees: "The EURAMOS group has developed strategies to deal with issues such as sponsorship and pharmacovigilance that might be applied to other trials and a single European safety desk for paediatric oncology trials should be considered".

To help future trials in Europe, the European Medical Research Councils are participating in a consultation initiated by the European Commission–Directorate General Enterprise and Industry on a paper *Draft guidance on specific modalities for non-commercial trials*, which was released for comment in June 2006.

Emma Cannell

This story originally appeared in Lancet Oncol 2007;8:10.

Mobile Phones: "No Large Risk"

Any large association of risk of cancer and cellular telephone use "can be excluded", say Danish researchers (*Jnl Nat Cancer Inst* 2006;**98**:23;1707–1717). They followed a nationwide cohort of 420,095 people for up to 21 years.

The study included those whose first cellular telephone subscription was between 1982 and 1995. It found no evidence for an association between cancer risk and mobile phone use among either short-term or long-term users.

A total of 14,249 cancers were observed. Rates among study participants were compared with those expected in the Danish population. The study found no association between mobile phone use and brain tumours, acoustic neuromas, salivary gland tumours, eye tumours or leukaemias. Among those who had subscribed for 10 years or more, there was no increase in brain tumours and no trend with time since first subscription.

The researchers acknowledge that mobile phone users who started subscriptions in the mid-1980s appeared to have a higher income and to smoke less than the general population. Nevertheless, they conclude: "The narrow confidence intervals provide evidence that any large association of risk of cancer and cellular telephone use can be excluded."

EUROFILE

Framework 7: Back on Track

The formal adoption on second reading of the 7th Framework Research Programme (FP7) by the European Parliament on 30 November, 2006, followed years of wrangling between the institutions involved. But, finally, Europe's biggest-ever research programme looked set to start in January, 2007, after FP6 ended on 31 December, once it had been adopted by the Council on 5 December. The Commission was due to formally adopt the work programmes and publish the first call for proposals before Christmas, 2006.

Amendments accepted by the Parliament in plenary session ensured that children's health, respiratory diseases, and neglected diseases would receive funding; attempted to ease the participation of small and medium sized enterprises (SMEs); and gave increased emphasis to the scientific training role of the Joint Research Centre (JRC).

"It is a great day," said Research Commissioner Janez Potočnik. The timely adoption of FP7 "will send a strong message to the scientific community, to industry and to the public at large".

The major changes compared with FP6 are the European Research Council (ERC), which "brings new logic" into the European Research Area (ERA), said Potočnik, referring to the fact that funding and other decisions by ERC will be taken by scientists only. This means that no political considerations will be taken into account when deciding on allocation of the ERC funds. "I think this is a major step forward for Europe and I hope this kind of new logical approach will bear fruit also in other discussions in other areas," added Potočnik.

The programme will have an overall budget of more than €54 billion over 7 years, and represents a 40% yearly increase in real terms compared with FP6. Health research gets one of the biggest shares of the money available, at €6 billion. "The FP7 constitutes a strong signal that promoting research and innovation has finally become a top priority for the EU", said the Parliamentary rapporteur, Polish MEP Jerzy Bucek. "We've made a clear choice; Europe wants to bet on R&D. Even though the budget could have been bigger, the increase in research financing is still the highest among all the EU programmes. It seems that something has changed for the better in relation to delivering Lisbon objectives. We want innovation to become the major slogan for FP7."

One area that remains controversial, however, is the funding for embryonic stem cell research. Speaking at the Parliamentary debate on 29 November, 2006, Commissioner Potočnik said that the Commission intended not to fund projects including research activities which would bring about the destruction of human embryos. "The exclusion of funding of this step of research will not prevent Community funding of subsequent steps involving human embryonic stem cells..... the FP7 decision refers to derivation, the Commission will not fund the activity of derivation which involves destroying a human embryo. The agreement on ethics reflects a careful and responsible balance", he said.

''INNOVATION HAS FINALLY BECOME A TOP PRIORITY FOR THE EU''

Simpler instruments and procedures for funding and participation are a feature of FP7, which will promote collaborative research based on broad research areas, with much continuity from FP6 plus two new topics, space and security. Funding will be organised around 4 specific programmes:

* *Co-operation*: a programme to support cooperation between universities, industry, research centres and public authorities, and between the EU and third countries.

* *Ideas*: a programme to create an autonomous European Research Council to support investigator-driven "frontier research".

* *People*: a programme to support training and career development of researchers.

* *Capacities*: a programme focusing on the coordination and development of research infrastructure, support for regional research clusters, SMEs, closer ties between science and society and international cooperation.

€7.5 billion is allocated to the ERC over the 7 years of FP7, leaving it with just over €1 billion a year to spend which many researchers consider the minimum for a viable funding agency, says Helga Nowotny, vice-chair of ERC's scientific council.

Jerzy Buzek is optimistic. "I am strongly convinced that the new proposed instruments and mechanisms have the potential to put Europe at the vanguard of global knowledge-based economies. Their implementation in the coming years will illustrate what can be created out of this potential", he said.

Far from taking a well-earned break, Messrs. Potočnik and Buzek are continuing to bang the drum for European research. The programme may now be all but implemented, but: "This is a non-stop, constant journey," said Potočnik, whose focus is now longer term. At a press conference on 30 November, 2006, he told journalists to look out for a new debate on the European Research Area (ERA) in 2007. Then in 2009 there will be a debate on the financial perspectives of the European Union. "This will be connected with the debate on the future of Europe. We have to be prepared," he said, prepared to illustrate to policy-makers exactly how important investment in research is for Europe's competitiveness.

''WE HAVEN'T FINISHED YET. THE WORK STARTS TODAY''

According to Mr. Buzek, "We haven't finished yet. The work starts today." The next step is to implement the programme, he said. And then, "We have to convince national governments, policy-makers, researchers, society that this is a good programme. We have to breathe new life into European research."

Mary Rice,
Brussels

Alemtuzumab versus Chlorambucil

Treatment with alemtuzumab (MabCampath) achieves significantly greater improvement in progression free survival than chlorambucil in patients with previously untreated B-cell chronic lymphocytic leukaemia (B-CLL), according to a study reported at the 48th Annual Meeting of the American Society of Hematology. (December 9–12, 2006, Orlando, Florida).

The international phase III CAM 307 study randomised 297 patients to alemtuzumab or chlorambucil. Alemtuzumab targets the CD52 antigen, which is upregulated in B-CLL, but the monoclonal antibody is not currently licensed to treat the condition. Chlorambucil is an alkylating agent and is the current standard first-line therapy.

Results from the open-label study (*Proc Am Soc Hem 2006 #301*) showed that progression free survival was significantly improved in patients treated with alemtuzumab compared to those given chlorambucil. Risk of disease progression or death was reduced by 42% with alemtuzumab compared to chlorambucil ($p = 0.0001$). The overall response rate was nearly 30% greater with alemtuzumab (83%) than with chlorambucil (55%); and complete response occurred in 24% of patients treated with alemtuzumab, compared to only 2% of those given chlorambucil.

Lead investigator, Dr. Peter Hillmen, (Leeds Teaching Hospitals NHS Trust, UK), said: "This study demonstrates that alemtuzumab is superior as a first-line therapy compared to chlorambucil."

Nine patients from the 34 showing complete response with alemtuzumab had no detectable minimal residual disease (MRD), with 8 of these showing no disease progression at a median follow-up of 2 years. This was not achieved in any of the three patients showing complete response with chlorambucil.

There were no significant differences in grade 3/4 thrombocytopaenia, anaemia or febrile neutropaenia between the two treatments. The most common grade 3/4 treatment-related adverse events in patients given alemtuzumab were infusion-related reactions associated with intravenous administration. Dr. Hillmen said: "The results support ongoing investigations of alemtuzumab in first-line combination therapy and as consolidation therapy."

Susan Mayor

Dasatinib versus Imatinib

The START-R study comparing dasatinib (Sprycel) versus escalated doses of imatinib (Glivec) in patients with chronic phase chronic myeloid leukaemia (CML) showed significant improvements in progression free survival for dasatinib at 15 months, according to results presented at the American Society of Hematology (ASH) meeting. The data formed part of the licence application for dasatinib, which received its EU licence in November, 2006.

In the open label randomised study, 150 patients with chronic phase CML with primary or acquired resistance to imatinib were randomized in a 2:1 ratio to dasatinib (n = 101) or imatinib (n = 49). At 15 months, the number of patients achieving a major cytogenetic response was 53% for dasatinib versus 33% for imatinib. The number achieving complete cytogenetic response was 40% for dasatinib versus 16% for imatinib and the number achieving major molecular response was 16% for dasatinib versus 4% for imatinib. Progression free survival results show 6% of patients taking dasatinib progressed, compared to 20% taking imatinib.

Similar side effects were observed between the two groups, although - pleural effusions were only seen in patients taking dasatinib.

"The overall risk benefit analysis favours dasatinib. Physicians should consider treatment with dasatinib in patients resistant to lower doses of imatinib," said principal investigator Professor Neil Shah (University of California, San Francisco, USA).

Janet Fricker

Genotype Predicts Survival from AML

Genotype is the strongest predictor of survival in adults with acute myeloid leukaemia (AML), according to a US study (*Proc Am Soc Hem 2006 # 4*). Researchers from Long Island Jewish Medical Center and Albert Einstein College of Medicine evaluated leukaemia cells in 872 AML patients.

They found the most common genetic abnormalities were NPM1 mutations (53%), FLT3 (31%) and CEBPA mutations (14%). Of those with the combination NPM1-positive and FLT3-ITD-negative genotypes, about 60% remained relapse-free after 4 years, whether or not they had received a stem cell donation.

Among those with other combinations of NPM1 and FLT3 mutations, relapse-free rates dropped to 47% for those with a donor, and to 23% for those without. Researchers believe the new data could allow a more tailored therapeutic approach for these patients.

JF

Rituximab in NHL

The addition of rituximab (MabThera) to CVP chemotherapy significantly improves survival in previously untreated advanced follicular non-Hodgkin's lymphoma patients, according to Canadian researchers (*Proc Am Soc Hem 2006 # 481*).

In a phase III study, 321 patients were randomised to eight cycles of rituximab plus CVP or to CVP alone. Of those who received additional rituximab, 81% were alive at 53 months, compared to 71% receiving chemotherapy alone ($p = 0.03$). Median time to progression or death in the R-CVP arm was 34 months compared to 15 months in the CVP arm ($p < 0.0001$).

"This is clear evidence that addition of rituximab to first line chemotherapy not only extends the time patients are free from disease, but lengthens their lives," said principal investigator Dr. Kevin Imrie (Toronto-Sunnybrook Regional Cancer Centre, Canada).

JF

Burkitt Lymphoma responds to EPOCH-rituximab

A study from the US' National Cancer Institute had promising results with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)-rituximab in patients with Burkitt lymphoma (BL) – a rare but aggressive cancer that is the commonest childhood cancer in Africa.

The study included 17 patients with untreated BL. Nine had advanced disease (stage III/IV), and 11 had disease that had spread to other organs. All achieved complete remission, which was sustained for an average follow-up of 28 months (*Proc Am Soc Hem 2006 # 2736*).

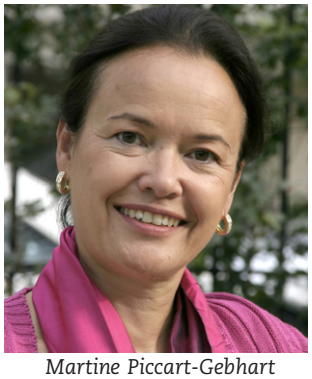
"These preliminary results suggest that DA-EPOCH-R is highly effective in treating Burkitt lymphoma and is very well tolerated in all age groups," said Dr. Kieron Dunleavy (NCI, Bethesda, Maryland, USA). "DA-EPOCH-R represents a fundamental departure from standard chemotherapy strategies and may significantly advance the therapeutic index of Burkitt lymphoma treatment."

SM

Susan Mayor was sponsored by Genzyme Corporation and Schering AG; Janet Fricker was sponsored by Bristol Myers Squibb.

PODIUM

The Future of EORTC



Martine Piccart-Gebhart

Martine Piccart-Gebhart is Director of Medicine at the Institut Jules Bordet (Brussels, Belgium). In 1996, she founded the Breast International Group (BIG), which now coordinates 38 clinical research groups based primarily in Europe, South America and Australasia. Dr. Piccart-Gebhart is an elected member of the ASCO Board and took over as President of EORTC in June 2006.

What shape is EORTC in?
EORTC went through a financial crisis but is in reasonably good shape again. The crisis stimulated brainstorming on the mission of the organisation, where we should devote our energy, and the direction of our research. This organisation has existed for more than 40 years and needed to adapt to a rapidly changing landscape.

What came out of the brainstorming?
We defined 5, 4 and 3 star clinical trials. Our goal is for one-third of our trials to be 5-star i.e. they can lead to changes in clinical practice, have a strong translational component, and address an important issue in patient management. The MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) trial is 5 star; it is investigating the selection of patients for adjuvant chemotherapy using gene signatures.

A second conclusion was that EORTC has too many centres which are not truly active in the organisation and create an administrative burden. On the other hand, our geographical distribution is imbalanced and we need to reinforce our collaboration with centres in northern, eastern and southern Europe.

How far have the aims been met?
We are disseminating information, we've had meetings with the Board, the Chair of the Protocol Review Committee (who conducts an independent review of all protocols submitted) and we're starting individual interviews with key people in the organisation, namely the Chairs of the groups. It will take at least 2 years.

What is the situation now?
The challenges we face are the same for other groups; we need to do translational research in clinical trials, which means overcoming financial, legal, and ethical barriers, and involving pathologists, surgeons, and so on, in each centre. But it is better to do 1 or 2 trials with a translational component than 10 trials without!

A lot of targeted drugs will be developed in the coming years. If we don't know who really needs them, we will face an exponential increase in drug costs that health care reimbursement systems may not able to cope with. Governments should help organisations like EORTC, because the money invested in these trials may be recovered once the new drug is licensed. We know from observations that only about half the *her2*-positive patients with advanced breast cancer benefit from trastuzumab, and the same probably applies in the adjuvant setting. With more extensive translational research in the adjuvant trials, we might have identified gene signatures associated with clear benefit or failure. It's frustrating.

Will this change?
The pharmaceutical industry has to show that, on average, a drug conveys a statistically significant benefit. Regulatory agencies don't currently ask for the profile of the patients who really benefit, but this may come. Some pharma companies are investing in translational research but the best model is a partnership with academic networks, to protect patients and to make sure that everything discovered is published. EORTC also needs to improve its efficiency to be more attractive to industry.

How does EORTC interact with BIG?
Some national groups such as the UK and Germany are extremely well organised, and capable of running large clinical trials efficiently. Some studies can best be done nationally, with a lower administrative burden than at European level. Others clearly need a large European-based network.

BIG is a consortium group which addresses the situation. The EORTC breast group is a member, and often plays an important role but it is not always the lead group. If a clinical trial is looking at a subgroup of those with a frequent tumour type (only one-fifth of those with breast cancer are *her2*-positive) then intergroup collaboration – the BIG model – may be the answer.

I'm encouraging colleagues in other frequent tumour groups such as colon and lung to consider this approach. We need to find models of collaboration that will enable Europe to compete with other continents.

In rare tumour types, the situation is different and one of EORTC's strengths lies in studying brain tumours, sarcoma, and melanoma. We have conducted important trials in these tumours in short periods of time.

Everybody will have a rare tumour once molecular biology takes off?
Breast cancer is already 5 very different molecular diseases. We need the courage to design prospective trials for different subgroups, rather than trying to understand retrospectively which groups benefited. But we're not there yet and few trials have adopted this philosophy.

Are you enjoying your role at EORTC?
It is a great privilege. I have worked in the organisation a long time and clearly see its strengths and weaknesses. I want it to be a better organisation in 3 years' time than it is today; that is an exciting goal.