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Mammography: Consensus in sight?

The debate on the value of screening for breast cancer is showing signs of reaching, if not a conclusion, at least a compromise solution. Confusion and controversy have reigned since the publication of a report from the Nordic Cochrane Center, Denmark, which concluded that there is 'no reliable evidence' that screening reduces mortality (*Lancet* 2000, **355**, 129–134). A later report from the same group (*Lancet* 2001, **358**, 1340–1342) 'confirmed and strengthened' this and added that mammography may actually be detrimental, as it results in the over-treatment of women.

However, a Working Group convened by the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO) (Lyon, 5–12 March 2002) stated that there is sufficient evidence for the efficacy of mammography. Screening programmes reduce mortality by about 35% among women between 50 and 69 years, it said. The group, which consisted of 24 experts from 11 countries, added that there is 'only limited evidence' for a reduction in mortality among women aged 40–49 years.

"CURRENT EVIDENCE SUPPORTS IT'S EFFECTIVENESS"

The original report from the Nordic Cochrane Center discounted 7 trials involving half a million women from the review, saying they were flawed. Other Cochrane researchers took issue with aspects of the review and insisted on modifications before it was published in the Cochrane Library.

The debate continued at the 3rd European Breast Cancer Conference (Barcelona, 19–23 March 2002). Dr Robin Wilson, secretary of the European Group for Breast Cancer Screening, said, "Whatever the issues are surrounding the claims and counterclaims about the validity of the trials and the review, the fact is that we have moved on a long way since the randomised trials that contributed to the review. Current evidence based on actual screening outcomes strongly supports its effectiveness," he said.

Professor Michael Baum (University College London) countered that the data included in the review are "the most complete available". Any improvements since they were collected need to be tested in further randomised controlled trials. The best estimate is that women have a one in a thousand chance of having their life saved by 10 years of screening. That must be set alongside the hazards of false alarms, unnecessary biopsies, the over diagnosis of borderline pathology and its over treatment, he said.

Dr Chris de Wolf (Geneva University) said that one of the problems with the review was that it had polarised discussion between the pro- and anti-screening camps. "Polarisation brings in emotional elements and this is blurring scientific objectivity. It is important in the current discussion to distinguish between the scientific, political and public health aspects," he said.

Countries which have introduced national screening programmes (including the UK, The Netherlands, Sweden, Finland, Luxembourg) are the only ones in Europe to show a clear reduction in breast cancer mortality. Dr de Wolf: "Maybe the results are not solely attributable to screening intervention, but the whole chain of prevention, cure and care has been made very effective and transparent and this may have nourished these results."

Dr Wilson agreed that screening programmes lead to the development of specialist multi-disciplinary teams who become highly skilled at diagnosing, treating and managing the disease. He also stressed that it was important to acknowledge that there could be drawbacks to screening. "Women must be properly informed about the benefits and disadvantages so they can decide for themselves whether they want to be screened. What is right for governments, who naturally tend to concentrate on benefits to the population as a whole, might not necessarily be right for the individual," he said.

"HAZARDS INCLUDE FALSE ALARMS, UNNECESSARY BIOPSIES AND OVER TREATMENT"

Capecitabine approved

The European Commission has granted marketing authorisation for capecitabine (Xeloda) for the treatment of metastatic breast cancer. Capecitabine monotherapy was approved for use after failure of intensive chemotherapy; the combination of capecitabine with taxotere was approved after failure of anthracycline treatment.

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3rd European Breast Cancer Conference, Barcelona, 19–23 March 2002

Music, drama and art were woven into the programme of the 3rd European Breast Cancer Conference in Barcelona (19–23 March) to illustrate the theme of 'Breast Cancer and the Humanities'.

Europa Donna, the European Breast Cancer Coalition, the EORTC Breast Cancer Group and the European Society of Mastology (EUSOMA) united again to organise EBCC-3, under the co-ordinating umbrella of the Federation of European Cancer Societies (FECS).

IBIS reports

Professor Jack Cuzick presented preliminary results from the International Breast Cancer Intervention Study (IBIS), which is looking at the use of tamoxifen to prevent breast cancer in 7000 healthy women at high risk of developing the disease.

Prof. Cuzick, from Cancer Research UK, told the conference that the incidence of breast cancer was reduced by a third in the women taking tamoxifen in the IBIS trial, with 68 cases of breast cancer compared with 101 among women taking the placebo.

When the results of four prevention trials were combined (IBIS, NSABP P1 Tamoxifen Prevention Trial in the US, the Royal Marsden Hospital chemoprevention trial and the Italian National Trial), Prof. Cuzick said the overall reduction in the incidence of breast cancer was 38%. In addition, results from nine trials using tamoxifen as an adjuvant treatment in breast cancer patients showed a slightly greater reduction (46%) of second cancers in the opposite breast.

But Prof. Cuzick warned that while the benefits of using tamoxifen to treat breast cancer patients was indisputable, IBIS still gave no conclusive answer as to whether the benefits outweighed the side effects for prevention in healthy women. "It is essential to continue to follow the participants to see if a particular group of high-risk women can be identified for whom the benefits of tamoxifen clearly outweigh the risks," he said.

IBIS was in line with other tamoxifen trials in showing a 2–3-fold increase in endometrial cancer and a similar increase in the risk of thromboembolism for women taking tamoxifen. When results from all the prevention trials were combined there was no effect on deaths from all causes, with 112 deaths in the tamoxifen arm and 122 in the placebo arm. However, there were variations, with statistically non-significant reductions in deaths in two trials, no difference in one trial and a statistically significant excess of deaths in the IBIS trial. He said the increase in deaths in the IBIS trial was "likely to be a chance finding".

Microarray predictions

Microarray technology is making a rapid impact on breast cancer research, said Dr Laura van 't Veer, of the Netherlands Cancer Institute. She told delegates the technology could help predict which breast cancers would metastasise, and this meant that the numbers of women who receive adjuvant chemotherapy could be reduced by between 30 and 40% in the future.

Dr van 't Veer and her team had validated data on a series of 73 patients diagnosed with lymph node negative breast cancer under the age of 55. She identified a "poor prognosis" signature consisting of genes involved in cell cycle, invasion and angiogenesis. "We have confirmed that we can predict with 90% certainty that a patient will remain free of breast cancer for at least five years," she said.

At present 90% of younger women with lymph node negative breast cancer receive adjuvant therapy, but 70–80% of these women would have remained disease-free without this treatment. Dr van 't Veer said: "Our 'poor prognosis' signature provides a novel strategy to accurately select patients who would benefit from adjuvant systemic therapy and can greatly reduce the number of patients that receive unnecessary treatment."

Future threats

Professor Michael Baum, chairman of EBCC-3, concluded the conference with a debate on threats to cancer research; these included increasing bureaucracy, EU regulations on clinical trials, the revised Declaration of Helsinki which branded some legitimate clinical research as unethical, and the activities of animal rights groups.

The debate was preceded by a satirical play entitled *2084*, written by Prof. Baum and based on George Orwell's *1984*. Some recognisable faces among the performers included the author as 'Winston Smith'—an oncologist whose attempts to carry out clinical research bring him into confrontation with the Ministry of Truth and Health—and Dr Martine Piccart as 'Martine Quickstart'.

The debate explored abuse, education (both of consumers and politicians), bureaucracy, advocacy, the recruitment of young scientists, and the needs of developing countries. A working group, headed by Professor Baum, will draw up a statement on the issue which, in collaboration with the patient advocacy group Europa Donna, they plan to present to the European Parliament.

Further information about the conference can be found on the FECS website: http://www.fecs.be/conferences/ebcc3

Emma Mason, Barcelona

Promising marker in invasive breast cancer

Lympho-vascular invasion (LVI) is a promising prognostic indicator in lymph node negative invasive breast cancer, according to researchers from Nottingham City Hospital, UK.

Researchers tested LVI status in 3931 women with primary operable invasive breast cancer, presenting between 1973 and 1998. They found that 43% of those with lymph node positive disease had LVI, compared with only 17% of the 2309 lymph node negative cancers. In the latter group, 10-year overall survival was 67% for women with LVI +ve tumours and 79% for those with LVI−ve tumours.

The marker retained independent significance in multivariate analysis and Dr Lee concluded, "LVI appears promising in adding prognostic discrimination in lymph node negative invasive breast cancer."

EUROFILE

Europe against Cancer: What's next?

The Europe against Cancer programme, greeted with such enthusiasm and high hopes at its launch in 1986, is giving up the ghost without any great outpouring of grief in the oncology community. It was considered by the European Commission to be an old-fashioned 'vertical' programme, unable to reach out across disease areas like the 'horizontal' measures now proposed. Nevertheless, its demise leaves gaps which will be difficult to fill.

Europe against Cancer aimed to support public information programmes, standardise data collection, facilitate exchange of experience and of individuals in order to disseminate best practice, create information networks, conduct pan-European studies, and, perhaps particularly importantly, establish effective quality control for early detection and prevention of cancer.

The European Society for Therapeutic Radiology and Oncology is one of the professional organisations which took advantage of this emphasis on quality control. "We have had a lot of support for different projects which we set up under the programme," says Professor Harry Bartelink, head of the radiotherapy department at the Netherlands' National Cancer Institute, and ESTRO President. "The courses we were able to run, and the exchange programmes we set up with support from Europe against Cancer, have led to huge improvements in radiotherapy standards across the whole of Europe."

"RADIOTHERAPY STANDARDS IMPROVED ACROSS EUROPE"

Other oncology specialities seem to have been less able to benefit from Europe against Cancer. The new 6th Research Framework creates possibilities for quality assurance programmes to continue, says Bartelink and "the challenge is to see whether others—for example, medical oncologists—take it up."

Why should the take-up of Europe against Cancer have been so limited? A quick glance through recent projects shows a plethora of tobacco control activities, a comprehensive system of cancer registries across Europe, epidemiological research related to diet and cancer, and, indeed, many projects connected with radiation oncology. The programme came under the Public Health Framework, rather than a research directorate which may have contributed to the general lack of enthusiasm from mainstream oncology. Or it may have been that they applied but didn't get the grants.

Oncologists were reluctant to comment on this, and many had a misconception of what was allowed under the programme. Some may have considered it too 'political', insufficiently concerned with medical science, or even just too high profile. This feeling may have led the Commission to dismiss the vertical programmes as not being sufficiently relevant to today's health needs.

If this is so, it is a great shame for people with cancer. Some of the programmes funded through Europe against Cancer have made far more difference to the lives of European patients than anything to have come out of DG Research. "We will miss the programme" says Bartelink. "Thanks to it, more than half the young European radiotherapists practising today have had the benefit of learning about quality assurance. And that in turn means that patients are benefiting from treatment which is now of the standard which previously was only available in the very best centres."

The new public health framework programme contains three strands:

- creating health information for all
- tackling health threats together
- health determinants, the key to health for all.

Unlike previous programmes it is not explicitly related to particular diseases, but it seems clear from a cursory reading of the text that inventive applicants can ensure that cancer continues to be well represented, in public education, research and data collection. Of course, the new Research Framework Programme will also support cancer research (See Eurofile, *EJC* News 2002, issue 4).

The health of Europe's citizens is at the heart of the success of the European Union. The influential European Public Health Alliance Participation says participation by health professionals is essential to build EU policies which protect and promote health—and which are acceptable and credible to Europe's citizens. Yet how many research oncologists have been involved in trying to influence public health policy? Precious few, says Paul Belcher of the European Health Management Association, the body representing health service managers in Europe. "Specialists seem to have the idea that public health is a bit down-market and somehow irrelevant to what goes on in the clinic."

"SPECIALISTS BELIEVE PUBLIC HEALTH IS DOWN-MARKET"

Cancer, mental illness, cardiovascular diseases, accidents and respiratory diseases make up the top five major disease burdens in the European region, according to the WHO World Health Report 2000. These public health challenges can be most successfully tackled by persuading the public people to address the determinants of their own health, for example, in the workplace or in schools. These are among the kinds of programmes that the Commission intends to continue to support. They need people to submit inventive proposals and then to run them. Let's hope that the oncology community heeds the call this time.

Mary Rice,
Brussels

Happy Birthday, EORTC!

The European Organization for Research and Treatment of Cancer (EORTC) marked the occasion of its 40th anniversary on 26 March 2002, at the EORTC Scientific Strategy Meeting (ESSM, Brussels). The meeting celebrated EORTC's achievements since 1962, and looked ahead to future challenges.

Professor Jaap Verweij, Vice-President of EORTC, said there had been huge advances in the delivery of cancer care over the past few decades. "The overall cure rate for cancer has risen to 40% over the last 50 years. It's a tremendous improvement. It is not only because of the EORTC, but the EORTC has had a major role in this."

EORTC has been a key player in progress in radiotherapy, chemotherapy and surgery, he said. It has been involved in setting standards for the quantity and quality of radiotherapy given. It has played a major role in assessing the positive and negative effects of chemotherapy "in the most appropriate way". EORTC trials have led to less mutilating surgery, particularly in breast cancer. 'Breasts were amputated as a matter of course 40 years ago. Now, breast sparing surgery is possible in the vast majority of breast cancers, and this has very important cosmetic and psychological effects for patients,' said Professor Verweij.

Professor Herbie Newell (Newcastle University, UK) agreed. "The EORTC has contributed to a number of significant advances in the management of cancer. And it remains the only pan European academic cancer research organisation focusing on the development and implementation of new treatments."

Virtual tumour banks

A virtual tumour bank, based on frozen tissue, is to be set up with a 1.8 million Euro grant from the EU. Known as TuBaFrost, it will allow translational researchers to view frozen tissue samples on the EORTC website. They will then be able to contact the European centre where the tissue samples are stored, for permission to use samples in research.

The project will be run by the EORTC Pathology Group, in partnership with the legal firm Medlaw; and involving eight other European research centres. TuBaFrost is an extension of an existing project to create a virtual tumour bank of samples stored in paraffin. Frozen samples have the advantage of allowing use of new technologies such as expression array studies.

Professor Wolter Oosterhuis (Josephine Nefkens Institute, Rotterdam, Netherlands), said that "perhaps the most important part of the project" will be to come up with a European code of conduct, acceptable to all countries, on the use of tissue left over from diagnostic or therapeutic procedures. Currently European countries all have their own legislation, enacted or pending, or code of conducts. "We hope to harmonise throughout Europe the regulations surrounding the use of left-over tissue."

Ethics, consent and the law will be considered. Professor Oosterhuis said that when the Netherlands code of conduct was developed, scientists, medical doctors and patient groups were all involved. The TuBaFrost project is expected to start in autumn, 2002.

Reducing animal use

Rodent-only toxicology studies are now acceptable to the European Medicines Evaluation Agency (EMEA), following data produced by EORTC and Cancer Research UK. Research presented at ESSM demonstrated that for 40 new anti-cancer treatments, decisions based on rodent-only phase I data would have been safe. Prior to this, the EMEA required the use of data derived from non-rodents, usually dogs.

Researchers showed that in the vast majority of cases, it is unnecessary to use non-rodent species. This should lead to a reduction in the number of dogs used for preclinical toxicology studies.

Efficacy data is increasingly based on studies of cancer cells grown in culture. "When the EORTC started, the vast majority of preclinical efficacy studies in cancer would have been carried out in animal models. Now the vast minority use animals," said a researcher.

Teaming up with Big Pharma

Patients will benefit from future partnerships between academic research networks and the pharmaceutical industry, said Professor Verweij. "We have to co-operate for patients to get the greatest benefits at the earliest possible stage."

Both sides stand to gain, he said. "Drug development requires tremendous investment, and that money is only available in industry. On the other hand, a lot of knowledge and understanding of cancer is held within academia."

However, prejudice remains. "Academics are suspicious of the scientific integrity of industry. Industry thinks that academic networks are too slow to take decisions and move on."

Professor Verweij chaired a workshop aimed at improving understanding and making each side aware of the other's needs. "Partnership is, undoubtedly, the future of clinical cancer research," he said.

No more compound screening

Random screening to find anti-cancer compounds is a dead-end, said Professor Newell. "The research community recognises that this barrel is dry," he said. The approach now is to identify molecular targets in cancer cells through molecular studies, and then develop a specific drug to interact with the target. "Initial clinical results with Glivec and Herceptin are very promising, and there are a great many more drugs in the pipeline, which have been developed to hit molecular targets," he said.

He added that translational research, on which the EORTC has placed a strong emphasis "will result in treatments being tailored to specific patients, resulting in greater efficacy and fewer side effects."

INTERVIEW

Françoise Meunier is the Director General of the EORTC in Brussels, which has just celebrated its 40th anniversary (see opposite). She joined the organisation in 1991 and, prior to her appointment, had spent 17 years in research into invasive fungal infections in patients with cancer. She is on the editorial board of numerous journals and is an editorial consultant of EJC.

Françoise Meunier

Where did you train?
I trained at the Institut Jules Bordet, Brussels, and then I spent two years as a research fellow at the Memorial Sloan-Kettering Cancer Center, New York.

Who inspired you?
First, my father, who was a surgeon dedicated to his work, and yet was able to fully appreciate and transmit his 'joie de vivre'. Then there was the scientific atmosphere at the Institut Jules Bordet, where I trained with Henri Tagnon and Jean Klastersky. Its multidisciplinary approach and full commitment to clinical research was exceptional. My early and numerous contacts with leading US experts in infectious diseases (Donald Armstrong, Jack Remington, John Bennett, Jack Edwards and numerous others) who always provided unconditional support and recognition to a young European woman willing to learn and change the world. Finally, my husband with his pragmatic approach towards solving problems.

Why did you choose to work in the field of cancer?
As a student at medical school in Brussels I was fascinated by the scientific and international framework at the Institut Jules Bordet where clinical research and care delivery were fully integrated. It was the obvious place to start my career.

Did any other branch of medicine appeal?
No.

Might you have done something else altogether?
No, I never considered anything except medicine. I was probably attracted to it by my father and the way he conducted his life. The decision was automatic, self-evident.

What has been the highlight of your career to date?
Invasive fungal infections, a life threatening complication for patients with cancer became a hot topic when I qualified as a medical doctor. Coming back to Belgium from the States, it was terrifically exciting to set up research in this new field to improve diagnosis, prevention and treatment of patients undergoing more and more aggressive autoneoplastic treatment.
When I joined EORTC, I created a new group, the Invasive Fungal Infections Group, which has established guidelines for diagnosis and treatment of fungal infections (in cooperation with a US group of experts). This is gratifying.
As Director General, my unbounded faith in the future of EORTC at a difficult time allowed me to identify and motivate outstanding scientific staff who became my close collaborators and to find the financial resources to restructure and expand the EORTC headquarters. My goal was to provide the EORTC network of scientists and investigators with a professional tool which fulfils the needs of cancer research in the 21st century.

. . . and your greatest regret?
The time and energy wasted in politically driven issues.

If you could complete only one more task before you retire, what would it be?
To contribute to the harmonisation of legal and scientific framework for pan-European cancer research. Health research is still governed by national laws and it is a real drawback in establishing pan European studies. European directives and guidelines on clinical research are interpreted differently in individual member States so studies have to meet all the legal and ethical requirements of every participating country. This causes delays and complications which do not improve the quality of research. It is of the utmost importance for the competitiveness of European research that we facilitate pan European studies as well as tissue research and simplify and harmonise the procedures imposed by health authorities.

What is your greatest fear?
The lack of European vision and missed opportunities due to nationalism, 'mentalité de clocher' or parochialism, and lack of long term strategy.

What impact has the Internet had on your working life?
It has a tremendous impact and I often wonder how we survived for so long without it.

How do you relax?
Reading, travelling, swimming and spending time with my husband and daughter.

Who is your favourite author?
I do not have one specific favourite author. I read a lot of biographies. I was particularly moved by the 'Mémoires de Jean Monet' and I would recommend that every single European citizen has access to this book and reads it.

What do you wish you had known before you embarked on your career?
As a young idealist person I wish I'd known that mankind is driven by the fight for power. Life is a collaborative effort and pure dedication and commitment is not enough. To face important challenges, you also have to rely on the goodwill of others.

What piece of advice would you give someone starting out now?
To find a field you really like, be persistent, become a specialist and thereby be recognised as an expert in your chosen field.

What is your greatest vice?
Good food and good wines.