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# NEWS. . .NEWS. . .NEWS

## Cervical cancer screening 'effective everywhere'

Cervical cancer screening programmes can lead to an 80% reduction in mortality from the disease, according to an International Agency for Research on Cancer (IARC) Working Group. Programmes can be effective in all countries, the Group said, as long they are organised and include quality control of every key step.

The Group, which met in Lyons, France (20–27 April, 2004), was chaired by Professor Nicholas Day (Cambridge University, UK). Sufficient evidence exists that screening by cytological examination of Pap smears prevents deaths, it concluded. Programmes should cover women aged 25–65 years, who need not be screened more than once every 3 years up to the age of 49, and every 5 years thereafter.

Advances such as improved handling of cell samples and use of computers for cytological analysis could also reduce the incidence of invasive cervix cancer and death from the disease, the Group said.

Infection with the human papilloma virus (HPV) is opening new avenues for control by means of screening and vaccination. Tests for the presence of viral DNA in a blood sample have been established as a step towards identifying potentially precancerous conditions. However, Dr. Peter Boyle, the recently appointed Director of IARC said, 'Much requires to be done to have an affordable, simple and reliable test available for widespread use around the world. This is the next major challenge in cervix cancer prevention.'

In developing countries, cytological screening should be encouraged where it can be implemented with good participation and quality control. Visual inspection of the cervix after application of acetic acid or iodine is promising in low-resource countries, but the Group said there is only limited evidence for the efficacy of this method.

Low-cost, low-technology screening methods should become a valid option for developing countries over the next few years, pending the availability of HPV vaccines on an industrial scale.

### *Ethics of a vaccine*

According to Dr. John Schiller and Dr. Philip Davies (*Nat Rev Microbiol* 2004, **2**, 265:343), these vaccines could have an immensely positive impact on women's health. Phase III clinical trials of an HPV vaccine based on vaccine-like particles (VLPs) are ongoing and, based on the positive results obtained in earlier trials, investigators are confident that an HPV vaccine will be licensed within the next 5 years.

However, the availability of a vaccine that targets a sexually transmitted disease raises complex social and ethical questions. How many parents will be willing to let their 12-year old daughter be vaccinated against an infection that she will only acquire when she becomes sexually active? Will the vaccination of adolescents lead to an increase in sexual promiscuity? Will there be a demand for the altruistic vaccination of adolescent boys?

For an HPV vaccination programme to be publicly accepted, it is imperative that these controversial issues are debated openly, Drs. Schiller and Davies say. The development of a co-ordinated public health education programme should be considered a priority by relevant governments and agencies, they conclude.

### *Head and neck cancers*

Sufficient evidence now exists to consider HPV a causative agent for some head and neck squamous-cell carcinomas (HNSCC), according to US researchers ML Gillison and DR Lowy (*Lancet* 2004, **363**, 1488–9). High-risk HPVs are not necessary for the development of all cases of HNSCC, but recent research 'has shown a strong and consistent association between high-risk HPV and a distinct subset of HNSCC', they write.

Clinically, HPV-associated HNSCC tend to be located within the lingual and palatine tonsils of the oropharynx, they have poorly defined histopathology and occur more frequently in non-smoking and in younger patients than in HNSCC not associated with HPV.

HPV status may have implications for prognosis, prevention and therapy, Drs. Gillison and Lowy say. Patients with HPV-associated HNSCC have a higher survival rate than those with HPV-negative HNSCC; possibly due to the absence of field cancerisation or enhanced radiation sensitivity. The finding has yet to be corroborated in a prospective study; even so, 'current clinical trials in patients with oropharyngeal cancer should stratify by their HPV DNA status, or at least include HPV status as a prognostic variable,' they write.

Screening for oral HPV might in future lead to early diagnosis and treatment has been raised, but its detection has yet to be associated with risk of HNSCC or its precursor lesions.

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## Bcl-2: gamekeeper turned poacher

Cell protector Bcl-2 is converted into a killer by binding to a nuclear receptor, Nur77/TR3, according to US researchers (*Cell* 2004, **116,** 527–40). Bcl-2 is overexpressed in approximately half of all human malignancies and this finding could be exploited in the development of anti-cancer drugs which promote its killer activity.

*''OVEREXPRESSION COULD BE TURNED TO OUR ADVANTAGE''*

Bcl-2 is a member of an evolutionarily-conserved family of proteins that can promote or prevent programmed cell death (apoptosis). Bcl-2 itself is an anti-apoptotic member, but when overexpressed can be converted into a killer in some cellular contexts. Its protective effects on cells are well characterised, but the mechanism by which it promotes cell death is poorly understood.

Now, Dr. Bingzhen Lin (Burnham Institute, California, USA) and colleagues have shed light on a possible mechanism. They showed that Bcl-2 undergoes a confirmation change in response to binding to Nur77 – a member of the steroid/thyroid/retinoid nuclear receptor superfamily. The receptor binds through its ligand binding domain to an N-terminal loop region of Bcl-2 and this results in the exposure of the Bcl-2 homology (BH)3 domain. This domain is thought to determine whether Bcl-2 family members are pro- or anti-apoptotic, with pro-apoptotic members having exposed domains. The rapid expression of Nur77 has been observed during apoptosis in several cell types. Whether this receptor mediates the phenotypic conversion of other Bcl-2 family members awaits further study, they said.

Apoptosis is important for the activity of many anti-cancer agents. Therefore, these opposing effects on cells have clinical implications. High levels of Bcl-2 protein have been associated with favourable outcomes for patients with several types of cancer. Further, somatic mutations in this loop region of Bcl-2 have been observed during the clinical progression of lymphomas. Deletion of this loop region has also been shown to block paclitaxel-induced apoptosis. This mechanistic knowledge could be exploited in the development of anti-cancer drugs that promote tumour cell death turning the overexpression of Bcl-2, observed in around half of human malignancies, to our advantage, they concluded.

*Emma Cannell*

## Insulin-like growth factor: cancer risk

Insulin-like growth factor-I (IGF-I) and its binding protein are associated with an increased risk of breast and prostate cancers, according to data from a meta-analysis (*Lancet* 2004, **363,** 1346–53). ''These epidemiological observations could have major implications for [the] assessment of risk and prevention of cancer'', said lead investigator Dr. Andrew Renehan (Christie Hospital NHS Trust, Manchester, UK).

IGF-I is a mediator of growth hormone activity and together with its binding protein, IGFBP-3, is a known modulator of cell growth and survival. These factors have been implicated in tumour development, but Dr. Renehan's study is the first meta-analysis to examine their role in the development of several major cancers. High concentrations of circulating IGF-I were associated with an increased risk of prostate and premenopausal breast cancers. An increased risk of premenopausal breast cancers was also seen with high levels of its binding protein (all Odds Ratios of around 1.5).

The meta-analysis has implications for the scientific and clinical community. An accompanying commentary (*Lancet* 2004, **363**, 1336) noted that this evidence leads to increased concern about the possible adverse eects of growth hormone use.

*''GROWTH HORMONE IS EASILY AVAILABLE ON THE INTERNET''*

Dr. Alicja Wolk (Karolinska Institute, Stockholm, Sweden) wrote, ''What do these results mean to individual consumers, when preparations of growth hormone are easily available for purchase, without prescription or physician's control, on the Internet, with comments that there great health benefits from using them and no risks?''

*Emma Cannell*

## Virtual EBCC-4 available

Oral presentations made at the 4th European Breast Cancer Conference (Hamburg,16–20 March, 2004), are now available online.

The captured sessions are the keynote symposia:

- Primary medical treatment of breast cancer: from empirical to tailored medicine.
- The management of elderly women with breast cancer.
- High risk women: who they are and what can be done.

A 'Hot off the Press' Session (New data on the use of aromatase inhibitors in the adjuvant setting: results from 3 trials), is also available.

For free access to these presentations, visit www.fecs.be/conferences/ebcc4/virtualmeetings.shtml

## Bortezomib receives European Marketing Authorisation

The European Agency for the Evaluation of Medicinal Products (EMEA) has approved Velcade (bortezomib) for the treatment of multiple myeloma patients who have received at least 2 prior therapies and demonstrated disease progression on their last therapy.

Bortezomib is the first in a new class of medicines called proteasome inhibitors, according to manufacturer Ortho Biotech. It received marketing approval from the US Food and Drug Administration (FDA) in May 2003, for the same indication. The EMEA decision grants the company a single licence, which allows bortezomib to be marketed in all 25 Member States, plus Norway and Iceland.

A phase II study (*New Eng Jnl Med* 2003, **348**, 2609–17) showed that the drug slowed, reversed or halted progression of disease in patients who had failed on 2 or more treatments, and was the basis for the FDAs decision. However there are no controlled trials demonstrating a clinical benefit such as an improvement in survival. Ortho Biotech said that approximately 50 ongoing clinical trials in Europe and the States are investigating the potential of bortezomib in all stages of multiple myeloma and other cancers.

The drug has a generally predictable, manageable safety profile with appropriate monitoring and, if necessary, dose modification. It is contradicted in patients with hypersensitivity to bortezomib, boron or mannitol.

# EUROFILE

## New visa 'will attract scientists to Europe'

While the US is placing additional restrictions on short-term visits from researchers from other countries, the EU has announced that it is going in the opposite direction. On March 18, 2004, the European Commission (EC) moved to introduce a 'scientific visa' to aid the movement of third country researchers both to and within the EU.

The Commission adopted proposals for a directive and two recommendations which would guarantee indefinite leave to stay for researchers from outside the EU, exempt them from immigration quotas, and make it easier for their families to come. ''Once a researcher has gained their residence permit, they will be able to move freely within the Schengen Member States in order to attend meetings and conferences, and if they want to extend their stay in the EU, it will no longer be necessary for them to return to their country of origin to submit the application'', said Raffaele Liberale, Director of 'the Human Factor, Mobility, and Marie Curie actions' within the Commission's DG Research.

*''SCIENTISTS WILL BE ABLE TO TRAVEL FREELY''*

The Commission wants to see both recommendations adopted in advance of its directive on the admission of third-country nationals to carry out scientific research in the EU.

John Marburger, head of the White House's Office of Science and Technology Policy, underlined the necessity of these proposals at the OECD science ministers meeting in February 2004. ''I would like to thank all the countries here for sending us your young people and supporting our economic growth'', he said.

To meet the objectives set by the Barcelona European Council – an increase of research and innovation spending to 3% of the EUs GDP – it has been estimated that an additional 700 000 researchers will be needed by 2010. The Commission has said that a directive on its own will not be sufficient to meet the Barcelona objectives since it ''inevitably takes several years before a directive is in full operation.'' Hence the two recommendations, aimed at producing a quicker effect.

*''700 000 EXTRA RESEARCHERS WILL BE NEEDED BY 2010''*

Labour markets do not need to be assessed before someone from a third country is allowed to take a research post, the Commission argues. The first recommendation proposes that member states should choose between granting automatic work permits and waiving them, and that countries should not use quotas to restrict the number of third country nationals taking up posts. Member states are requested to issues residence permits to such researchers within 30 days and to guarantee that these permits will be renewed indefinitely. They should also refrain from imposing waiting periods for the admission of family members.

The second recommendation states that short term visas should be issued so that researchers can travel easily for short periods – to conferences, for example. However, this provision would only apply to countries that have signed the Schengen agreement on border controls, so would still pose problems for scientists on short-term visas who wished to visit the UK, Ireland, or Denmark.

The definition of a researcher under these measures has been kept deliberately broad. ''It relates to all qualified individuals in the knowledge and innovation process'', said Mr. Liberale. The single residence permit will also cover all types of researcher contract, such as fellowships, traineeships, and scholarships.

The Irish presidency of the EU at the time announced that adopting these recommendations was an urgent priority, and was hoping to place them on the agenda of the next Competitiveness Council, which deals with research issues. The ensuing Dutch presidency has also agreed this as a priority.

Meanwhile, the new, post-September 11 security measures introduced in the US are having a negative effect on their scientific research. Speakers at an American Association for the Advancement of Science meeting in April 2004 warned ''to win the war on terror, we may lose our scientific preeminence.'' Applications to US graduate schools from international students have declined by 32% in the last year, the decline affecting all major countries of origin and all disciplines.

Even so, Europe still has a long way to go to match the attractions of the US for scientists, and agreement on visas is only part of the equation. Some kind of harmonisation of social security and healthcare systems is also needed if researcher mobility is to be more than just a fashionable expression. Hard-earned qualifications are not always accepted in other countries. Then there is the language problem. And working conditions and salaries in publicly funded research institutes in Europe, which lag way behind what is available in the US. The anger expressed recently by French researchers sounded a chord with scientists in many other EU countries, who complain not just about lack of opportunity but also a scarcity of resources and a damaging lack of transparency in recruitment processes.

But the proposals have been developed co-operatively between the Directorates General for Justice and Home Affairs and Research, and by 33 countries, which seems to signify the start of a genuine commitment to improving the current situation. ''These proposals represent a real opportunity to make a change for the better'', says Raffaele Liberale.

*Mary Rice*
*Brussels*

## Eudract 'should be available to all'

The new European clinical trials database (Eudract) should be available to all, according to Dr. Gerd Antes, head of the German Cochrane centre. Currently, only European and national authorities will have access to Eudract, which was established on May 1, 2004, under the European clinical trials directive.

All clinical trials on medicinal products for human use that take place in any of the 25 member states have to be registered. Eudract will be linked with a European data base of suspected unexpected serious adverse reactions reported during trials. It is intended to increase protection for trial participants and patients receiving medicines.

Dr. Antes, quoted in German newspaper *Die Zeit* and *BMJ* (*BMJ* 2004, **328**, 1094) said that doctors and researchers should also have access to the information so that they can form a more accurate picture about the safety, side eects and dangers of drugs.

The pharmaceutical industry has opposed making the information public saying that it would fall into the hands of competitors. But Dr. Antes said that in the US, where the Government database of ongoing trials is generally available (www.clinicaltrials.gov), the industry has benefited from greater openness, because it has become easier to recruit trial subjects.

In a *BMJ* Rapid Response, Dr. Frank Buntinx and Dr. Bert Aertgeerts (Belgian Center of Evidence-Based Medicine), argue that, even if the registry with the new and ongoing trials is kept confidential, researchers should at least have access to information on completed studies. 'This should avoid publication bias and permit the production of systematic reviews with all the relevant data,' they say.

## ACTION assesses costs in practice

A pan-European, prospective observational study is evaluating the costs of first-line chemotherapy for advanced non-small cell lung cancer (NSCLC) in everyday clinical use. Assessment of Cost and ouTcomes of chemotherapy In an Observational setting in patients with advanced NSCLC (ACTION) will follow 1000 patients with advanced NSCLC starting first-line chemotherapy for 18 months.

To date, 778 patients have been enrolled, from Portugal, the UK, the Netherlands, Finland, and Germany. Key outcomes include treatment patterns and costs, clinical results, complications and quality of life. Insurance coverage and other determinants of patient care will also be analysed.

Randomised controlled trials (RCTs) have shown that new agents offer NSCLC patients significant survival benefit and better quality of life (*Anticancer Drugs* 1995, **6,** 39–48; *Br J Cancer* 2000, **83,** 447–53). But RCTs have narrowly defined populations and treatment patterns, and a strictly limited environment, and cost assessments may not be typical of normal clinical practice.

The observational study, which is sponsored by Eli Lilly & Co, aims to provide meaningful data about treatment costs relevant to clinical practice. It will evaluate the usual care provided to a heterogeneous group of ''real'' patients.

Participating investigators are enthusiastic about ACTION. ''In these times of limited funds for health care, we have to be able to provide hard data to our superiors'', says Dr. Henrik Riska, Chief Physician, Department of Internal Medicine, Helsinki University Hospital, Finland. ''An observational study can show many interesting results concerning the economic outcome of treatment where the relationship between outcomes and costs is not always well understood.''

## Can CT screening increase smoking cessation?

A 4000-patient study has been established to examine whether CT screening for lung cancer can be effectively linked to smoking cessation. The study, which will be carried out at Weill Medical Center, Cornell University, USA, is funded by matching grants of $1.8 million each from the UK-based Medicsight Foundation and the American Legacy Foundation.

The study, which was due to begin in June 2004, is to use advanced image analysis software. Lead investigator Dr. Claudia Henschke, Professor of Radiology at Weill Cornell, said, 'We want to make screening programmes an economic and life-saving reality. The International Early Lung Cancer Action Program (I-ELCAP) is proving that CT screening is an effective tool for early diagnosis of lung cancer.

*''WILL SCREENING ENCOURAGE SMOKERS TO QUIT?''*

This newly funded study represents a unique opportunity to understand how to best increase smoking cessation in the context of CT screening. At the same time, we will be incorporating and developing advanced image processing software to make screening as effective as possible.'

Dr. Cheryl Healton, President and Chief Executive Officer of the American Legacy Foundation said, 'The pressing question in the minds of many is whether or not CT screenings for lung cancer will encourage smokers to quit or make them put off this decision even longer. With lung cancer being the leading cause of death in this nation, the Foundation is especially interested in answering this vexing question.'

## Selenium 'beneficial' in ovarian cancer treatment

Selenium (Se) may be 'a supportive element' in chemotherapy for ovarian cancer, say Polish researchers (*Gynecol Oncol* 2004, **93**, 320–7). Daily supplementation in patients receiving multidrug chemotherapy resulted in beneficial biochemical changes and in a reduction of side eects, they said.

The randomised controlled trial included 31 patients. Analysis at 2 and then 3 months found patients receiving the supplement had higher concentrations of the microelement in serum than the placebo group. Taking the supplement was significantly associated with increased activity of glutathione peroxidase in erythrocytes and an increased concentration of malondialdehyde, and of white blood cells. Significant decreases in hair loss, flatulence, abdominal pain, weakness, malaise and loss of appetite were also associated with the supplementation.

The authors note that selenium has antioxidant properties and is a scavenger of free radicals, thus preventing damage to lipid membranes. 'Exogenous factors such as cytostatics, seem to increase the oxidative damage of the cells,' they say.

PODIUM

# Why we need to revive the autopsy

*Professor James Underwood (University of Sheffield, UK) is President of the Royal College of Pathologists and was recently President of the British Division of the International Academy of Pathology. He has advised the Department of Health (England), Medical Research Council and General Medical Council on aspects of consent, organ retention and post-mortems. His main research interests are breast and liver disease and the autopsy.*

*Professor James Underwood*

## How far have autopsy rates declined?

When I trained in London in the 1960s, approximately half of those who died in hospital had the cause of death confirmed by autopsy. The rate has declined internationally since then, and even in teaching hospitals, it is now 5% or less.

## Why has this happened?

There is concern among bereaved families about examination of the body after death, but the decline is mostly because surgeons, oncologists and other physicians are not requesting autopsies. Obtaining consent has become a labour intensive procedure. The consent form used to take up one side of A4; concerns about organ retention have now led the Department of Health to produce an 8 page document, which takes longer to go through with relatives. Clinicians want to attend to living patients rather than concentrating on those who have died. But they have too much faith in modern diagnostic techniques.

## Haven't these techniques helped in assessing causes of death?

The increasing sophistication of medical investigations with the growth of medical imaging, biopsies, clinical biochemistry, and so on, means patients are more investigated during life. There's a feeling that little more will be learnt by examining the body after death.

However, peer reviewed studies in Europe and North America consistently show that up to 30% death certificates are wrong or incomplete.

## Why are autopsies important?

It's not just to establish the cause of death. Autopsies enable side effects of medical or surgical interventions to be detected, and new diseases to be discovered. They're important to give families get a full and reliable explanation for their loss.

Among patients who have been diagnosed and treated for cancer, it's easy to assume that effects of the cancer caused the death. But post-mortems often uncover unexpected conditions. Most pathologists have experience of someone who apparently died of cancer, yet autopsy found no evidence of cancer at all. For example, I recollect a patient who had a mastectomy and radiotherapy a few years before she died. The cause of death was given as carcinomatosis, but autopsy revealed a perforation of the large intestine. She could have been treated for this if a correct diagnosis had been made in life.

## Are there implications for research?

Our knowledge of neurodegenerative conditions such as Alzheimer's, Parkinson's and Creutzfeldt–Jakob disease, relies almost entirely on post-mortem tissue, as it's rare for biopsies to be taken from the brain of a living patient. In cancer, most of our knowledge is based on research on tissue from living patients, so cancer research relies less on post-mortems. But in clinical trials where survival is the outcome measure it is important to ascertain that the cause of death is cancer rather than a complication of treatment. A study (*BMJ* 1997, **314**, 217) found that only 13% of clinical trials in which death or survival is an outcome measure have the cause of death ascertained by autopsy.

## What about issues of cost?

I'm not aware of economic pressures on clinicians to deter them from asking for autopsies. It's more that young doctors have little or no experience of autopsies and the information that can be obtained from them. In the UK, most doctors graduate without having witnessed an autopsy. In the 1960s it was a core part of the curriculum.

## Do autopsies have an impact on clinical care?

They should if used properly. It is not sufficient to examine the body and issue a report. Information should feed into research programmes, be entered in data bases and included in clinical audit. We have to make sure the information is used to lead to improvements in clinical care.

## Are there are international variations?

Yes. In the former Warsaw Pact countries, the law stated that all hospital deaths should be examined by autopsy and in Hungary in the 1990s, the post-mortem rate in hospitals was 80%. In Israel and the Gulf countries, for religious and cultural reasons, autopsies were only carried out for forensic purposes so rates are extremely low. But interest in autopsies is increasing in some of these countries.

## What barriers exist to increasing autopsy rates?

The organ retention scandal in the UK has increased doctors' reluctance to approach relatives for permission and may have increased public suspicion. There are similar issues in Australia and New Zealand but doctors everywhere need to open and public about what they are doing because the same situation could arise anywhere.

## Do you see any prospect for reversal of the current trend?

Our arguments are being well-received and we can turn this around, but it will take decades to change the culture within clinical practice.