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'Catastrophic smoking epidemic' in India

Smoking in India is set to cause 900,000 deaths per year by 2010, an international team of researchers predict. It will cause one in 5 of all male deaths, and one in 20 of all female deaths at ages 30–69, they say.

'The extreme risks from smoking that we found surprised us, as smokers in India start at a later age than those in Europe or America and smoke less,' said lead author Professor Prabhat Jha (University of Toronto, Canada).

The research, led by a team from India, Canada and the UK, is the first nationally representative study of smoking in India. About 900 field workers surveyed all adult deaths in 2001-2003 in a sample of 1.1 million homes in all parts of India. They compared smoking histories of 74,000 adults who died with 78,000 living controls.

Among men who died aged 30–69, smoking caused 38% of all deaths from tuberculosis, 31% of all deaths from respiratory disease, 20% of all deaths from vascular disease and 32% of all deaths from cancer (*N Eng J Med 2008 REF*). Smoking deaths were far more likely to be from tuberculosis in rural areas and from heart disease (chiefly heart attacks) in urban areas. Over half of the tobacco deaths occurred in illiterate men or women.

'THE EXTREME RISKS FROM SMOKING SURPRISED US'

'I am particularly concerned about protecting India's 600 million young people below the age of 30,' Dr Anbumani Ramadoss, India's Health Minister, said. 'We plan to take comprehensive steps against tobacco, and strengthen our Tobacco Regulatory Authority to enforce the laws.'

Even low levels of smoking raised the risk of death. Among those who smoked 1–7 bidis (which contain 25% of the tobacco of a cigarette) per day, smoking caused one quarter of all deaths from medical causes.

Stop cervical cancer!

A campaign to eliminate cervical cancer in Europe has been launched by the European Cervical Cancer Association (ECCA) and the International Union Against Cancer (UICC).

The STOP Cervical Cancer Petition is based on the Citizen's Initiative of the EU Lisbon Treaty, which compels the commission to act on a petition of 1 million or more European citizens.

'Cervical cancer could be virtually eliminated in Europe today,' said Dr Philip Davis, director general of ECCA. But organised cervical cancer prevention programmes are still only available to a minority of the women in Europe, and, even where these programmes are available, many women do not take advantage of them.

'Both these problems can be solved by increasing awareness; politicians need to be made aware of the benefits these programmes will bring so they prioritise their implementation and women need to be made aware of the benefits so they access the programmes,' he said.

The European Parliament Cervical Cancer Interest Group (ECCIG) hosted an official signing ceremony in the European Parliament in Brussels in January, 2008. It was attended by MEPs, MPs from across Europe, current and former national Ministers, representatives from the European Commission, the European Council, the European Centre for Disease Control and ECCA's institutional members (including cancer societies, cancer treatment centres, medical associations, university teaching hospitals and patient groups).

Former British MEP Imelda Read signs the petition

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Shall we agree to disagree?

The question of whether sequential chemotherapy is more effective than combination treatment in palliative metastatic colorectal cancer (mCC) was debated at the ASCO GI meeting (January 25–27, 2008, Orlando, Florida).

Professor Matt Seymour (Cancer Research UK Centre, University of Leeds, UK), principal investigator of the FOCUS, favours sequential therapy

Combination chemotherapy provides a high response rate, and for many patients this is incredibly important first-line: most obviously when disease might become operable for cure; or when there are major cancer symptoms. But the majority of our patients are not in either of these categories: for them, we have to ask whether first-line combination chemotherapy provides a real advantage – better duration or quality of life – over other strategies.

In the FOCUS study (*Lancet 2007;**370**:143–152*), 2135 patients were randomised to initial combination therapy, or sequential treatment starting with single-agent fluorouracil then changing on progression to irinotecan or combination therapy. Median survival was 16.7 and 15.4 months respectively with initial combination 5FU/irinotecan or 5FU/oxaliplatin. This compared with 15.0 or 15.2 months respectively with sequential plans using 5FU/irinotecan or 5FU/oxaliplatin second-line, and 13.9 months when the planned second-line treatment was single-agent irinotecan. Log-rank comparisons showed sequential plans involving second-line combinations were non-inferior to first-line combination therapy (HR=1.06, 90%CI 0.97–1.17).

CAIRO (*Lancet 2007;**370**:135–142*) compared sequential or combination strategies with capecitabine, irinotecan and oxaliplatin. Median survival was 16.3 (95% CI 14.3–18.1) months for sequential treatment starting with single-agent capecitabine, versus 17.4 (15.2–19.2) months with first-line combination (p=0.3). Three further trials, reported as abstracts, have compared initial combination versus planned sequential therapy: LIFE (ASCO 2005, abstract #3517), FOCUS2 (ASCO 2007, abstract #9030) and FFCD2000-05 (ASCO 2007, abstract #4069). None showed a survival difference.

These results are unexpected and counter-intuitive since earlier trials comparing first-line combination versus single-agent chemotherapy without a sequential plan had, in some cases, shown survival benefits. With a planned sequential strategy, not all patients receive the full plan, and in FOCUS, one-third of sequential patients only ever received fluorouracil, so one might have expected survival to be worse – but it

(*The story continued on page 4*)

Professor Dirk Arnold (Martin–Luther University, Halle-Wittenberg, Germany), championed the combination approach

FOCUS, CAIRO, and the other 3 recent studies have shown that it might be beneficial to use chemotherapy sequentially, starting with a less active (and less toxic) single agent strategy.

I believe the findings are restricted to the subgroup of patients with multiple metastases unsuitable for resection, and those without symptoms or risk of rapid deterioration. Patients with potentially resectable tumours or poor performance status (PS) were either excluded or underrepresented, whereas most mCC patients with both good and poor performance status achieve greatest benefits from combination therapy.

After an 'induction period', all patients need to be assessed to see whether they might be candidates for resection or ablative techniques, as this can be hard to gauge before treatment starts. There are inequalities of care across Europe: France and Spain routinely offer curative resection for metastases, but this is rarely available in Germany and the UK. Large case series indicate that patients who undergo resection for secondary metastases have as good an outcome as those who undergo primary resection (*Ann Surg 2004;**240**:644–57*).

Patients with poor performance status also benefit from combination therapy. The side effects of combination treatment need to be balanced against the advantages of greater tumour control: symptoms caused by tumours are often more distressing than drug side effects. Indeed, a meta-analysis demonstrated that the overall survival gain was higher for patients with poor performance status than good performance status when the impact of 'optimal combinations' on the outcome was analysed (*Proc. ASCO 2007 JCO Supplement 18S #4011*).

With upfront combination therapy, all patients benefit from the full armamentarium of drugs. Results from FOCUS and CAIRO show that only 19% and 36% of patients starting on initial monotherapy, respectively, went on to receive all 3 agents; around 30 to 40% of patients are lost to each subsequent treatment. There is evidence that people with mCC who receive all 3 drugs fare better; which may explain the trend for

(*The story continued on page 770*)

EUROFILE

Speaking up for medical research

Europe's medical research councils are mobilising in an attempt to increase public funding for their work. They argue that investment should double over the next decade; they also want greater collaboration between research institutions, a more sympathetic regulatory environment and improved career paths for medical scientists.

The initiative comes from the European Medical Research Councils (EMRC), a forum for collaboration between medical research councils overseen by the European Science Foundation. In December 2007, it issued a policy document, or white paper, on the future of medical research in Europe. The proposals were debated at a meeting in Frankfurt in January 2008, attended by research council heads, deans of medical faculties, journal editors and representatives from learned societies.

The white paper's proposals spring from an analysis of the state of European medical research compared with its global competitors, most notably the USA, and of the future health needs to the European population. 'If funding for medical research in Europe is doubled within the next 10 years, and this is combined with the implementation of 'best practice' for collaboration and organisation of medical research, there will be major benefits for European society,' the EMRC argues, 'with better health, welfare and hospital treatment, and a thriving medical industry.'

Part of this 'best practice' is investment in research infrastructure, from laboratory equipment in basic science labs and research facilities in hospitals, to the largest pan-European infrastructures. In particular, the EMRC wants to see direct funding for a league of top-performing biomedical research centres, integrated into regional clusters.

The European Commission has been positive about the initiative, although it is probably not in a position to offer new funds until the next round of EU research programmes, after 2014. However it has said that medical research could be one of the pilot areas for a new push towards joint programming of national and European funds that it will bring forward in the second half of 2008.

According to Liselotte Højgaard, chair of the EMRC, the warm welcome received by the proposals in Brussels and at the Frankfurt meeting is partly due to a past lack of coordinated lobbying from the medical community. 'Medical research has lacked a voice speaking on our behalf in Europe,' she says. 'Some other research areas have been very strong in Europe, very persistent and energetic. We have somehow taken care of our own specialities, but the role of all the medical specialities together … for some time we have forgotten to do this.'

Højgaard, who is professor of clinical physiology, nuclear medicine and PET at the Rigshospitalet, Copenhagen, thinks that cancer research has successfully made a case for itself, in particular by bringing on board patient organisations. Cancer has been the forerunner, she says. 'The enthusiasm and the high quality of cancer research in Europe are perhaps role models for some of the other areas where people haven't got their act together so much.'

This view is reflected in the white paper, where the cure rates of childhood cancer and the development of an effective vaccine against human papillomavirus are cited as examples where sufficient research funding has resulted in public health benefits.

Other diseases may have a greater claim on new funds than cancer research, Højgaard says, but it will benefit from action on the white paper's other priorities: 'For the cancer area it is important to think about where we need large research infrastructures, where we need more collaboration between East and West,' she says. 'It will also be important in the cancer area to raise the level of the new member states of the European Community.'

John Caldwell, dean of the faculty of medicine at the University of Liverpool, attended the Frankfurt meeting. While he supports the white paper's aims, he is concerned that implementing them on a Europe-wide basis could be extremely difficult. For cancer research, however, there would be a significant benefit if reform of the regulatory environment for clinical trials could be moved forward.

'That's something where EMRC, speaking on behalf or the medical research community, working together with the Commission, could well be extremely helpful,' he says.

The same point is made by Alexander Eggermont, president of the European Cancer Organisation. 'The EU Directives on this are well intentioned and meant to safeguard patients' interests,' he says. 'However, the regulatory hoops through which cancer researchers have to jump in order to set up a clinical trial are so cumbersome and complicated that it has dramatically increased the costs of such trials. This has hurt, in particular, academic trials that are conducted outside the track of well-funded drug development trials.'

The EMRC has begun a study on non-commercial, investigator-driven clinical trials that is being carried out under the European Science Foundation's 'forward look' programme. Workshops will be held in April 2008, with recommendations on how to strengthen and better coordinate national and European initiatives ready in October 2008.

Eggermont is concerned that EMRC's white paper should not give the impression that cancer research is well-funded in Europe. 'The 2007 report from the European Cancer Research Managers Forum revealed that the US spends five times as much per capita on cancer research than the average per capita spend in Europe – €17.61 compared to €3.42,' he points out. 'These figures show how important it is that European cancer research receives better and more co-ordinated funding.'

Ian Mundell
Brussels

Sequential versus combination therapy

(continued from page 768)

Prof. Seymour on sequential therapy

wasn't. May be that one-third are the least likely to have benefited from combination therapy; or perhaps the other two-thirds live longer thanks to the sequential approach.

In FOCUS and CAIRO, survival in all arms was lower than in some other recent trials. That was expected since we excluded patients who might potentially become operable. Another criticism is that patients on sequential strategies are less likely to receive three cytotoxic drugs in their lifetime. The 3-drug/survival relationship was observed across trials and does not prove causality. In all these trials of planned sequences, patients randomised to initial combinations were more likely to receive 3 drugs but did not live longer.

All oncologists need to look carefully at these data and ask themselves exactly what are their reasons, for each individual patient, for recommending combination chemotherapy.

Prof. Arnold on the combination approach

superior overall survival (the OS in the recent trials is not significantly better for the combination). Finally, why use a less active and maybe less toxic monotherapy until progression – followed by the (more toxic) combination in this unpleasant situation? Initial combination therapy does not mean a lifetime's treatment, patients may get longer treatment holidays since the smaller you shrink the tumour, the longer you can hold off starting second-line therapies. We are undertaking a randomised trial looking at treatment holidays after an 'induction' phase, and their effect on outcome and quality of life.

As interviewed by Janet Fricker, who was sponsored to attend the meeting by Pfizer Oncology.

'Increased public support' for use of human tissue in research

Public support for the use of human tissue in research has risen over the past decade, say researchers at Sheffield, UK. They found that 96% patients were happy for their tissue to be used in research, up from 89% in 1996.

This is despite the adverse publicity surrounding tissue removed from children at post-mortem examinations, and stored without parental consent. The furore in the UK led to the implementation of the Human Tissue Act in 2004, which requires specific consent for the use of human tissue, except that taken during surgery and stored.

In 1996, the researchers questioned patients recovering from operations about their views on the use and ownership of tissue removed during surgery. This time (*J Clin Pathol 2008; doi:10.1136/jcp.2007.0531173*), 220 patients undergoing surgery over a period of 11 weeks in 2005 were asked to take part. In all, 203 completed questionnaires.

Patients were happy for their tissue to be used in research, and for teaching medical students. They found that an overwhelming majority of patients wanted residual tissue from their operations to be used in biomedical research and medical education. The researchers caution, though that consent from the vast majority of patients 'should not affect the rights of the few who would not, and appropriate systems need to be designed to accommodate this.'

The Human Tissue Act states that living patients must consent to retention and use of their organs and tissue for particular purposes beyond their diagnosis and treatment. Anonymised archival residual tissue may be used in research without specific patient consent, provided there is ethics committee approval. Similarly, consent is not required for use of surplus tissue in audit, education, public health monitoring or quality assurance.

'The sample of public opinion in this survey would appear to align closely with this legislation,' the researchers conclude.

Breast cancer vaccine prevents recurrence

A peptide vaccine might lower recurrence in women treated for breast cancer who were disease-free after treatment but at high-riskof recurrence (*Clin Cancer Res 2008;**14**:797–803*). The vaccine incorporates the E75 immunogenic peptide from ERBB2, a protein which is overexpressed in many breast cancers.

In this combined phase I and II study, 186 patients were vaccinated, 85 women were not, and all were followed up for a median of 20 months. 5.6% of women who were vaccinated had recurrence of their breast cancer compared with 14.2% of those in the control group (p=0.04).

'The goal was to determine whether ERBB2 immunity protects women from breast cancer recurrence', says researcher George Peoples (US Military Cancer Institute, San Antonio, TX, USA). Women receiving the vaccine initially were inoculated six times over a 5-month period; after 6 months, the vaccine-specific E75 immunity decreased. Therefore, women continuing in the trial were offered boosters every 6 months—of the 48 receiving boosters over the past 2 years, none have had recurrences.

'ERBB2 is an excellent target for a vaccine to prevent breast cancer relapse and the data are quite interesting. However, the study highlights some of the problems encountered with designing vaccine trials with rate of relapse as an endpoint', says Nora Disis (University of Washington, Seattle, WA, USA) whose research group also develops vaccines to target breast-cancer-associated proteins. 'Combining phase I and II studies to get adequate numbers, evaluating patients who received a variety of doses of vaccine and had varying levels of ERBB2 expression in their tumours, and trying to assess patients who are all at different stages of disease over a relatively short period of follow-up make interpretation of the results a bit difficult.'

Vicki Brower

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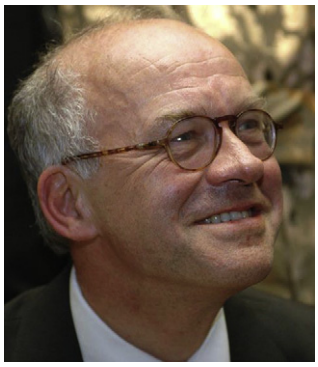
PODIUM

Cancer Control in Europe



Professor Jan Willem Coebergh (Erasmus Medical Centre, Rotterdam, the Netherlands), EJC's epidemiology editor, has co-edited a forthcoming EJC Special Issue, 'Cancer control in Europe: state of the art in 2008'

Why do we need a European-level strategy on cancer control?

Countries can learn from each other; differences between them are instructive. Countries working as individual units do not adapt quickly enough to challenges such as the rising number of patients, especially elderly patients, and new possibilities for cure, care and detection. A European perspective makes it obvious that some adapt more quickly than others.

A population approach also implies that investment needs to be made to strengthen the whole of Europe, rather than each country looking after its own healthcare. The more the European community brings together professionals to produce independent guidelines or vision documents the more that helps in practice.

Where has this happened?

European guidelines for mass screening mean that not every country has to go through the lengthy process of committees and decision-making, but focus on implementation. In breast cancer screening, developments that started in Finland, the Netherlands, UK, and Sweden were taken up elsewhere. Cervical cancer screening programmes spread but rather more slowly (*see EJC Special Issue 2000;**36**:17*).

Are there other examples?

There are many. The Portuguese EU Presidency took up research policy development as an issue and this has been continued by Slovenia. Both emphasised the importance of good psychosocial care, of having cancer registries of a certain standard everywhere, and emphasised that good psychosocial care is absolutely necessary for good oncology.

What about primary prevention?

There is unanimity over the importance of primary prevention, though few specific examples of effective programmes, other than tax policy and protection of other citizens. Government interventions on tobacco, alcohol, diet and exercise need to take a long term view for investments in anti-addiction services to work. And it takes 5-10 years of political awareness, if not more, before concrete steps are taken, and to be effective they should also serve other purposes. Obesity relates to many chronic conditions besides cancer and we need to change lifestyles in a way that also saves energy by, say, not only changing dietary habits, but encouraging people all over Europe to use more public transportation or ride bicycles. This will take decades but the spin-offs would include a reduction in car use and less congested cities.

Is enough being done?

No. The underlying trends are going in the wrong direction. It took 20–40 years to make the changes necessary to cut tobacco use, but it finally happened. The solution in a democracy has to be political, there is no better way.

What are the obstacles to progress?

Each programme differs. There may be vested interests such as the tobacco industry or fast food and soft drinks manufacturers. It may take collaboration between many organisations and wholesale changes to the infrastructure of society; it is not easy to reduce the age of women at their first birth, which impacts on their breast cancer risk. Standards of childcare will have to rise and efforts made to ensure that having children does not interfere with career development.

Why is change so slow?

It was widely recognised in the 1990s that the UK was lagging behind other countries after 30 years of underinvestment. A national plan was instigated in 2000, but it will take 10 years from then before the money goes into productive investment – operational radiotherapy services and manpower – and another 5-10 years before it has an effect. The best way of reducing delays is to work with scenarios of the future, start addressing trends early, and involve patients – who are also voters – in the process.

How is the situation in Central and Eastern Europe?

The gap between this part of Europe and the rest is now closing. More preventive measures are needed, legal measures to restrict use of tobacco and alcohol, and an environmental clean-up. The medical infrastructure needs strengthening, and the use of expensive new drugs must be restricted in order to leave sufficient resources for the development of infrastructure.

How important is it that Europe acts as a single unit?

IARC's Eurocan project is looking at ways of increasing collaboration in cancer research across Europe. Many believe that money from all sources should be brought together, and that we should move towards having a European cancer institute along the lines of the US' NCI. This is still, unfortunately, some way off. But, the process of discussion and exploration should lead to fewer obstacles to European collaboration. Europe has added value because of the potential high quality of study questions that can be examined here. If we work together, we make each other stronger and our research better.