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Europe pulls plug on cancer projects

Major European cancer projects are set to be disbanded following a decision by the European Union's Public Health Directorate to exclude cancer from its 2003–2008 Programme. The European Network of Cancer Registries (ENCR) and the European Prospective Investigation into Cancer and Nutrition (EPIC) are likely casualties.

Dr Max Parkin, Head of Descriptive Epidemiology at the International Agency for Research on Cancer (IARC), Lyons, co-ordinates ENCR and said the decision was "a tremendous shock. We put in a very strong application. ENCR is a paradigm for what Europe should be doing. It brings together people from different countries, builds on national cancer registries which are a great resource and produces European data."

'ENCR IS A PARADIGM FOR EUROPEAN RESEARCH"

EPIC has been running for 13 years, and involves 10 European countries. Nutritional data and biological samples have been collected on 522,000 Europeans. Dr Elio Riboli, Chief of Nutrition and Cancer at IARC and European Coordinator of EPIC, said the study had involved major investment so far. 'EPIC is now coming to fruition and articles are starting to appear in major journals. It is very difficult to understand why investment is being stopped now that the study is in a position to provide useful results, helping us to understanding the causes and possibilities for prevention of cancer in Europe. Millions of Euros of past investment are just being thrown away by this decision.'

He said the decision jeopardises the funding contributions made by national public sources, which have contributed half of the costs. It was also a matter of 'moral responsibility' to the half a million participants who made a 'wonderful contribution' to medical research, for no reward.

Other major projects affected include the European Breast Cancer Network (EBCN), the European Cervix Cancer Screening Network (ECCSN), and the EUROCARE study, which compares cancer survival rates across Europe.

The decision is particularly galling in the light of a resolution by the European Parliament, adopted on 5 June 2003, which requested the European Commission to "promote in an appropriate manner, in the future as well, the innovative projects, such as the European Breast Cancer Network, the ENCR and the EPIC network, set up on the basis of the earlier Europe against Cancer programme which formed part of the programme of Community action in the field of public health (2003–2008)."

Dr Max Parkin

To date, no express reasons have been given for the decision. "The only reason we could find was in the answer to a parliamentary question given by an MEP. He said that it was too expensive and that the whole of the Public Health programme concerned with health determinants only amounted to the same as the Europe against Cancer programme. But this is a political answer. Health determinants only make up a third of the Public Health programme—15 million Euros out of a total of 45 million Euros. And we were asking for 820 000 Euro."

"MILLIONS OF EUROS ARE JUST BEING THROWN AWAY"

The application is currently with a review committee and the final decision will be taken by Commissioner David Byrne. Dr Parkin said he was not optimistic that the current decision would be overturned. "The Commissioner has to have a good reason not to accept the advisory committee's view," he said.

Two antismoking projects have been given the go-ahead, presumably, Dr Parkin said, because they touch other disease areas, not just cancer. He said he suspected there was a feeling among bureaucrats that "cancer has had a good run", that other areas of health should enjoy priority, and that they may think these projects can re-start in future. ENCR will continue in name only once its current funding expires, but without funding, staff will have to be dismissed, and expertise will be lost.

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HRT in the dock

Women on hormone replacement therapy (HRT) should discontinue its use "as soon as possible", and those with postmenopausal symptoms should take it "for no longer than 3–6 months", researchers from The Netherlands and Canada say (*Lancet* 2003, **362**, 414–415). The comments follow the publication of three large studies into the relationship between HRT and breast cancer.

Previous research has shown that HRT increases the risk of breast cancer, but its impact on mortality was unclear. It has been suggested that HRT-associated cancers may be less invasive than others. However, the new work throws doubt on this and concludes instead that HRT increases risk of advanced breast cancers, and death from it.

The most recent, the UK-based Million Women Study (*Lancet* 2003, **362**, 419–427) found a 66% increase in incidence of breast cancer, and a 22% increase in breast cancer deaths among current users, compared with never users. It included women attending for routine mammography as part of the NHS screening programme. Combined oestrogen-progestagen preparations were associated with a 4-fold greater increase in incidence than oestrogen alone. Risks declined after use of HRT was stopped and the study found "little or no overall increase in the relative risk of breast cancer in past users of HRT".

Oestrogen-only preparations increase risk of endometrial cancer. The Million Women study concludes, "If the additional breast and endometrial cancers associated with each type of HRT are added together there seems to be little advantage to using oestrogen-progestagen in preference to oestrogen-only HRT for women who still have a uterus."

The second study, the US-based Women's Health Initiative (WHI) Randomized Trial (*JAMA* 2003, **289**, 3243–3253) compared combined oestrogen–progestagen with placebo in a randomised trial among 16608 postmenopausal women aged 50–79 years. The HRT group had more cancer, more invasive cancer and more abnormal mammograms, compared to those on placebo.

The study did not routinely measure mammographic breast density, but previous work has shown that it is increased by combined HRT. Breast cancers among women on HRT were diagnosed initially at a lower rate, subsequently at a higher rate and at a more advanced stage, than those on placebo. The authors say this pattern, coupled with the frequency of abnormal mammograms, suggests the hypothesis that combined HRT may stimulate breast cancer growth and delay diagnosis.

"The demonstration of an increased number of more advanced breast cancers without favourable characteristics directly challenges the concept that hormone therapy might simply lead to earlier diagnosis of more favourable cancers," the authors conclude.

The third study (*JAMA* 2003, **289**, 3254–3263), based in Washington, USA, looked at the effect of different durations and patterns of HRT use. It found no increase in breast cancer risk with unopposed oestrogen among women aged between 65 and 79 years even for those who took the HRT for 25 years or longer. However, combined HRT increased risk of ER+/PR+ tumors and the magnitude of risk increased as duration of HRT use increased. "The progestin component of combined HRT is particularly important with respect to altering the risk of breast cancer," the researchers wrote.

A *JAMA* editorial (*JAMA* 2003, **289**, 3304-6) said the WHI study "demonstrates that alteration of a woman's basic hormonal physiology over decades in the interest of long-term disease prevention is fraught with hazard."

The *Lancet* editorial went further and said that the story if HRT is "a lesson of how not to introduce new developments. Analysis of potential harms and benefits should precede introduction, followed by close surveillance. This process must be independent from the pharmaceutical industry and other stakeholders with an interest in financial profits."

The "explicit position" for general practitioners is that HRT should be discouraged, or prescribed for no longer than 3–6 months for postmenopausal symptoms. It is estimated that between 20 and 50% of all women aged between 45 and 70 years in the western world are taking HRT. "This group should discontinue HRT use as soon as possible," it states.

Dietary fat and breast cancer risk

Imprecision in dietary fat measurements may mask its link with breast cancer risk, authors report in the *Lancet* (Bingham *et al.* Lancet 2003, **362**, 212–214). Inconsistencies between experimental and epidemiological data could be due to problems with the methods used in cohort studies to measure diet, they said.

The relationship between dietary fat intake and breast cancer risk is still controversial. Case–control reports have, in general, shown a positive association, but this has not been confirmed in cohort studies. The inaccuracy of food-frequency questionnaires (FFQ)—often used in cohort studies—may account for these negative findings, they said.

Women recruited into the European Prospective Investigation of Cancer and Nutrition (EPIC) Norfolk study completed FFQs (23,656 in all) and results were compared with those from a 7-day diary. From 1993 to 2002, 168 incident cases of breast cancer were recorded and each case was matched to four controls.

The link between dietary fat and breast cancer risk was shown by the diaries but not by the FFQ. The FFQ overestimated the intake of fat overall, but more cases were grouped into the lowest quintiles when compared with classification by food diary. Diary measurements of total and saturated fats in the higher quintiles were associated with a significantly increased risk of breast cancer compared with those in the lowest quintile. "Our preliminary findings suggest that use of the food diary can detect relations between diet and cancer risk," they said.

Emma Cannell
EJC Scientific Editor

EUROFILE

A new voice for cancer patients

The emergence of cross-Europe policies on health and related issues mean that cancer patients need a voice at European level to lobby effectively for their cause. The two existing pan-European groups are disease specific: Europa Donna for breast cancer and Europa Uomo for cancer of the prostate. The new European Cancer Patient Coalition (ECPC), launched in September 2003, is the first pan-European patient group to represent all major forms of the disease.

It is chaired by television presenter and former patient, Lynn Faulds Wood, who set up the Bowel Cancer Campaign in the UK after being diagnosed with bowel cancer 12 years ago. She said that one of ECPC's first priorities will be to tackle the many inequalities in access to treatment and knowledge of best practice across Europe. "We hope that this new group will enable us to highlight some of these problems to policy makers, and empower patients—the people who are the most directly affected—to ask questions about them. No-one with cancer should have to put up with sub-standard treatment just because they don't know that there is anything better in another country, or even another region of the same country," says Faulds Wood.

The Coalition hopes to become the natural first point of reference for European institutions when seeking the opinions of cancer patients. "To date there has been no fully representative body to which the European Commission, for example, could turn," says Faulds Wood, "and this has meant that they have often been given inappropriate advice by groups which are not able to see the full picture."

Members of the Coalition intend to influence European health policymaking, affirm the rights of cancer patients, ensure access to appropriate screening, treatment and care, and to promote the advancement of cancer research. They intend to work together with the scientific and professional cancer community to ensure that their voice is both strong and representative in lobbying policymakers.

According to Kathy Redmond from Milan, Italy, an ECPC steering committee member and proponent of patient advocacy, there are many challenges to be faced in building an effective patient organisation at European level. "It is difficult to define common concerns because of the variability of health care systems," she says. "The European legislative system is extremely complicated, even to Brussels insiders, and ECPC will have to learn how to navigate and influence it."

But one of the largest obstacles to patient collaboration at European level is language. "Relatively few Europeans have the same mother tongue, with just over 25% speaking German, and 16% speaking English. Just over 50% of Europeans claim to speak a second language with around 40% speaking English, 10% German, 7% Spanish, and 3% Italian." Additionally, fluency in English as a second language declines with age, says Ms Redmond.

ECPC Founding Members

Associazione Italiana Malati di Cancro, parenti ed amici (Italy)
Association National des Malades du Cancer de la Prostate (France)
CancerBACUP (UK)
CML Support (UK)
Europa Uomo—The European Prostate Cancer Coalition (Belgium)
International Myeloma Foundation (UK)
Leukaemia Care (UK)
Longkanker Informatiencentrum (The Netherlands)
Lynn's Bowel Cancer Campaign (UK)
Mamazone (Germany)
Riding's Asbestos Support and Awareness Group (UK)
Roy Castle Lung Cancer Foundation (UK)
Selbsthilfe Prostatakrebs (Austria)

This list was compiled on 15 September 2003. The Coalition hopes to

Linguistic difficulties also contribute to the digital divide in Europe. Given that 70% of the content of the Internet is in English, it is not surprising that there is a huge variation in the number of houses with Internet access across Europe. In countries with high levels of English fluency such as The Netherlands, Sweden and Denmark, around 65% of households have Internet access. In Greece, Spain and Portugal, Internet access at home is as low as 9%.

One of the biggest challenges facing ECPC will be to ensure adequate funding to overcome the linguistic divide and to enable the coalition to operate effectively. Recent speculation about the independence of patient groups who take funding from the pharmaceutical industry has made the group particularly keen to draw up watertight guidelines to avoid any perception of bias. "We all know that some patient groups are influenced by the bottom line of their financial sponsors," says Redmond, "but we have strict guidelines about conflicts of interests and transparency about funding sources, and intend to stick to them."

"There is a growing political ideology that patients should be involved at all levels of health decision making. Coupled with the increase of consumerism, and the growing freedom to express dissatisfaction with health services, this has helped fuel the patient advocacy movement," says Redmond.

HIV/AIDS patients have shown the way, says Faulds Wood. "Their activism, coupled with their understanding of how to influence policymakers, drug regulators, and clinicians, forced their inclusion into the decision-making process. We see the Coalition as becoming the same kind of potent political force for good, and achieving results not just for those who have been diagnosed with cancer, but for those in whom it can be prevented before it starts," she says.

Mary Rice
EJC Brussels

Computer-aided screening

Computer analysis of CT scans could form the basis of screening for lung and colorectal cancer, UK researchers say. The first release of the system has just received CE approval and software developer Medicsight says it has been shown to be as good as the cumulative opinions of three radiologists in identifying lung nodules.

Essentially, the software interprets scan data from the new generation of Computerised Tomography (CT) scanners, and highlights abnormalities. Data presented to the Radiological Society of North America (Chicago, December 2002) were based on 350 CT scans of the thorax. The three radiologists identified 508 nodules between them; respectively, 319, 343 and 156. All of these nodules were detected by the software.

Dr John Costello, former medical director of King's College London, now Medical Director of Medicsight, said that the software was originally developed to help in the detection of early lung cancer, but had been adapted to find pre-malignant colorectal polyps. Other software systems for the measurement of coronary artery calcium are in an advanced stage of development.

The system is being used at the Ravenscourt Park Hospital Hammersmith Trust in London, and is accepting patients referred by GPs. Nationally, the shortage of radiologists means that a CT-based screening programme for colorectal cancer is not feasible in the UK at present, since each study would take around 30 minutes for an experienced practitioner to read, Dr Costello said. "Screening programmes which depend on radiologists will not happen without software because of the volume of data for analysis. There must be an automated system for the analysis of data otherwise the workload is too great," he said.

Oops!—Correction

In our article on a FECS pilot study on continuing medical education (*'CME Online - Your views, please!' EJC News*, **39**(9), 1185), the website address was given incorrectly. It is www.FECSETC.org. Our apologies.

"New approaches needed" for Tissue Banks

Health professionals and managers require new approaches "to ensure that consent procedures are appropriate and that high quality material is available" from tissue banks, say Scottish researchers *(EJC Editorial Comment, this issue).* New systems which guarantee quality at each step of the process will have to be introduced, they say.

The researchers were commenting on the publication of "Human tissue research: EORTC recommendations on its practical consequences" (*EJC this issue*). EORTC guidelines stress that, where material is collected prospectively, patients "must be adequately informed about the translational research project".

Where the material has already been collected, but without consent for future research "reasonable efforts should be made to recontact the patient". However, if this is not possible, research projects might still be allowed under certain conditions.

Intellectual property rights acquired through use of tissue samples from patients in EORTC trials should lead to compensation to the EORTC. The Scottish researchers agree that this is a "sensible way to proceed" but says participating hospitals may require a "Materials Transfer Agreement" with the EORTC.

Such changes have 'significant' resource implications and they say that "much of the cost of tissue provision will have to be seen as an integral part of biomedical research budgets."

All European countries are governed by the European Union (EU) Data Protection Directive, but some place additional demands on research. In Sweden, patients have to provide separate consent for each research protocol involving their material. At the other end of the spectrum, The Netherlands has an opt-out system, by which research on anonymised tissue can be performed until the patient raises an objection. The EORTC guidelines warn that proper European/US collaboration "will only be possible if there is harmonisation of the rules" at national or European level.

NSAID acts through p21

Scientists have uncovered a possible mechanism of action for a non-steroidal anti-inflammatory drug (NSAID). They suggest "p21 could be the molecular link in the chemopreventive effects of NSAIDs" (Huls et al. *Lancet* 2003, **362**, 230–232).

NSAIDs have chemopreventive activity through the inhibition of the cyclooxygenases (COXs), but also through COX-independent mechanisms. They believe that p21 could act as the mediator of a COX-independent differentiation/proliferation switch.

The *APC* and *B-catenin* genes are commonly mutated during colorectal carcinogenesis and both are part of the Wnt signalling pathway that is active in 85% of sporadic colorectal carcinomas. These mutations result in the accumulation of nuclear B-catenin that can bind to and activate the TCF4 transcription factor. This activation results in decreased p21 levels and cells are prevented from differentiating. Instead, they are allowed to proliferate inappropriately. *The Lancet* report hypothesises that B-catenin/TCF4 activation acts as a differentiation/proliferation switch that may be mediated through p21.

The activity of B-catenin/TCF4 is likely to affect several cellular processes. However, micro array analysis suggests COX-2, a gene through which the NSAIDs commonly act, is not a target of this complex.

The NSAID, sulindac, induces p21 expression in vitro leading to cell cycle arrest and apoptosis. Furthermore, small intestinal tumours in mice were reduced by sulindac treatment, but this activity was lost following the inactivation of p21 in these mice. This points to a role for p21 in mediating the effect of NSAIDs through a COX-independent pathway. Confirmation of similar effects to sulindac exerted by the other NSAIDs is required. "The role of B-catenin–TCF4 activity as a master switch that controls proliferation versus differentiation in the intestinal epithelium, by controlling the expression of p21, extends the possible mechanisms by which NSAIDs could mediate their anti-cancer effect," they said.

Emma Cannell
EJC Scientific Editor

PODIUM

Challenges facing Cancer Research UK

Professor Alex Markham took over as Chief Executive of Cancer Research UK in October 2003, having previously been Professor of Medicine at University of Leeds, UK. He trained initially in chemistry at University of Birmingham and later qualified in medicine in London and Oxford. He worked in the pharmaceutical and diagnostics industries for 20 years in the UK and US, and has chaired and been a member of influential Government, Medical Research Council (MRC) and Wellcome Trust committees.

Professor Alex Markham

Congratulations on your new appointment! Do you have a long-standing involvement with Cancer Research UK?

Not particularly, partly because much of my research has been conducted within the pharmaceutical industry, and the rest at University of Leeds in Yorkshire. Historically, neither Imperial Cancer Research Fund nor Cancer Research Campaign had a presence in the area; until the mid 1990s, money was raised and research funded exclusively by a local charity, Yorkshire Cancer Research Campaign.

Is it important that you came from outside the loop?

That rather presupposes that there is a major remaining schism between the two original charities, which needs a pair of healing hands. That is not the case; the charities have been successfully merged. We have our own institutes, in which staff are employed directly by Cancer Research UK, and we also fund peer-reviewed projects within universities. I am not partial to one or other way of working and we will continue to do both.

What are the issues facing Cancer Research UK?

It will be a question of looking at our portfolio and deciding whether we have got the overall balance right. We have to balance basic research, prevention, epidemiology, translational research, new drug discovery, clinical trials, and psychosocial issues. We are active in all these areas and the biggest challenge of my first year will be to see whether the portfolio needs slight changes, and if so, how we can achieve this in a sensible, measured way.

What sort of changes do you envisage?

In the UK, the National Cancer Research Institute (NCRI) and its companion body, the National Cancer Research Network, have succeeded in increasing the numbers of cancer patients entering clinical trials from 3% 18 months ago, to 6% now. That's an absolutely fantastic achievement, but it raises a strategic question at Cancer Research UK: an increase in clinical trials activity puts increased demands on our budget. If we, as a major charity, were to say we couldn't make money available to fund this extra work, it would send out a strange and unacceptable message. But bringing new activity into our portfolio can only be done after careful thought and we need a robust and transparent decision-making system.

How will the Clinical Trials Directive affect Cancer Research UK?

This current piece of legislation from the European Union is a major cloud on the horizon, and I am extremely concerned about it. The particular issue for us is the requirement for clinical trials to have a named sponsor who shoulders all the responsibility. Costs of trials could increase four-fold, which means my budget will in future only cover one-quarter the present number of trials.

The Directive will have a disproportionately adverse effect on UK-based research, which is funded by charities to a significant extent. In Europe, the proportion of studies funded by pharmaceutical companies is very high, so the need to name a sponsor will pose less of a problem.

If the Directive and draft UK legislation is imposed as it stands it will compromise our ability to take early stage, highly experimental novel approaches into patients, particularly those areas that the pharmaceutical industry has no interest in. Another area which could suffer is the exploration of new uses for existing drugs which are out of patent. Cancer Research UK often undertakes this work in collaboration with the NHS through the NCRN. Thalidomide, for example, has been re-discovered as a potential agent to treat a number of cancers. No drug company is going to sponsor a trial into an agent which is out of patent.

Are there any other worrying moves from Europe?

There's a proposal to look at charities' VAT exemption. If it were removed, the UK stands to be the biggest loser, again because we have the biggest charitable sector. If we have to pay 17.5% on our retail activity, for example, we will not be able to put up prices by 17.5% so that will be money lost to research. We are outliers in Europe in this respect; we stand to be most disadvantaged and there is something not right in the way our message is being put across in Brussels.

How optimistic do you feel about the future of cancer research in the UK?

Very. Cancer research is in a very good state in the UK, thanks in part to Professor Mike Richards, the National Cancer Director at the NHS, who has done a superb job. Sir Paul Nurse is an almost impossible act to follow at Cancer Research UK, but I'm getting a huge amount of support in my new role. Sadly, I can promise I won't win the Nobel Prize! However, I can make a valuable contribution across all our activities.