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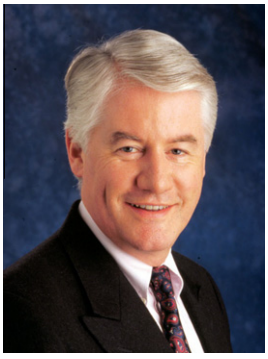
End of an era at EJC

After 10 years at the helm of *EJC*, Professor John Smyth is to step down as editor-in-chief. Editorial board members Professor Jaap Verweij, Professor Maurizio d'Incalci, Dr. Giovanna Damia, Professor John Kurtz and Professor Mike Stevens will also retire from the journal at the end of 2010.

Professor Alexander (Lex) Eggermont has been appointed as the new editor-in-chief, from 2011 and will be



Professor John Smyth

announcing the new editorial board in due course. Ms Sarah Jenkins, publisher of *EJC*, said: "John has led the *EJC* with vision and dedication for 10 years, and I am sad to see him go. At the same time, I'm delighted to welcome Lex, and look forward to working with him.

"Under John's leadership, *EJC* has become one of the premier European oncology journals. The Impact Factor rose for 5 consecutive years and now sits above 4. *EJC* has differentiated itself from other journals; it is committed to the ideal of multi-disciplinary working and to European oncology in general.

"The current success of the journal is a testament both to John and the team and reflects their enthusiasm and plain hard work over the last decade.

"John has steered the journal through dramatic changes in the publishing world. When he arrived, most manuscripts arrived by post. Now both submission and publication are online and *EJC* receives 1 million downloads a year. More than one in four is from North America, and a further 20% from Asia, which demonstrates that *EJC* is now read worldwide.

"John and the editors have pulled together through these and other challenges. The editors have shown steadfast support for authors in their careful management of submissions. The team has been united in its determination to keep a balance across all areas of cancer and to ensure that *EJC* is essential reading for those committed to multidisciplinary working. I, for one, will miss the lively debate at the editorial board meetings!" Professor Smyth said, "I and the editors are proud of the way the journal has developed over the past 10 years. The challenges are constantly changing, particularly now with online readership. The educational demands on cancer professionals, coupled with the increasing number of meetings, also have an impact on the readership of a multidisciplinary journal.

"The world is becoming super-specialised and, especially for those in training and early in their careers, access to a multidisciplinary journal is at least as important as access to journals specific to their own area of expertise.

"Working with the editorial team has been a tremendously enjoyable experience. I'd like to congratulate everyone for all they have brought to the journal, and I wish Lex luck in taking the challenge on."

Professor Eggermont is Head of Surgical Oncology at the Erasmus University Medical Center Rotterdam (the Netherlands), and former President both of ECCO and of EORTC (where he was also Secretary General, Chairman of the EORTC Clinical Research Report Devision, and of the

Professor Alexander Eggermont

Melanoma Group). He co-founded and is currently President of the European Academy of Cancer Sciences.

He said: "I'm involved in many different aspects of cancer, from cancer research all the way through translational research and clinical cancer practice to oncopolicy. I believe the *EJC*'s task, similarly, is to cover the continuum of cancer, including epidemiology, research,

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EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

doi:10.1016/j.ejca.2010.08.016

Bevacizumab's future in breast cancer in doubt

The Oncologic Drugs Advisory Committee (ODAC) of the US's Food and Drug Administration (FDA) voted 12 to 1 to recommend removal of the advanced breast cancer indication from bevacizumab (Avastin).

The vote applies to the use of bevacizumab in combination with paclitaxel as first-line treatment for advanced HER2-negative breast cancer. It has no impact on the drug's approved uses for other cancer types – lung, kidney and colon – nor on its use in other countries.

The ODAC's recommendation came after consideration of two large clinical trials, which included nearly 2000 women. They voted that, when added to standard chemotherapy, bevacizumab did not extend progression-free survival (PFS) long enough to be clinically meaningful.

In the trials, AVADO, and RIBBON 1, the extension to PFS ranged from 1 to 3 months.

Dr. Sandra Horning, head of clinical development in haematology/oncology for manufacturer Genentech said, "We are disappointed by the committee's recommendation and believe Avastin should continue to be an option for women with this incurable disease. We will continue to discuss the data from the more than 2400 women who participated in three phase III studies with the FDA."

The FDA is due to announce a final decision by September 17th, 2010.

'Large differences' in breast cancer mortality

Wide variations in breast cancer mortality across Europe were found in a study by the International Agency for Research on Cancer (IARC). Researchers looked at mortality rates between 1989 and 2006 and found that for most countries there was an overall reduction, though the extent of the decrease 'varied considerably' (*BMJ 2010; doi:10.1136/bmj.c3620*).

Of 30 countries considered, half showed death rates in 2006 to be more than 20% lower than in 1989. In 4 countries – Greece, Estonia, Latvia and Romania – there was an overall increase over the same period.

Dr. Christopher Wild, director of IARC said, "There is a need to examine what innovations contributed to this reduction in breast cancer risk in Europe and how these lessons may bring valuable public health benefits globally, as well as in Europe itself. The notable increasing or static trends in mortality in some European countries represent avoidable cancer deaths."

The UK was among the countries with the largest decreases, and these, the researchers said, 'were only partly linked to high mortality at the end of the 1980s.' Other factors were the 'high screening coverage of women aged 50–64 after 1995, a rapid and general use of reasonably priced tamoxifen and adjuvant chemotherapy by UK doctors, and the reorganisation of breast cancer services on the basis of the Calman-Hine and Campbell evaluation reports.'

The small decreases or continued increases in breast cancer mortality rates seen in central European countries 'were correlated with low, usually non-organised, screening activities, low numbers of mammography machines, slow uptake of anticancer drugs, and health expenditures below the European average,' the researchers say. Rapid changes in risk factors such as decreasing fertility and increasing age at first birth were seen in the 1990s after the collapse of the communist regimes and may also be linked.

'INCREASING OR STATIC TRENDS IN MORTALITY REPRESENT AVOIDABLE CANCER DEATHS'

Some efforts to combat breast cancer appeared to have disappointing results. France has high numbers of mammography units, the highest spending on cancer drugs per person in Europe, being at the forefront in use of new costly treatments, and devotes much effort to enhancing adherence to guidelines. Despite this, the decline in breast cancer mortality see was 'quite modest', the report stated.

'Clearly, improving the collection of relevant screening and management data is warranted for understanding the strong variations in breast cancer mortality in Europe,' the researchers conclude.

End of an Era *continued*

prevention, screening, early diagnosis and clinical practice. These elements are interlinked and must all feed into oncopolicy; there is a pressing need for cancer research and care to be better structured and organised in Europe.

"Running a multidisciplinary, multifaceted cancer journal is a difficult but necessary challenge. We need articles of importance from all disciplines, which allow us to give a broad, helicopter view of the field. We want to promote consideration, discussion and awareness of the big issues in cancer today and to inform policy.

"Clinical life is becoming highly specialised, but oncology is a big, general, societal problem and we need to write about that, and put specific research findings into perspective. *EJC* has the task – not only of publishing good research from individual fields – but of integrating them and taking a pan-European and global view of the major issues. We need to make sense of the vast amount of information coming from the various specialties."

Ms. Jenkins said: "Lex has extensive knowledge and wide-ranging experience across oncology. He is well-known in the international cancer community and brings with him editorial experience from Clinical Cancer Research. I am impressed with Lex's vision for the development of the journal – his energy and enthusiasm for the *EJC* is inspiring! He is the right person to take the journal into its next phase and I am looking forward to working with him to continue the journal's upward trajectory."

EUROFILE

Early claims for funding under Framework-8

Europe's cancer researchers are thinking ahead on essential areas for funding from the EU's next multi-billion research programme, Framework 8, which begins in 2014. As well as research priorities, they are pinpointing areas where current EU funding practices require reform.

Both the budgets for the overall programme and for cancer research face a long process of political negotiation over the next three years. EU commentators speculate they will be in line with the current EU research programme, Framework 7. This stands at 50.6 billion Euros for seven years, from 2007 to 2013, of which cancer activities will account for approximately 370 million Euros by the end of the programme.

Research funding for prevention and prevention strategies tops the wish list of many oncologists across Europe. "We know that with prevention strategies we can reduce the incidence of cancer but nobody is doing the research," says Håkan Mellstedt, professor of oncologic biotherapy at the Karolinska Institute, and director of the Karolinska cancer centre, Stockholm.

Researchers argue cancer prevention studies should be conducted at EU level precisely because they tend to involve large cohorts followed over a number of decades. According to Mellstedt, "They are manpower intensive, but we already have the networks in place to conduct them, and we are rather good at collaborating in Europe."

The size of prevention studies also makes them expensive to conduct for any one institution or country. Being partly EU funded would add value says Mellstedt. "Moreover, if one project of this type is funded by the EU, it gives a very strong signal that this is an important area."

'FUNDING FOR PREVENTION STRATEGIES TOPS THE WISH LIST'

"The major problem is that prevention is not sexy enough for policy makers. But you have to be objective and see that in the realm of prevention and detection we can do big things for relatively little financial support," he says.

There is a growing consensus among cancer researchers that EU funding should be directed to fields where there is sparse research activity. Eduardo Moreno, European Research Council grant holder and group leader of research on cell competition at Spain's national cancer centre CNIO, explains, "Funding European groups leading the field by doing something unique, not being done anywhere else is a good thing, since the technologies and patents that arise bring money back into Europe, a return on the research investment."

Moreno is one of many oncologists citing early detection as a priority for funding. "Cancer as we treat it now is mostly a very advanced disease. We deal with big tumours, probably evolved over years. This makes research into the early stages, before we can even call it cancer, very important. It has been neglected for a long time, but those who are studying it, are European" he says. His own group leads in field cancerisation phenomena.

Work on treatment strategies also features high on the list. "Research focusing on strategies for the best use of existing cancer treatments is in the domain of non-profit research in all countries but it is poorly funded, and countries don't share results," says Rossana Berardi, lecturer and consultant medical oncologist at the Universita' Politecnica delle Marche, Ancona, Italy. "At EU level, determining best sequences using existing drugs or collecting biomarkers to predict prognosis or a patient's response to treatment does not require big amounts of money," she says. Berardi would especially like to see prevention and treatment strategies directed to lesser researched cancers, such as pancreatic or urological cancers.

Along with prevention studies and research into better models, Clare Isacke, leader of the molecular biology team at the Breakthrough Breast Cancer Research Centre, London supports all aspects of biomarker research at EU level. "It is often not at all clear with standard treatments how well they will work, even with established drugs like Avastin or antiangiogenic treatments," she says.

Developing software that can combine and aggregate data into formats easily understood by physicians and clinical workers is an essential part of this work according to Ladislav Dušek, director of the Institute of Biostatistics and Analyses and new Cetocoen cancer centre at Masaryk University, Brno, Czech Republic. "We need to implement molecular diagnostics into clinical practice. Many EU countries have built up national databases but most cannot combine data from hospital information systems, outcomes of laboratory research and real routinely performed daily clinical practice. The situation is lacking not only in the Czech Republic, but in Hungary, Poland and other neighbouring countries including Germany," he explains.

'FUND PEOPLE DOING GOOD WORK; IT'S DANGEROUS TO GUIDE RESEARCH FROM THE TOP DOWN'

"In Europe there are no relevant functional tools to do this. It is time to do it and move into the age of personalised medicine," he says.

However, areas where there is little or no research activity are the hardest to fund at EU level, according to Isacke who has both evaluated EU research proposals and won EU funding. "If nobody else is doing it, it becomes very hard to judge funding applications," she says.

In addition, "when a collaborative grant is only part of your portfolio, you can't get through your workload and manage a collaboration," she adds.

In order to ensure excellence and reduce the administrative burden placed on researchers, Isacke proposes moving away from funding the large pre-defined collaborations that are currently favoured, to financing individual groups with proven track records. Moreno agrees, "Fund people doing good work, this is where the big breakthroughs occur. It's very dangerous to guide research from the top down. And people collaborate naturally if it's in their interests anyway."

Saffina Rana, Brussels

NICE issues guidance on cancer of unknown primary

On July 26, 2010, the National Institute for Health and Clinical Excellence (NICE), the clinical effectiveness agency for England and Wales, issued a new guideline for management of patients with cancer of unknown primary (CUP). Stating that patients with CUP "are disadvantaged in many ways", the guideline identifies numerous problems that plague diagnosis and treatment of this type of cancer, such as lack of agreed-upon clinical definitions and referral guidelines, uncertainty over the use of diagnostic tests and optimum treatment, insufficient specialist oncology expertise, and inadequate patient education and support. In an effort to remedy these deficiencies, the guideline offers specific diagnostic and referral pathways for clinicians treating people with CUP.

CUP is diagnosed when patients have metastatic tumours but the primary site cannot be found. Its incidence has been estimated at 2–6% of all cancer cases, and is one of the ten most commonly occurring cancers worldwide. CUP is the fourth leading cause of cancer death in England and Wales, where about 10 000 people present with this type of cancer annually. In the USA, CUP occurs in more than 32 000 people each year. Often the primary tumour is not discovered even at autopsy, leading some investigators to argue against extensive searches for it.

'A LOT OF PEOPLE SPEND TIME AND MONEY OVERINVESTIGATING PATIENTS'

Some primary tumours have two different clones, says Michael C Perry (University of Missouri, Columbia, USA). Citing a hypothesis advanced by Larry Norton of the Memorial-Sloan Kettering Cancer Center (New York, USA), Perry says that one clone "may be self-renewing and perpetuates the growth of the primary tumour, while the other clone keeps sending metastases out elsewhere. In some patients, the self-renewing clone may die out, and so you'll never find it because it's no longer there. That's why even at autopsy series, a good deal of the time you can't find the primary tumour."

The guideline recommends that investigations be undertaken only if the results will affect treatment decisions and if the patient understands the reasons for and risks and benefits of the investigation and the possible further treatment indicated. "I think it's good to have some guidelines, because a lot of people make a hash out of managing CUP and spend a lot of time and money overinvestigating patients", especially since their life expectancy might be only 3–6 months, Perry adds. Even if there is a good chance of finding the primary tumour, "you have to pick your shots. If the patient is in very poor shape, riddled with disease, then that person may not benefit from knowing where their primary tumour is from, unless you've got a treatment that is very highly successful, and we often don't have that for solid tumours."

Patients with CUP can be divided into those with favourable and unfavourable prognoses, says Nicholas Pavlidis (University of Ioannina, Greece). In general, "favourable subsets are more sensitive to chemotherapy, such as women with primary peritoneal carcinoma of serous or papillary histology or patients with neuroendocrine CUP, or to locoregional treatment, such as female patients with cervical nodal involvement of a squamous-cell carcinoma or isolated axillary metastatic adenocarcinoma. Unfavourable patient subsets are considered to have a poor prognosis. Therefore, the therapeutic management of CUP is very challenging because it requires a good knowledge of the different clinicopathological entities."

In general, tumours in the brain or liver suggest a poor prognosis, Perry says. "If it's in a lymph node, it's conceivable that the patient may have had a tumour in the breast that has spread to an axillary lymph node and may have stage II disease. But most of the time, when somebody presents with a nodule in the lung, liver, bone, or brain, that's stage IV disease, and depending on the extent of the metastases and where the primary is from, that will determine how long and how well the patient will live."

Since the primary tumour dictates most treatment approaches, treatment of CUP can be challenging. Chemotherapy often consists of a platinum-based therapy plus etoposide. Recently, addition of taxanes to the regimen has been associated with improved outcomes. As a general rule, treatment of CUP with favourable prognostic features should be similar to the treatment used for tumours of the presumed primary site, says Pavlidis. For example, "a woman with primary peritoneal carcinoma with serous or papillary histology is managed as if she had an International Federation of Gynecology and Obstetrics stage III ovarian cancer". On the other hand, if the patient is in an unfavourable prognostic subset, "there is no strong evidence that they will respond to systemic treatment similarly to the known primary tumours".

'OFTEN THE PRIMARY TUMOUR IS NOT DISCOVERED EVEN AT AUTOPSY'

Pavlidis believes the guideline will offer clinicians some much needed assistance in management of these difficult cases. "My personal opinion is that the guideline is of high value, very well written, and extremely helpful for the oncologists who treat patients with CUP."

Norra MacReady

For the NICE guideline see http://www.nice.org.uk/guidance/index jsp?action=byID&o=13044

This story originally appeared in Lancet Oncol 2010; 11:824

PODIUM

Time for action to prevent cancer

Dr. Andrew Renehan (University of Manchester, UK) is an honorary consultant colorectal surgeon and heads the obesity and cancer research group at the Manchester Cancer Research Centre. His research focuses on the links between obesity, diabetes and cancer, and he is one of the guest editors of the forthcoming EJC Special Issue, 'Cancer Prevention in Europe' (EJC 2010 46:14)

What proportion of cancer is preventable?

It depends on how wide a definition you use for lifestyle. But the minimum number of major lifestyle risk factors should be four - Smoking, Obesity, Alcohol, Physical inactivity or the pneumonic, SOAP – considering these, 50% of all cancers could probably be prevented.

So these key risk factors are now well-established?

They are. There has been a fundamental shift in the last 5–8 years in how we think about risk factors. We have moved away from a reductive approach which meant looking narrowly at all components of diet: proteins, meat, fibre, vitamins and other micronutrients. The list went on and on. Now we have stepped back and are taking a more holistic, global approach. We're looking at the big factors, and while some details still need to be pinned down, we can all agree on the 4 main lifestyle factors that contribute to cancer.

Why then is the basic prevention message so difficult to get across?

There is awareness among health professionals, educated people in the media, and even among politicians, but this hasn't converted into changes in behaviour and changes in policy. We need a clear and consistent message and to get away from confusing daily headlines in the mainstream press. The media picks up on sensational findings but the stories are often based on studies that are flawed or biased. It is hugely important that our message is as precise as possible and not over-exaggerated.

How does the obesity story compare with tobacco?

There are parallels. Obesity is a slow problem; it has arisen over decades, and will take decades to reverse. It took 40 years for smoking rates to come down after the classical smoking data published by Richard Doll in the 1950s and 60s. There are lessons that could be learned: we know we need public health and political changes at the level of taxation, legislation on fat in foodstuffs and so on. We'd love to be able to say that we will be able to tackle obesity more quickly than smoking but what is becoming clear is that, complex as smoking is, obesity seems to be even more so. In the UK, the Government-commissioned Foresight report (*Tackling obesities: Future choices, 2007*) came up with a complex network of 35 or more factors that drive obesity in a population and, hopefully, ultimately reverse it. It made clear that there isn't just one cause. You can re-introduce school playing fields but if 80% of kids are still being driven to school, it won't necessarily change their activity levels. It is complex.

What is wrong with current public health approaches?

They tend to be directed towards people who are already overweight and obese. It would be simpler if we could prevent occurrence of weight gain in the first instance. That's why the availability of cheap high fat foods needs to be tackled.

We need robust studies to show what is and isn't effective. The smoking story has written itself. We haven't got a prescription for how to get a population back to a relatively normal body mass index. No country has done it.

Were there any surprising findings in the Special Issue?

I was involved in an analysis of colon cancer in collaboration with a Dutch group. The modelling showed that preventing weight gain and encouraging weight reduction would be most beneficial in men. In women, a strategy with greater emphasis on increasing physical activity would be more effective. Here was an attempt to use the science to make advice more individualised or at least gender-specific. It has a direct impact on public health campaigns; women read different magazines and get their healthcare and advice from different sources.

This kind of approach will eventually get us away from the problem of people thinking that various pieces of advice do not apply to them. It will start getting us into the position where we can give specific advice to different parts of the population.

What do you hope the Special Issue will achieve?

The need now is to implement what we know. Epidemiology has quantified and described the problem but this knowledge hasn't made it into public health policy and the political arena of legislation and taxation. We hope the Special Issue will underpin fresh attempts at implementation. We focused on areas where there is good evidence of cancers and risk factors and produced a series of specific examples which we hope will convince politicians and policy makers to take action.

Helen Saul