ELSEVIER

European Journal of Cancer 40 (2004) 467–471

European Journal of Cancer

www.ejconline.com

NEWS. . .NEWS. . .NEWS

Aspirin 'increases risk of pancreatic cancer'

Aspirin may increase risk of pancreatic cancer, an Austrian-US research group has concluded (*JNCI*, 2004, **96**, 1 22–28). Women who reported more than 20 years of regular aspirin use had a relative risk of pancreatic cancer of 1.58, compared with non-users. The study included 88,378 women in the US Nurses' Health Study. During 18 years of follow-up, 161 cases of pancreatic cancer were documented. Aspirin use was assessed in 1980 and updated biennially; among those who reported aspirin use on at least 2 of 3 consecutive questionnaires, the risk increased with dose.

The study was established on the basis of limited evidence suggesting that aspirin may inhibit pancreatic cancer. However, it concluded, 'Extended periods of regular aspirin use appear to be associated with a statistically significantly increased risk of pancreatic cancer among women.'

In an accompanying editorial (*JNCI* 2004, **96**, 1 4–5), Dr John Baron (Dartmouth Medical School, New Hampshire, USA), a member of the Advisory Board for the Nurses' Health Study, described the findings as 'provocative'. They 'force us to think carefully about the actions of aspirin and other non steroidal anti-inflammatory drugs (NSAIDs) and the mechanisms underlying pancreatic cancer,' he wrote.

Aspirin in many ways has been 'a wonder child of chronic disease prevention', he says, but 'there is no reason that all cancers in the abdomen should respond in the same way to aspirin and/or NSAIDs.' Aspirin increases expression of some prostaglandins thought to be anti-carcinogenic (13-S-hydroxyoctadecadienoic acid) but decreases expression of prostacyclin, shown to inhibit the malignant phenotype of neoplastic pancreatic cancer cells in nude mice.

'There are no easy answers to the question of what aspirin and other NSAIDs do to pancreatic carcinogenesis,' according to Dr Baron. Previous epidemiological studies and limited laboratory work have produced conflicting results, and he concludes, 'Fortunately, conflicting data from diverse threads of research are often a very effective push towards scientific progress.'

Worm gene sheds light on BRCA1

Scientists have discovered a gene in the nematode worm which may help them explore how BRCA1 works in humans, they say (*Current Biology* 2004, **14**, 1). The researchers have found a gene in the soil-dwelling worm, Caenorhabditis elegans (*C. elegans*), which is similar to human BRCA1.

Previous scans of the genomes of yeast, worms and flies have failed to find an equivalent of human BRCA1. However, scientists from the Cancer Research UK London Research Institute, with colleagues in the US and Germany, undertook a comprehensive search for DNA repair genes in *C. elegans*. They identified an orthologue of BARD1, which in humans forms a complex with BRCA1. This led them to a homologue of mammalian BRCA1.

Lead researcher Dr Simon Boulter (Cancer Research UK) said, 'It's nearly a decade since the BRCA genes were discovered and implicated in the development of breast and ovarian cancer but we are still very much in the dark about how they function.'

'Our new finding is somewhat unexpected but very exciting. The detailed genetic analysis we can do in cells of the worm is not really possible in more complex human cells.'

C. elegans has less than a thousand cells and is around one millimetre in length. It is one of the simplest multicellular organisms with a nervous system. Studying it is 'a fast and easy way to address some bigger questions about humans,' Dr Boulter said.

The researchers showed that the BARD-1 orthologue, Ce-BRD-1, interacted with a homologue of mammalian BRCA1. Animals depleted for either *Ce-brc-1* or *Ce-brd-1* display similar abnormalities, including defects in meiotic chromosome segregation, elevated levels of p53-dependent germ cell death before and after irradiation, and impaired progeny survival and chromosome fragmentation upon irradiation.

'Our results show that these worm genes are involved in the DNA repair process and are essential for surviving DNA damage. This, along with the fact that the genes look similar to the human versions, tell us we've found the worm BRCA1 and BARD1,' said Dr Boulter.

The discovery, coupled with the observation that other components of the BRCA1 pathway are conserved in *C. elegans*, including orthologues of FANCD2 and BACH1 'suggest that mechanistic dissection of this pathway in a genetically tractable organism is now a real and exciting possibility,' the researchers conclude.

EJC News is compiled by:
Helen Saul
Tel.: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.co.uk

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.01.001

Quality of RCTs 'may be better than assumed'

Poor reporting of methods in randomised controlled trials (RCTs) does not necessarily reflect the conduct of the trial, researchers say (*BMJ* 2004, **328**, 22–25). Members of the US' Radiation Therapy Oncology Group (RTOG) concluded that reviewing research protocols and contacting trialists 'should be integral' to assessing the quality of RCTs.

The study included RCTs conducted by RTOG since its inception in 1968. Of 59 terminated phase III RCTs, 3 were unpublished. For the remaining 56 protocols, poor reporting of methods did not reflect poor methods. For example, a priori sample size calculations were performed in 76% of trials but the information given in only 16% of the published papers. All trials had adequate allocation concealment but this was reported in only 41% of the papers.

Efforts, most notably the Consolidated Standards of Reporting of Trials (CONSORT) statement (*JAMA* 2001, **285**, 1987–91), have been made to improve the quality of studies and their related publications. However, they imply 'that if certain design or methodological features are not reported then they were not done', the BMJ paper states.

The study noted that although RTOG researchers were cognisant of key features in the design and conduct of good quality trials, 'they were less aware of the need to report these to a standard that would meet contemporary (CONSORT) requirements.'

The study's findings are based on a select sample of findings, which may not be representative of RCTs. 'Further studies to confirm the generalisability of our findings are needed and would be helpful,' they say.

A commentary points out that this finding may mean that systematic reviews have excluded potentially good quality papers. The scoring of the quality of papers in meta-analyses would also have been affected. One solution, suggested by the study authors, is to assess the original protocol and contact trialists to check the accuracy of reported methods.

The commentary concludes that, until researchers can download crude data for meta-analysis, 'it should be bourne in mind that although papers fail to report important design and methodological features, they were probably done, especially if the papers are authored by a body such as the RTOG, the protocols of which undergo rigorous review.'

Mammography debate continues

Population-based mammography screening significantly improves survival among women aged between 40 and 74, according to new data from Finland (*The Breast* 2003, **12**, 308–313). The survival advantage was demonstrated in all 10-year age groups, they said.

From 1987, when screening was first established, to 1997, 176,908 screening examinations were performed in 36,000 women in the city of Turku. Primary invasive breast cancers were found in 685 women who were screened, and in 184 who were not screened. Survival was far better in the screened group (HR 2.55).

The Finnish group refutes claims that screening detects less aggressive breast cancers that will never be a threat to the affected women's lives. They say there was no difference in the type, grade, size or lymph node status between the cancers found in the first and later screening rounds in their study. Furthermore, all of the women in the study were treated according to the same guidelines.

The most important explanation for the beneficial effect of screening is, they say, the absence of axillary lymph node metastasis, good histological differentiation, grade of breast cancer and small tumour size. Screening in Turku 'has been a successful health policy', they concluded.

However, in a related editorial (*The Breast* 2003, **12**, 299–301), Dr HJ de Koning argued that improvement in survival of screen-detected cases is not necessarily equivalent to benefit. The use of survival in comparing the screened and non-screened groups is biased, because mammography screening brings forward the diagnosis by an estimated 3–4 years.

'This simply means that even if there were no true benefits of mammography screening, the survival curve for screen-detected cases has been shifted by 3–4 years and just looks more favourable,' he said. The Finnish data 'would have been more appealing' if it had been adjusted for this lead-time bias.

Too often, survival curves are used as clear-cut evidence on benefit. 'Prudence is needed, the more when going to other cancer screening programmes where these biases may even be larger,' he concluded.

Unbounded enthusiasm for screening in US

The US public is 'at risk of overtesting and overtreatment' through its enthusiasm for cancer screening, researchers say (*JAMA* 2004, **291**, 71–78). The enthusiasm 'is not dampened by false-positive test results or the possibility that testing could lead to unnecessary treatment' and 'creates an environment ripe for the premature diffusion of technologies such as total-body computed tomographic (CT) scanning,' the study found.

The survey was based on telephone interviews with adults selected by random digit dialling. It included 500 adults without a history of cancer, interviewed between December 2001 and July 2002.

Most (87%) believe routine cancer screening is almost always a good idea and more than 40% thought that an 80-year-old woman who chose not to have a mammography was irresponsible. More than a third of respondents had experienced at least 1 false-positive screening test, and more than 40% of these said the experience was frightening. Yet 98% were glad they had had the initial screening test.

Over half (56%) said they would want to be tested for cancers growing so slowly they would never cause problems even if untreated; and 73% would rather receive a total-body CT scan than US $ 1000 cash.

EUROFILE

No resolution to stem cell debate

The long-running European Union debate on stem cell research ended in stalemate in December 2003, when Member States' Ministers responsible for research failed to agree on whether EU funding should be available. The impasse looks unlikely to be resolved in the first half of 2004, but the Commission is preparing to issue a call for proposals involving human embryonic stem cells for funding under the 6th Framework Research Programme. Fireworks can be expected later in the year.

When the Ministers met in September 2002 to approve the 6th Framework programme, they included a surprise moratorium on EU funding for stem cell research. This moratorium expired on December 31, 2003, and, since there has been no move to extend it, the Commission is now free to fund future projects that use embryonic stem cells. Although some Member States are opposed to such research, the Commission says that it will look at individual projects on a case-by-case basis.

'LEGALLY, THE COMMISSION IS SKATING ON THIN ICE'

On 26 November 2003, and again on 3 December 2003, ministers were unable to agree either on the Commission proposal (amended to take account of the European Parliament's position) or on a new text put forward by the Italian Presidency, but not supported by the Commission. Ministers from Germany, Austria, Italy, Portugal and Luxembourg formed a blocking minority to ensure that agreement could not be reached. The issue is unlikely to be revived during the 6-month term of the Irish Presidency, which started on 1 January 2004.

Subsequently, the European Parliament voted in plenary session to approve the part of the human tissues and cells directive that would allow research on embryonic stem cells. They had dropped their original opposition to such research on the grounds that, under the subsidiarity principle, ethical questions fall under the domain of individual member states.

Proposals for projects involving stem cells will now be eligible for funding from January 2004. However, German MEP Dr. Peter Liese, rapporteur on the tissues and cells directive and a vehement opponent of stem cell research, warned that the Commission "is skating on very thin ice- legally, this is very unclear."

As yet the budget for the new call is undecided, though it is likely to be in excess of 30 million euros. A scientific and ethical review committee will look at each project, but this will be complicated by the lack of an agreed ethical framework. "The Commission will use its own proposal and take into account some of the Parliament's concerns, in order to steer the ethics committee", the spokesman said.

Projects that survive the first stage will then be discussed by an advisory committee made up of Member State officials. The committee will be able to block a proposal for funding with a qualified majority vote. If the committee is unable to reach an agreement on a project proposal within three months, the proposal will go to the Council of Ministers. If they cannot decide, the Commission will make the final decision.

Another complicating factor is the use- or not- of the cut-off date. In January 2003, Commission officials said that participants in the 6th Framework Programme could only use embryonic stem cells derived before the end of 2002. They gave the European Parliament and the Council a year to develop clear rules on whether new cell lines derived from spare embryos created in IVF clinics could be used.

The Parliament removed the cut-off date in its version of the guidelines, but in the Council of Ministers' discussions, opinions ranged from scrapping it altogether to moving it back a year and applying it to the creation of cell lines and not just the collection of embryos. The Commission is still considering how best to handle this issue.

What will happen next? By the time this comes to a head, the June elections will have passed and both the Parliament and Commission will have changed. Even now, there are many variations in national legislation. For example, the UK allows research involving the creation of embryonic stem cells to be carried out with public funds, whereas in Germany only existing cell lines can be used. The addition of another 10 countries to the European Union, all with different views, can only complicate matters. "Everything is still as open as it ever was", says Octavi Quintana Trias, head of life sciences at DG Research.

Since Framework 6 began, the Commission has only received one proposal involving embryo research, and nothing on human embryonic stem cells. However, the moratorium on such work was well publicised and scientists will probably have held back. Given the ongoing confusion, it seems unlikely that there will be any big rush on the part of the scientific community to apply for EU funding for stem cell research in the next call for proposals. This is a shame, says Research Commissioner Philippe Busquin. "If we truly want European research to become a global reference we have to move away from the national approach, even in contentious areas such as this."

'WE HAVE TO MOVE AWAY FROM THE NATIONAL APPROACH'

Mary Rice
Brussels

Maggie's Centres offer support

The latest 'Maggie's Centre' was officially opened in Dundee, UK, in September 2003. It is open to anyone affected by cancer, whether patient, former patient, friend or family, and aims to help support people through diagnosis, treatment and beyond.

The charity was established by the architectural writer, the late Maggie Keswick Jencks, who died of breast cancer in 1995. Her philosophy was that your immediate environment affects your well being. Consequently the architecture of the centres is stunning- the Dundee centre was designed by Frank O Gehry and has a spectacular view of the River Tay- yet each is within walking distance of a major cancer hospital.

The Dundee centre is the third to be built, after those in Edinburgh and Glasgow, and 10 more are being planned elsewhere in the UK. Ms Mary Wells, Head of Research and Centre Head at the Dundee Centre, says that the Centres are a conduit to help people regain control. They provide access to information, and help people navigate their way around and make the most of the resources available to them through the NHS. 'People fall through nets however good the service is. We try to identify where people might be able to get support and have a less difficult time through diagnosis, treatment and recovery.'

The Centres operate a programme with 3 core elements: information, emotional support, relaxation/stress management, all within an environment designed to be uplifting, supporting and safe. The library and kitchen are central features in the domestic-style Centres (*see www.maggiescentres.org*).

Maggie's centre, Dundee, UK

Smoking and health: 40 years on

40 years after the publication of the US Surgeon General's report on smoking and health, the antitobacco lobby is 'still wandering in the desert', according to a Lancet editorial (*Lancet* 2004, **363**, 97–98). 'The inability to curb cigarette use represents the worst public-health failure in history,' researchers write.

Congress, the mass media, medical organisations, and academia 'have all been chronic recipients of largesse from the tobacco industry, and have not been prepared to bite the hand that fed them,' the editorial states.

The editorial calls for a return to grassroots activism 'building broad public constituencies instead of elitist academic oligarchies'. New and imaginative leadership is needed in the antitobacco lobby, and less reliance on 'Bug Government, which has failed the test of courage time and time again.'

'Rather than training more nicotine addictionologists and epidemiologists, we need to cultivate more creative strategists and steadfast troublemakers. In other words, we need less research and more action.'

- India has become the 7th country to ratify the Framework Convention on Tobacco Control (*Lancet* 2004, **363**, 135). The new law includes a ban on tobacco advertising, sponsorship of sports and cultural events by tobacco companies, smoking in public places, and sale of tobacco products to people under 18. On paper, it is the toughest antitobacco legislation in the world, but much will depend on how the law is implemented.

HPV in the mouth

The oral cavity is a reservoir of human papillomaviruses (HPVs) in childhood, including high-risk types for cancer, Japanese researchers have found. Many HPVs, including the high-risk HPV-16, are present in the mouths of 3- and 5- year old children (*Oral Oncology* 2003, **39**, 821–828).

Oral squamous cell specimens were taken from 77 children, and the DNA evaluated for HPV infections by polymerase chain reaction methods. Of the 77 specimens, 37 (48%) were positive for HPV DNA. Among 3-year olds, the positive rate was 45%; this rose to 50% among 5 year olds.

The older children more frequently had mucosal HPV types, such as HPV-16, where the younger children more frequently had cutaneous types, especially HPV-2. This suggests, the authors say, that the frequency and type of HPV transmission in the oral cavity will change during one's lifetime 'and may be associated with the immune response and hormonal influences of the host'.

It is not clear whether early infection predisposes a person to later HPV-associated diseases such as recurrent respiratory papillomatosis, oral or even genital cancer, they say. The mouth appears to act as a reservoir for these HPVs. 'In the future, HPV vaccination in childhood could be useful in preventing oral cancers,' they conclude.

PODIUM

An improving image for radiotherapy

Professor Søren Bentzen trained at the University of Aarhus, Denmark, and now heads the Human Cancer Biology & Informatics Group at the Gray Cancer Institute, London, UK. He is a former chairman of ESTRO's Radiobiology Committee and a current member of EORTC's Translational Research Advisory Committee. He has received numerous awards for his work.

Professor Bentzen

Does radiotherapy have the reputation it deserves?
No, perhaps partly because the treatment modality has been around for 100 years and people wonder whether it is still exciting and relevant today. The emergence of long term side effects—which reflects the fact that people with radiotherapy survive long term—does not help. Study into the chronic late effects of treatment is more advanced in radiotherapy than in other fields and the spectrum of effects seen has changed. Improved knowledge and equipment means that side effects seen 20–30 years ago are rare today, but they still exist because we try to treat patients to tolerance and some will have a reaction. But patient advocacy groups lobby against radiotherapy in some countries.

What is happening in radiotherapy?
We are seeing a revolution. Technological advances have led to the development of intensity modulated radiotherapy (IMRT) which has dramatically improved our ability to plan and deliver non-uniform dose distributions in the clinic. Molecular imaging allows us to look at the function of the tumour tissue so we can map areas likely to be resistant and titrate treatment accordingly. We can also selectively avoid normal tissue of functional importance, such as certain regions of the lungs or the brain. It's been said that radiotherapy needs imaging, but imaging also needs radiotherapy in the sense that if you have a 3 dimensional map of a tumour's properties, you need a treatment you can modulate in 3 dimensions to make use of it. Radiotherapy is the only treatment modality which can be modulated in time and space.

How do advances in radiotherapy compare with those elsewhere?
They go hand in hand. Basic radiation biology is beginning to throw light on the biological responses to radiation damage and preclinical studies are improving our understanding of how cells process damage. We may then be able to modulate this response. The emergence of new biologically-targeted therapies will expand rather than contract the role of radiotherapy; there is a lot of mileage in combining drugs with radiotherapy.

Are these benefits available in the clinic?
Increasingly, but there is more to come. In future we will be able to tailor treatment to individual patients. We will use prognostic and predictive markers to estimate individual risk profiles for each patient and work out how much of their tolerance we should spend on local treatment-surgery and radiotherapy- and how much systemically, with drugs. In order to optimise outcome we want to know the relative risk of local versus systemic relapse for each patient.

Does radiotherapy's image problem influence other cancer specialists?
Not really- the problem is mainly the public's perception. Co-operation between different cancer specialists is routine in cancer centres; we are all trying to optimise a patient's outcome. Surgery and radiotherapy aim to preserve organs and have better functional or cosmetic outcomes- such as breast conserving surgery with radiotherapy in breast cancers.

Will the potential of radiotherapy be maximised?
This is a real concern. There is a danger that undervaluing radiotherapy has led to under-investment in radiotherapy research and equipment even in affluent countries. An expectation has existed that the right combination of drugs will eventually cure cancer and there has been political reluctance to invest in radiotherapy equipment. This has led to long waiting lists in the West, and little access for patients in developing countries.

Is the situation universal?
The status of radiotherapy is definitely higher in North America than in Europe, and there are regional differences across Europe. It's not only related to affluence, there are also historical and cultural differences; radiotherapy has been underutilised in Sweden and other fairly affluent countries, for example. ESTRO is undertaking a large EU-funded project comparing the number of patients in each country who would benefit from radiotherapy with those who actually receive it. There is a large variation and it will increase with the expansion of the EU. We hope that a map of the differences can be used to harmonise radiotherapy provision across Europe.

Are you optimistic for the future of radiotherapy?
Yes. Things are improving with the exciting new developments in science and increasing numbers of collaborative studies. Image is important as it affects policymakers- and therefore the provision of equipment- and the recruitment of young people looking for a career in academic radiotherapy.

The only way to combat this is through more evidence. In terms of health economics, despite the high capital costs of equipment, radiotherapy is very cost effective in a lot of situations. The more successful we are in producing the evidence, the more objective decisions will be.