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Studies strengthen aspirin's preventive role

Two new studies provide further backing for the role of aspirin in the prevention of colorectal cancer. However, its mechanism of action remains poorly understood and researchers held back from recommending its use to the general population.

A prospective, observational study (*N Eng J Med* 2007;**356**:2131–42) used data from the US' Nurses Health Study and Health Professionals Follow-up Study. Participants completed questionnaires every 2 years and results were based on 2,446,431 person-years of follow-up.

Regular aspirin use (at least twice a week) reduced the incidence of colorectal cancers that over-express COX-2 by more than one-third. Risk was reduced with increasing aspirin dose and increasing duration of use. By contrast, the drug had no influence on tumours with weak or absent COX-2 expression.

An accompanying editorial (*N Eng J Med* 2007;**356**:2195–8) pointed out that chronic use of aspirin or COX-2 inhibitors 'carries attendant toxic effects.' Other agents 'with better efficacy or lower rates of adverse effects' are needed.

The authors concluded: 'Our results support the importance of continued investigation in to COX-2 and related pathways for the development of new treatments and the potential use of COX-2 as a molecular marker for tailoring chemoprevention in participants with a history of colorectal cancer.'

The second study (*Lancet* 2007;**369**:1603–13) analysed data from two randomised controlled trials, set up originally to explore aspirin's effect on stroke and heart disease. It found that taking at least 300mg aspirin per day for about 5 years was effective in the primary prevention of colorectal cancer. The effect was only seen after a latency of 10 years which, researchers said, is consistent with our understanding of the adenoma-carcinoma sequence.

An editorial (*Lancet* 2007;**369**:1577–8) said that the study provides 'convincing evidence that aspirin, at biologically relevant doses, can reduce the incidence of colorectal cancer' and provide proof-of-principle that 'chemoprevention of colorectal cancer with aspirin is feasible'.

It stresses that 'these findings are not sufficient to warrant a recommendation for the general population to use aspirin for cancer prevention' and says that 'more work is needed to characterise those for whom the potential benefits of aspiring outweigh the hazards.'

Suicide gene therapy kills bowel cancer cells

An innovative type of gene therapy has succeeded in making bowel cancer cells commit suicide. Known as Gene-Directed Enzyme Prodrug Therapy (GDEPT), the treatment uses an adenovirus to attack cancer cells.

The virus has had an extra gene added, which programmes it to switch on the gene only if it reaches a tumour. When the gene is switched on, the virus produces a protein that activates an otherwise harmless prodrug, given separately.

Researchers demonstrated that the system worked on 10 human cell lines (*Cancer Res* 2007;**67**:4949–55); the first time, they say, that such a system has proved successful at killing colorectal carcinoma cells, albeit *in-vitro*.

Lead researcher was Cancer Research UK's Professor Caroline Springer (The Institute of Cancer Research, Sutton, Surrey, UK). She said, 'Normal cells are spared because the virus doesn't produce the protein that activates the drug unless it is inside a tumour.

'The beauty of our approach is that the cancer cells are made to commit suicide both by the virus and the activated drug – the two work in tandem. And once activated, the drug has the added bonus of causing the virus to produce more of the activating protein, which activates more of the drug, and so on. It's the first time we've seen a 'positive feedback loop' like this in a GDEPT therapy.

'We also see a significant bystander effect. The cells killed by the virus or the drug release signals into the tumour that tell neighbouring cancer cells to die too,' she said.

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Railway workers 'are at increased risk'

Some cancers appear to be linked to extremely low frequency electromagnetic fields, according to Swiss researchers. They found a raised risk of myeloid leukaemia and Hodgkin's lymphoma among train drivers, who had the highest levels of exposure.

The researchers followed 20,141 Swiss railway employees between 1972 and 2002 – a total of 464, 129 person-years of follow-up with most study participants remaining in the same job over the whole period. Data from employment records was linked with that from nationally-held death certificates (*Occup Environ Med 2007* doi:10.1136/oem.2006.030270).

Exposure to electromagnetic fields varied, depending on post. Drivers were exposed to around 3 times the levels of shunting yard engineers and 9 times the levels of ticket collectors on trains. Station masters were exposed to the lowest levels.

There was little difference overall in deaths from cancers, including most haemopoietic and lymphatic malignancies and brain tumours. However, there was evidence that higher levels of electromagnetic field exposure had an impact on rates of myeloid leukaemia and Hodgkin's lymphoma. Drivers were more than 4 times as likely to die of myeloid leukaemia, and more than 3 times as likely to die of Hodgkin's lymphoma, compared with station masters.

This association was less pronounced than has been previously observed because leukaemia mortality rates among train attendants and station masters, who were only exposed to low levels, have been increasing since the early 1990s.

'DRIVERS WERE 4 TIMES MORE LIKELY TO DIE OF MYELOID LEUKAEMIA'

The authors stress that passengers spend considerably less time in trains than the groups studied and their exposure levels and potential health risk 'are therefore negligible.'

However, efforts should be made to minimise levels of exposure among train drivers in new rolling stock, they say.

Lapatinib approved in Switzerland

Lapatinib (Tyverb), in combination with capecitabine (Xeloda), has received approval from Switzerland's regulatory authority, Swissmedic, for the treatment of patients with advanced or metastatic breast cancer whose tumours over-express ErbB2 (HER-2) and who have relapsed after, or not responded to trastuzumab (Herceptin).

This is the first European approval of an oral inhibitor of both ErbB1 and ErbB2, according to manufacturer GlaxoSmithKline (GSK). Lapatinib is a small molecule which enters the cancer cell and inhibits the tyrosine kinase components of ErbB1 and ErbB2 receptors, which are responsible for tumour growth. This is a different mechanism of action from trastuzumab.

The approval was based on a phase III trial (EGF100151) in women with advanced or metastatic ErbB2 positive breast cancer whose disease had progressed following treatment with trastuzumab and other cancer therapies. The median time to progression was 27.1 weeks on the combination versus 18.6 weeks on capecitabine alone. The response rate was 23.7% versus 13.9%.

GSK says that lapatinib may play a role in decreasing brain metastases as the site of first relapse. CNS relapses were lower in the combination arm and studies are ongoing in an effort to confirm this preliminary finding.

Lapatinib has not received regulatory approval in the European Union; a registration dossier has been filed with the European Medicines Agency. Tyverb is the proposed trademark in the European Union; it is Tykerb in the US. Lapatinib is available in the US and registration dossiers (using the Tykerb trademark) have been filed elsewhere, including Australia, Canada and New Zealand.

Approval for Herceptin in combination

The European Commission has approved the use of trastuzumab (Herceptin) in combination with any aromatase inhibitor for the treatment of postmenopausal women with HER2- and hormone receptor co-positive metastatic breast cancer.

The approval is based on data from Roche's international phase III TAnDEM (Trastuzumab and Anastrozole in Dual HER2/ER co-positive Metastatic breast cancer) study. It found that the addition of trastuzumab to hormonal therapy doubled median progression-free survival, from 2.4 months to 4.8 months.

Trastuzumab is already approved for the treatment of early and advanced HER2-positive disease. The new approval also allows it to be used in combination with hormonal therapy for advanced breast cancer.

Totect is 'approvable'

The US' Food and Drug Administration (FDA) has issued an approvable letter for Totect, a catalytic inhibitor of the enzyme topoisomerase II, which is used as an antidote following accidental anthracycline extravasation.

The drug has already been approved as Savene in Europe and was launched widely by biopharmaceutical company, TopoTarget, in October 2006. It is a detoxifying agent which is administered intravenously and prevents the effect of anthracyclines which have accidentally leaked into surrounding healthy tissues.

Extravasations occur in up to 1% of all treatments and cause severe and cumulative damage to the skin, subcutaneous tissue, muscle and nerves. Current treatment often involves surgical removal of the tissue followed by plastic surgery and rehabilitation.

TopoTarget says that the 'approvable' letter, rather than the expected 'approved' letter was due to a technical issue at one of 2 subcontractors. The company is confident that the issue will be solved 'to the full satisfaction of the FDA and ourselves' but says that, if not, 'We may opt to include only the already approved subcontractor in our application.'

The drug is still expected to be launched in the US in the second half of 2007.

EUROFILE

Deadline approaches for animal experimentation directive

A new and diverse grouping of European scientists was unveiled in Brussels in the spring of 2007. The European Coalition for Biomedical Research (ECBR) was formed to address a single piece of EU legislation; the directive that regulates the use of animals in scientific research. Scientists from Lithuania to Portugal, and from Hungary to Greece, are among the founding members of the Coalition, which currently represents some 48,000 academics.

The existing directive regulating animal experimentation dates from 1986, and there has been pressure to revise it for some time. It was not until the summer of 2006, though, that the European Commission gave the first indication of what was likely to be included in the revision, by holding a public and expert consultation on a number of issues. 'Whilst there is much that is sensible, there are also some rather dangerous suggestions', said Dr. Mark Matfield, Scientific Advisor to the Association for International Cancer Research, and newly-elected General Secretary of the ECBR. 'For example, there is a proposal to limit the use of non-human primates in research to those that have been bred for two or more generations in captivity. It's a worthy sounding idea, but one that was based on completely inaccurate information and would almost eliminate the use of macaques in research – there aren't enough of these two-generation captive bred laboratory primates, and it would take years for sufficient numbers to become available.

'THE PUBLIC CONSULTATION GENERATED 42,655 RESPONSES'

'These animals are essential for several important areas of virology and neuroscience research as well as biotechnology development. Currently, they are needed to test new treatments for cancer and multiple sclerosis, and for or the development of vaccines against AIDS and malaria,' he said.

In addition to debating issues with the Commission, the Coalition will be helping its members inform MEPs in their respective countries about the reasons for needing to continue to use animals in medical research. Some of the previous debates on the issue have shown that there is a considerable knowledge gap which needs to be filled, said Coalition members.

The results of the public and expert consultations on the revision of Directive 86/609, published by DG Environment in December 2006, held few surprises. The public consultation generated 42,655 responses from all 25 EU Member States, as well as from other countries. This was the third largest number of responses ever to a Commission internet consultation, said a spokesman.

'MEPS HAVE CALLED FOR THE PHASING OUT OF ALL PRIMATE USE'

The draft directive was expected to be presented to the European Parliament and the Council in June 2007, but the timetable has slipped again. DG Environment, which is taking the lead in the drafting, has apparently run into trouble with the Commission legal services over the inclusion of basic research within the directive's scope. The previous directive applied only to the commercial sector, although in practice all European Member States also applied it to their academic research. But the legal services have pointed out that there is no legal basis for the Commission to apply the directive in universities. The directive is also expected to place much emphasis on the application of the '3 Rs' (refinement, reduction, and replacement of animal use) and legal services have told DG Environment that there is no legal base for them to include this in the new legislation.

Additionally, the Commission is known to have serious concerns about the primate issue, which is already being hotly debated by MEPs, with two 'written declarations' calling for the phasing out of all primate use circulating for signature in the last year. This is an area where scientists and animal rights groups are firmly ranged on either side, and it seems unlikely that those drafting the legislation will be able to find a solution which suits everyone. DG Environment's hopes of introducing the new directive under the German Presidency, which ends on 30 June 2007, look likely to be dashed. The Portuguese, who hold the next Presidency from July – December 2007, have confirmed that it is not on their work plan.

'This process has been going on for 6 years now', said Matfield, 'and it would be good for everyone – animals, scientists, industry and animal welfare organisations – if we could see an end to it soon. We would all like to see legislation that does more to protect laboratory animals and ensures a level playing field across Europe for scientists, as long as it does not inhibit legitimate medical research.'

Members of the Coalition say that they will be scrutinising the draft directive line by line and, where there are clauses that need changing, they will seek the help of MEPs to ensure that appropriate amendments are tabled. The objective is to achieve a new directive which balances the need to have animal research properly regulated with the need to allow the research to proceed without undue delays, bureaucracy or hindrances.

'We think that having such a broad coalition, both in geographical terms and as far as different scientific disciplines are concerned, should be of great help in ensuring that these messages are promulgated effectively and to the right audiences and that the voice of the European scientific community will be heard loud and clear', said Professor Edith Olah, from the Hungarian Cancer Society, and ECBR Chair.

Mary Rice
Brussels

RECIST: right time to renovate?

Researchers at the MD Anderson Cancer Centre in Houston, USA, have confirmed that the RECIST (response evaluation criteria in solid tumours) guidelines for the assessment of tumour response in clinical trials, which are currently based on measuring tumour anatomical longest diameter, are insufficiently sensitive for use with imatinib-treated gastrointestinal stromal tumours (GIST; *J Clin Oncol* 2007;**25**:1753–59). They propose that Choi criteria be used instead. Together with other reports published over the past 6 years, these findings suggest the need for a review of RECIST.

RECIST officially came into being in February, 2000, through collaboration between the European Organisation for Research and Treatment of Cancer, the US National Cancer Institute, and the National Cancer Institute of Canada Trials Group. The task was to replace the WHO tumour-response criteria used since 1979 and to provide a set of principles that could be used to objectively measure tumour response in phase II clinical trials. RECIST introduced the unidimensional measurement of tumours, explained how to

'TUMOUR SHRINKAGE IS NOT THE GOAL OF ALL NEW DRUGS'

select target lesions to measure, set out criteria for use with different imaging techniques – especially CT and MRI tomographic slice thicknesses and intervals – and provided a new threshold for objective disease progression. Research groups around the world quickly adopted the new guidelines, including many undertaking phase III trials. Indeed, the same criteria are often used to monitor patient progress and, therefore, to provide objective information for making treatment decisions. In fact, the RECIST guidelines have had a greater effect than their authors ever suspected. Not unexpectedly, however, a number of shortcomings have been reported over the years. New imaging instruments now allow far more accurate measurements of tumour size and volume than in the last 1990s, and because the RECIST guidelines are based on the examination of anatomical structure, they cannot take into account the mechanisms of action of many new drugs that might reduce a tumour's functionality but cause no immediate reduction in its size. The time might have come, therefore, to adjust RECIST.

Robert Benjamin, one of the lead authors of the new reports, explains, 'What our results show is that RECIST is not sensitive enough for evaluating responses in imatinib-treated GIST. We found that our responses by RECIST, as measured by CT, did not correlate with time to tumour progression or disease-specific survival, whereas responses by Choi criteria did. We therefore suggest that Choi criteria, which take into account both smaller changes in tumour size and also changes in tumour density, be used for evaluating tumour response in this form – and perhaps other forms – of cancer.'

Until recently, most cancer drugs were designed to shrink tumours, and the RECIST criteria provided a good system for monitoring any change. But tumour shrinkage is not the immediate goal of all new drug candidates. Indeed, imatinib, a tyrosine-kinase inhibitor, can even cause GIST to initially increase in size, a consequence of a metabolic response leading to intramural haemorrhaging or mixoid degeneration. Clearly RECIST would return the incorrect verdict that the tumour was not responding to treatment.

Further problems lie in the fact that the RECIST criteria categorise patients as either responders or non-responders. 'It would be better to measure response, for example, based on change in tumour size and/or density, and compare the results to prospective controls,' explains Mark Ratain (University of Chicago, IL, USA 'One could conduct a prospective randomised trial using change in tumour size at a landmark time point as the primary endpoint.'

The RECIST guidelines are reported hard to use with mesothelioma (given its particular growth characteristics), prostate cancer (the endpoint of tumour regression might not be applicable), in paediatric tumours (in clinical practice), and in tumours that produce bone metastases (which are RECIST-immeasurable), among others.

Advances in imaging technology suggest the need to modify RECIST. A partial response requires an arbitrary 30% reduction in the sum of the longest diameters of the target tumours – perhaps too wide a margin now that thin-slice CT and MRI allow tumours to be measured within tenths of a millimetre. Volumetric analysis can simultaneously provide boundary geometry, Hounsfield number, inhomogeneity, and tumour diameter measurements.

RECIST IS A PRAGMATIC SIMPLISTIC TOOL

'One should always consider RECIST to be a pragmatic, simplistic tool, subject to scrutiny in the contest of its use. Its conclusions are not to be accepted uncritically', explains Carl Jaffe (National Cancer Institute, Bethesda, MD, USA).

However, RECIST is far from having seen its day. 'It is true that RECIST is not optimal in some areas,' explains Jaap Verweij (Erasmus Medical Centre, Rotterdam, Netherlands, and RECIST group leader). 'But it should also be remembered that GIST are rare tumours, and that the use of Choi criteria requires special imaging equipment not commonly available even in rich countries. Additionally, many of the papers that have questioned the use of RECIST have involved very small numbers of patients, and none have yet validated the alternatives they propose.' Verweij continues, 'We are developing new RECIST criteria which we hope will be available in 2008. These will focus on the major cancers and will be validated in a group of 14,000 patients – 11,000 more than were involved in the original validation. Our aim is to provide a system that can be used by [most] research groups, but which takes into account the data that has accumulated over the years. RECIST undoubtedly has an important role now, and a renewed RECIST will have an important part to play in the future.'

Adrian Burton

The full version of this story appears in Lancet Oncol 2007;**8**:464–5.

PODIUM

Prevention of cancer through healthy workplaces

Dr. Andreas Ullrich is the World Health Organization (WHO)'s Medical Officer for cancer control. He is developing the WHO's Global Action Plan Against Cancer which includes national and international policies on the prevention of occupational and environmental cancer.

How serious a problem is workplace cancer?
Every tenth lung cancer death is closely related to risks in the workplace. About 125 million people around the world are exposed to asbestos at work and at least 90,000 people die each year from asbestos-related mesothelioma. Thousands more die from leukaemia caused by exposure to benzene.

This has been thought of as a problem for the developed world?
Most of the deaths currently occur in the developed world because of the widespread use of carcinogenic substances 20 or 30 years ago. Today there are much tighter controls on these carcinogens in developed countries. The use of asbestos, pesticides and carcinogens used in tyre production and dye manufacturing is moving to countries with less stringent occupational health standards. If the unregulated use of carcinogens in developing countries continues, a significant increase in occupational cancer will occur in the coming decades.

What are you proposing in response?
We collaborate closely with the WHO's International Agency for Research on Cancer (IARC, Lyons, France) which provides evidence about the causes of cancer including the classification of carcinogens. WHO through the comparative risk assessment project (www.who.int/healthinfo/boddocscra) estimates how many cancer deaths are due to specific risk factors. Our final goal is to convince governments to develop comprehensive cancer plans which include reducing the risk from occupational and environmental carcinogens.

What has prompted the campaign to reduce exposure?
In 2005, the World Health Assembly (WHA)'s resolution on cancer prevention and control asked WHO to increase its efforts to fight cancer. In response, the Global Action Plan Against Cancer will recognise that reducing exposure to carcinogens is part of the comprehensive approach to prevent and control cancer.

What measures need to be taken?
WHO has just finalised a prevention module: each risk factor needs a specific approach which involves specific policy regulation and different stakeholders. We are recommending a stepwise approach for industrial interventions. Countries should stop using all forms of asbestos and provide safe drinking water. A core intervention in some countries is to reduce the risk from biomass – the exposure of women to indoor pollution from coal or wood fires is a major problem in China. Food safety systems need to be implemented. Aflatoxin is a common food contaminant in Africa which leads to infection and as many cases of liver cancer as are caused by hepatitis B.

Specific occupational measures will involve regulatory mechanisms in the workplace and involve labour ministers and economists and going far beyond the classical health sector.

Does the political will exist to make these changes?
The WHA resolution on the prevention and control of cancer was accepted by all WHO Member States reflecting the increasing awareness of the public health problem due to cancer in many parts of the world. This resolution indicates growing political awareness. The Framework Convention on Tobacco control is an international treaty which implies legal leverage to implement strategies for cancer prevention regarding tobacco use including at the workplace.

How much progress has been made?
Countries with national cancer plans are easier to work with because they have recognised cancer as a priority and they have a common goal.

Implementing measures involves negotiation with private industry and an economic evaluation of what is feasible. We have to be realistic; it might be difficult for some countries to substitute asbestos with another product, which limits the usefulness of rules and regulations. Every country has to find its own way. We have started to put together a global monitoring project including the cancer burden country by country and this should assist ministers of health.

How do national cancer plans help?
If national cancer plans follow our guidance, they are obliged to take into consideration occupational and environmental exposure to carcinogens. Vietnam has a cancer plan, which is approved by the prime minister, and it makes planning straightforward. Morocco has government backing for cancer planning; it also has a strong non-governmental organisation which is supported by the Queen.

What barriers do you face?
Efforts to improve treatment have an immediate effect. Cancer prevention is a long term investment which is difficult to sell to politicians with their short shelf-lives. Up to 40% of cancer deaths could be prevented by changes to behaviour and environment, but this implies something different from the classical medical model. It will require political debate.