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NEWS. . .NEWS. . .NEWS

Unexpected dietary links with cancer

The risk of cancers of the blood was 45 percent lower in vegetarians than in meat-eaters in a study from the University of Oxford, UK. Overall, vegetarians were 12 percent less likely to develop cancer than meat eaters, but the most striking difference in incidence was seen in leukaemia, multiple myeloma and non-Hodgkin lymphoma.

The Cancer Research UK study included 61,000 people followed for 12 years. The results include data from 2 previous studies: Oxford Vegetarian Study and EPIC-Oxford.

The incidence of stomach and bladder cancer was also significantly lower among vegetarians. Sara Hiom (Cancer Research UK), said, 'It's understandable that there's a link between what you eat and cancers of the digestive system. But we are surprised to see an association between leukaemia, non-Hodgkin lymphoma and multiple myeloma; more research is needed to understand the mechanisms involved.'

The researchers suggest that potential mechanisms for these differences could include mutagenic compounds and viruses. But they stress that their results are descriptive: 'More detailed analyses of individual cancer sites are needed to explore, for example, whether the differences observed might be linked to particular types of meat or to other dietary or lifestyle characteristics of non-meat eaters that were not adjusted for in the current analysis' (*BJC doi: 10.1038/sj.bjc.6605098*).

The study supports advice that healthy balanced diets are high in fibre, fruit and vegetables, and low in saturated fat, salt and red and processed meat. It was backed up by an unrelated US study in which researchers at the National Cancer Institute (Bethesda, Maryland) examined the link between dietary fat and pancreatic cancer.

They analysed a cohort of 500,000 people from the US National Institute of Health – AARP Diet and Health Study. Participants completed a food frequency questionnaire in 1995 and 1996 and were followed prospectively for 6 years.

Men and women who consumed high amounts of total fats had 53% and 23% higher relative rates of pancreatic cancer, respectively, compared with men and women who had the lowest fat consumption. Those with high consumption of saturated fats had 36% higher relative rates of pancreatic cancer than those with low consumption (*J Natl Cancer Inst 2009, 101:1001–1011*).

The authors say their results 'suggest a role for animal fat in pancreatic carcinogenesis', but an accompanying editorial (*J Natl Cancer Inst 2009, 101:972–3*) points out that, as with the *BJC* finding, there is still insufficient epidemiological evidence to confirm that meat is the important factor, as opposed to other dietary or lifestyle preferences associated with meat consumption.

The dangers of green tea

Green tea, the so-called 'miracle herb' lauded for its anticancer potency, may in fact block the therapeutic effects of bortezomib (BZM) and other boronic acid-based proteasome inhibitors, US researchers say (*Blood 2009, 113:5927–37*).

They set out to examine whether the combination of green tea and proteasome inhibitors would increase efficacy in multiple myeloma and glioblastoma cell lines.

'Unexpectedly, we discovered that various green tea constituents, in particular (-)-epigallo-catechin gallate (EGCG) and other polyphenols with 1,2-benzenediol moieties, effectively prevented tumour cell death induced by BZM in vitro and in vivo,' they said.

The antagonistic effect was not seen with several non-boronic acid proteasome inhibitors such as nelfinavir.

They concluded that green tea polyphenols may have the potential to negate the therapeutic efficacy of BZM, and 'would strongly urge patients undergoing BZM therapy to abstain from consuming green tea products, in particular those widely available, highly concentrated GTEs (polyphenol E) that are sold in liquid or capsule form.'

Constituents of green tea might not only neutralise the therapeutic efficacy of BZM, but also some of the side effects. Patients taking the EGCG/GTE products might therefore feel better, encouraging further increased EGCG/GTE dosages 'while at the same time, and unknowingly, the therapeutic efficacy of their BZM treatment is severely blunted, if not entirely obliterated,' the researchers concluded.

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Cancer and Schizophrenia

People with schizophrenia have a 50 percent higher risk of death from cancer compared to the general population, French researchers say. They call for extra efforts to improve cancer prevention and early detection in this group.

Professor Frédéric Limosin (Robert Debré Hospital, Reims, France) and colleagues prospectively studied 3470 patients with schizophrenia and tracked cancer incidence from 1993.

During the 11 years of the study, 476 patients died, a rate nearly 4-fold higher than in the general population. Cancer was the second most frequent cause of death behind suicide: 74 patients died of the disease (*Cancer doi: 10.1002/cncr.24383*).

The proportion of patients who were smokers was significantly higher than in the general population (56.3% versus 33.0%). In men with schizophrenia, the risk of death due to lung cancer was significantly higher than that in the general population, but the risk of overall cancer death was not significantly raised.

In women with schizophrenia, there were significantly more breast cancer deaths than in the general population. Possible explanations include a delay in diagnosis through patients paying less attention to symptoms, and less compliance with treatment, the researchers said.

Sound treatment for prostate cancer

High-Intensity-Focused Ultrasound (HIFU) may treat prostate cancer with fewer side effects than traditional treatments, London researchers say.

The experimental day-case procedure was used in a series of 172 men with localised prostate cancer. Only one man of the 159 followed up had incontinence a year later. 30–40% had impotence; none had bowel problems.

No evidence of disease was found in 92.4% patients, but the researchers stressed that further studies are needed (*BJC 2009; **101:** 19–26*)

European Action Against Rare Cancers

A new campaign is urging European policy-makers to prioritise treatment and care for patients with rare cancers within the scope of the European Commission (EC)'s Communication on Cancer and other recent policy initiatives.

European Action Against Rare Diseases has established an international petition appealing to policy-makers and stakeholders to initiate targeted actions and policies that will address the challenges that rare cancers entail for patients, physicians, and researchers. Organisations and private individuals are invited to endorse the petition (*See the Call for Action* on www.rarecancers.eu).

The campaign is a joint initiative based on partnership between a range of European professional societies, including ESMO and European Institute of Oncology, and patient groups, along with Novartis Oncology as the initiating sponsor.

Paolo Casali, ESMO representative said the campaign 'clearly identifies the challenges of rare cancers and outlines concrete, integrated and sustainable solutions which the various stakeholders can implement to solve them.'

UK moves to increase data sharing

The UK's National Cancer Research Institute (NCRI) is attempting to streamline governance requirements for biomedical research. It has produced a guide to help custodians of databases ensure that their policies covering data and biological sample sharing are legal, ethical and effective.

The aim is to encourage more effective sharing in order to reduce unnecessary duplication of data and sample collection.

Professor Sir Kenneth Calman, NCRI chair, said: 'The creation of an access policy can be daunting; it is often easier to say no to sharing, and avoid the difficulty, than to venture to say yes. But there is a great deal to be gained if we can all say yes more often.'

NCRI worked in partnership with the National Cancer Intelligence Network (NCIN) and onCore UK, to produce the guide, intended as a template for research organisations' policies. Each can adopt or adapt points relevant to their circumstances, ensuring, NCIN says, that any policy developed reflects best practice in a consistent manner.

Organisations can modify terms in the template to suit their needs, but

'IT'S OFTEN EASIER TO SAY NO TO SHARING'

greater consistency between access policies will help to encourage researchers to share samples and data in a way that is consistent with regulatory requirements.

Mr. David Ardon, chair of the NCRI consumer liaison group, said. 'Cancer patients are often surprised or even dismayed by how little use we make of their samples and information. Where patients agree to it, we have an ethical duty to generate the most knowledge possible from the data and samples they provide.'

Chemotherapy planning tool revised

An online tool designed to help plan chemotherapy delivery has been made more user-friendly, developers say. The new version of Chemotherapy – Planning Online Resource Tool (C-PORT), as used by 20 cancer networks and 100 hospitals in the UK, is now live.

C-PORT allows cancer professionals to input data about their service: staff, equipment, patient numbers, appointment schedules and drug regimens; and to model different ways of organising resources to improve chemotherapy delivery without risking expensive mistakes.

Mark Milovic of the developer Concentra said that a financial module is being piloted which will model 'the true cost of service delivery with all staff, equipment and medicine costs including overheads down to heating and lighting.'

The system is expected to contribute information to the national reference tariff for costing chemotherapy.

Further information from www.concentra.co.uk *or* jane.whittome@gstt.nhs.uk.

EUROFILE

Cancer a priority in IMI's second round

After being left out of the first round, cancer research priorities have finally been drafted for the EU's flagship programme of collaboration between academia and the pharmaceuticals industry.

The Innovative Medicines Initiative (IMI) was politically agreed by Europe's research ministers in December 2007 to address bottlenecks in the process of drug development, rather than aiming to deliver new medicines. It's a bold move away from the traditional pattern of collaboration in the pharmaceutical industry, where companies work on a one-to-one basis with partners such as universities.

The agenda concentrates on developing tools and methodologies that can be used by all companies, to predict the safety and efficacy of new medicines in the early stages of development for a variety of diseases. These would enable faster access to more targeted medicines and an earlier return on research investment. It also seeks to develop education and training programmes, and establish infrastructures for knowledge management between industry, academia and clinical centres to avoid the duplication of both public and private sector research.

'IT REMAINS TO BE SEEN WHETHER THERE IS AN OPENING FOR SMALL COMPANIES'

The scheme was ready to roll in 2008 with a budget of €2 billion up to the end of 2013. Half of the budget comes from the EU Framework 7 research programme and funds public sector participation. The other half comes from the pharmaceutical industry, represented by European Federation of Pharmaceutical Industries and Association (EFPIA), with EFPIA member companies covering their own costs.

In an attempt to reduce bureaucracy, by the end of 2009, the funds and calls for proposals will be managed by industry through a separate autonomous body based in Brussels. Although the Commission already comprises half the IMI governing board and has a strong role in overseeing its work, this devolution of power is a radical departure for EU research programmes.

According to Janez Potoènik, the EU Commissioner for Science and Research, 'In times of crisis, such a model of cooperation is proving well-suited to answering both EU competitiveness objectives and public health needs.'

Priorities for the first round of funding were set by industry and included diabetes, asthma, psychiatric and neurodegenerative disorders. From 150 proposals received, 15 were selected in May 2009 and will command €246 million of the overall budget. One, in the area of non-genotoxic carcinogenesis, is expected to play a role in the prediction of cancer development.

For the second call, the board is currently discussing three specific cancer priorities, along with inflammation and infectious diseases. Identified by EFPIA, in consultation with the public healthcare sector, they are:

- Creation of a network of imaging centres to allow clinical validation of imaging biomarkers of tumour cell proliferation and death across multiple sites.
- Systems biology: The search for new tools for target validation to improve drug efficacy, including improved models and integrated bioinformatics to generate testable hypotheses.
- Molecular biomarkers for accelerating cancer therapy development and refining patient care, in particular the characterisation of predictive, prognostic and pharmacodynamic biomarkers and the standardisation of analytical methods and data retention and sharing.

A call for proposals is envisaged in autumn 2009, and the Commission will invest €80 million, to be matched by EFPIA companies. The EU funding will be solely used to support the participation of academics, clinical centres, patient organisations, public authorities and small and medium-sized enterprises in the consortia formed.

Richard Sullivan, chair of the European Cancer Research Manager's Forum feels these are reasonable priorities. 'I'm less convinced about systems biology as so much has gone on, but the others are hard to argue with. Utility-wise, the imaging priority is very important,' he says.

'Imaging is a big area for institutes, countries and the commercial sector.

'IT'S A THIN LAYER OF GLUE TO BRING INSTITUTES TOGETHER'

The cost of imaging work is astronomical. This will simply be another cog, unless it can really bring centres together that would otherwise walk their own way.'

Whether all parts of the drug development process are really being addressed is a moot point. According to oncologist Klas Wiman at the Karolinska Institutet, 'The translation process from lab to clinic is seen as a problem by everyone. Speeding this up should be a priority,' he says.

He is also concerned about the composition of consortia.

'It remains to be seen whether there is an opening for small companies. They are better at innovation and coming up with new strategies.'

Sullivan also has concerns about what's missing. 'With all the new drugs coming through, what's scary is how we are going to test these all out in the time required, in all the different combinations we are going to have to look at, with an increasingly difficult patient population to treat. There's a real issue with how we are going to clinically test these out in the future.'

More broadly, Sullivan has concerns about the role the IMI will play. 'With less than 80 million Euro spread over these three priorities, it's a thin layer of glue to try and bring together institutes that have been well funded in their own countries by their own public and commercial sectors. And that's what the EU should be doing. That's the added value. It is not there to substitute.'

'It's going to be hard to judge if the IMI is a success apart from the usual things like papers and people saying what a jolly good thing it is.'

Saffina Rana
Brussels

Ofatumumab in CLL

The US' Food and Drug Administration (FDA) Oncology Drugs Advisory Committee (ODAC) voted 10 to 3 that data on the investigational treatment ofatumumab (Arzerra) 'are reasonably likely to predict clinical benefit'. The favourable recommendation applies to patients with chronic lymphocytic leukaemia (CLL) whose disease is refractory to fludarabine and alemtuzumab.

Ofatumumab is a monoclonal antibody which binds to both small and large loops of the CD20 molecule, which is highly expressed in most B-cell malignancies. It is being developed by a collaboration of Genmab, GlaxoSmithKline and Biopharm.

ODAC's decision was based on an interim analysis of a pivotal trail presented both at American Society of Hematology 2008, and American Society of Clinical Oncology 2009.

Partial hold on zalutumumab studies

The US' Food and Drug Administration (FDA) has placed a partial clinical hold on new studies on zalutumumab, along with those conducted under the US Investigational New Drug (IND) application. It has requested an updated analysis of safety data from biotech company Genmab.

The affected studies are the phase II study in patients with head and neck cancer considered incurable with standard treatment, and the phase I/II front line study of zalutumumab in combination with chemo-radiation. Patients already enrolled in these studies may continue to receive treatment if they are not experiencing serious adverse events, but no additional patients may be enrolled.

The two ongoing phase III studies of zalutumumab in head and neck cancer are unaffected, as is the phase I/II study of the drug in combination with radiotherapy, as these trials are outside of the IND.

Results from the phase III study in refractory head and neck cancer, for which 264 patients have been recruited, are still expected by the end of 2009.

Statistician recognised at St Gallen

Professor Richard Gelber (Harvard School of Medicine, Boston, Massachusetts, USA) was presented with the St Gallen Breast Cancer Award at the opening ceremony of the *Primary Therapy of Early Breast Cancer* conference (St Gallen, Switzerland, 11th March, 2009).

The award, which is presented biennially at the St Gallen conference, consists of a research contribution of 50,000 Swiss Francs (30,000 Euros) plus a Swiss wrist watch of the awardee's choice.

Professor Gelber, who is group statistician of the International Breast Cancer Study Group (IBCSG), was chosen for his academic leadership in biostatistics 'especially his outstanding contribution to the development and interpretation of innovative and meaningful international breast cancer trials, and his promotion of sound biostatistical standards as the indispensable cornerstone of scientific excellence and practical progress in evidence-based cancer therapy.'

Positive opinion for pemetrexed

The European Medicines Agency (EMEA)'s Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion on the use of pemetrexed for injection (Alimta) as monotherapy for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC). The opinion covers patients whose disease has not progressed immediately following platinum-based chemotherapy.

CHMP's positive opinion was announced at the end of May, 2009; approval by the European Commission normally follows within 2 months. Manufacturer Lilly has also filed for approval of pemetrexed for the same indication with the US' Food and Drug Administration (FDA).

Pemetrexed is already approved in Europe and the US as a first-line treatment for locally-advanced or metastatic nonsquamous NSCLC, in combination with cisplatin. It is indicated as a single agent for the second-line treatment of patients with locally advanced or metastatic nonsquamous NSCLC after prior chemotherapy. Furthermore, it is indicated, in combination with cisplatin, for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

The EU submission is based on data from a phase III trial in which patients received pemetrexed or placebo to evaluate the overall survival benefit of pemetrexed in the maintenance NSCLC setting (*Proc Am Soc Clin Onc 2009 # CRA8000*).

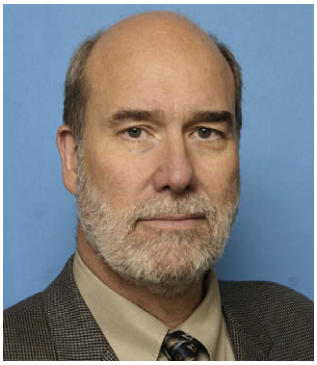
NICE approval of cetuximab

The UK's National Institute for Health and Clinical Excellence (NICE) has recommended the use of cetuximab (Erbitux) in combination with chemotherapy as a first line treatment for some groups of patients with metastatic colorectal cancer. The Final Appraisal Determination (FAD) applies to patients in whom the cancer has spread only to the liver and who have wild-type KRAS tumours.

The CRYSTAL study (*N Engl J Med 2009 360: 14 1408–17*) provided pivotal evidence for NICE's decision. Final guidance from NICE is due to be published in July 2009, and to be implemented within 3 months of publication (see www.nice.org.uk).

PODIUM

The problem with chemoprevention



Professor John Potter (Fred Hutchinson Cancer Research Centre, Seattle, Washington, USA) received the 18th Annual AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention. The award recognised his work on the aetiology and prevention of colorectal cancer, including the roles of diet, exercise, hormones and genetics. His award lecture was entitled, 'Chemoprevention: why do we keep getting it wrong?'

So what is going wrong?
If you're testing the hypothesis that some agent reduces the risk of cancer and you get a neutral answer, then you could conclude that the theory is right but the agent was ineffective. If, on the other hand, an agent you thought would be preventive actually increases risk, it tells you that the theory, not just the agent, is wrong. We keep seeing agents (folates, β carotene, Cox-2 inhibitors) fail in trials; they are increasing cancer risk. I have been saying since 1996 that there is something wrong with the theory.

Is anyone listening?
There's certainly reluctance to take the idea on board; everybody wants to think that each failure is a one-off. But there has been a run of failures now: some nulls, some increasing risk. I'm not saying there is never success - tamoxifen prevents contra-lateral breast cancer in women who've had a first cancer – but overall, the results aren't inspiring. Aspirin reduces the growth of polyps but its effect against colorectal cancer is equivocal; Cox-2 inhibitors are clearly worse than placebo. Hormones don't have the effects that were expected of them.

Why is the research continuing?
For one – there's money to be made. But part of the motivation is compassion: a genuine desire to find ways of preventing tumours. It's all very well to say that lifestyle modification will alter cancer risk but changing human behaviour is hard. It may be easier to pop pills. But 'First do no harm' is the opening of the Hippocratic Oath and I'm not sure we're following that.

Why are the agents failing?
One possible explanation is that – unlike chemotherapy – we're using them as single agents. It is Darwinian: where you have a lot of cells changing rapidly and mutating, and you put pressure on them with treatment, some will escape from the agent. That's why the most effective chemotherapy regimens are multi-agent; the same arguments might apply to chemoprevention. A smoker's lungs are filled with mutated cells; β carotene may suppress normal cells and let the abnormal cells expand.

This may be one reason why lifestyle choices, including exercise and dietary measures, can have an impact; they are multi-agent sources of possible prevention.

There must be many differences between dietary components and nutritional supplements?
Yes; we should not push people into strange exposures, whether in relation to dose, formulation, or combination. These agents are potent and have effects on cells; that's why we take them. But the effects can be deleterious, which is an argument against using them singly, or over a prolonged period. There's no evidence in favour of taking a multivitamin pill, and it could be harmful. More generally, you could be taking the wrong dose of the wrong compound, at the wrong time of life.

What impact would time of life have?
In the case of folate, timing is everything. The epidemiology shows that people with higher intake of folate as a nutrient – and higher blood levels – have a lower risk of polyps, and probably cancer. But when people who have already grown polyps take it, the reverse happens, and their risk increases. Reasonably high levels of folates at a young age may indeed be preventive, but in the subset of people who grow polyps, once this process has started, the folate feeds the growing abnormal cells. Cells that are rapidly dividing need folate; it's a major building block of the bases that make up DNA. In this context, remember that many effective chemotherapy agents are anti-folates.

You've spoken of human 'set points'?
What I'm suggesting is that human beings are able to make physiological sense of almost any environment. We live between the poles and the equator and adapt to the climate and food supply we experience in utero and in early life. The foetus receives signals from the mother's circulation about the availability of various minerals, for instance, and this may determine a set point. There is some evidence to back this: from David Barker about the importance of the in utero environment in determining the risk of adult-onset disease, and from Mel Greaves on possible causes of childhood cancer.

It could mean that – in utero or in early life – you develop the expectation that your system can handle a certain amount of folate, beta carotene, protein, carbohydrate, and so on. If you later start messing with these levels, it could be harmful.

Is your viewpoint being heard?
I'm not quite swimming against the tide, but it's a bit like that. But I won't give up.

Helen Saul