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First common bowel cancer gene found

Scientists have located a gene which increases the risk of colorectal cancer and is present in half the general population. The gene, which is located on the 8q24 region of the genome – an area previously associated with prostate cancer –, increases the risk of developing colorectal cancer by 20%.

The known colorectal cancer genes are rare – carried by one in 2,500 people – and account for less than 5% of colorectal cancer cases. A combination of lower risk genes is thought to exist; overall, genetic risk is thought to contribute to around one third of cases.

In the first study, an international team of researchers led by Professor Malcolm Dunlop (Western General Hospital, Edinburgh, UK), compared the DNA of 7,480 people with colorectal cancer from North America, France and Scotland, to that of 7,779 healthy controls (*Nature Genetics 2007 doi: 10.1038/ng2089*).

They identified a locus on chromosome 8q24 with a 'highly significant' association – a 17% increase in risk – with colorectal cancer.

Lifetime risk of the disease rises from around one in 20 for people who do not carry the variant, to one in 16 for those that do. The new research suggests that around one in 10 cases of colorectal cancer are linked to the variant. The increased risk associated with the variant is small and it would not be suitable for genetic testing. But it may be possible to designs a test for a combination of genes as more 'low risk' variants are found.

Professor Dunlop: 'Understanding all the genes involved is a bit like putting together a jigsaw puzzle in the dark. First we have to feel around for the genes involved and only then will we be able to find out how they all fit together to contribute to increased risk. By identifying these genetic variants, we will be in a better position to understand how such changes can lead to cancer.'

In a second study, led by Professor Ian Tomlinson (Cancer Research UK's London Research Institute, UK), researchers examined the DNA of a similar number of patients and healthy controls in England (*Nature Genetics 2007 doi: 10.1038/ng2085*).

They identified a variant in the same site (8q24.21). Heterozygotes had a 27% increase is risk, the rare homozygotes had a 47% increase in risk. Professor Tomlinson: 'This is an important first step but we still have a long way to go before we have a complete picture of all the genes that are involved in inherited bowel cancer risk.'

Both teams used a multistage genetic association approach. They studied thousands of DNA tags that act as signposts for genes, in 100s of people. Tags which were more common among bowel cancer patients were then reassessed in new, larger groups of patients and controls.

A third study by American researchers (*Nature Genetics 2007 doi: 10.1038/ng2098*) found that a variant at 8q24 known to be associated with prostate cancer (rs6983267) was also significantly more frequent in colorectal cancer patients than in healthy controls. However, 5 other variants associated with prostate cancer were not linked to colorectal cancer. 'Our results show that variants at 8q24 have different effects on cancer development that depend on the tissue type,' they concluded.

- Results presented at the 9th World Congress of Gastrointestinal Cancers (June 27–30, 2007, Barcelona, Spain) suggest that cetuximab (Erbitux) significantly increases progression-free survival in patients with previously untreated metastatic colorectal cancer.

The Crystal trial (cetuximab combined with irinotecan in first line therapy for metastatic colorectal cancer), a randomised, controlled, phase III study, included 1200 patients. One year after the trial started, 34% of patients receiving cetuximab plus the irinotecan-based therapy FOLFIRI in the cetuximab arm had not progressed, compared with 23% of controls, who received FOLFIRI alone.

Complete resections of metastases in a subgroup of patients who had liver metastases only were possible in twice as many patients in the cetuximab group (9.8% versus 4.5%).

Lead author Professor Eric van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium) said, 'These findings are remarkable because they point towards the potential for this combination to provide a cure for those patients who were able to undergo a complete resection.'

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Link between low cholesterol levels and cancer

An association between low levels of low-density lipoprotein (LDL) and cancer risk emerged unexpectedly from a meta-analysis into the side effects of statins. The study (*Journal of the American College of Cardiology* 2007;**50**:409–18) found one additional case of cancer per 1000 patients with low LDL levels.

Further work will be needed to confirm the risk, and to identify whether the increased risk is a side effect of statins or of the low LDL itself. Lead author Professor Richard Karas (Tufts University School of Medicine, Boston, Massachusetts, USA) said, 'This analysis doesn't implicate the statin in increasing the risk of cancer. The demonstrated benefits of statins in lowering the risk of heart disease remain clear; however,

'CARDIOVASCULAR BENEFITS MAY BE OFFSET BY AN INCREASED RISK OF CANCER'

certain aspects of lowering LDL with statins remain controversial and merit further research.'

The analysis included randomised controlled trials of statins published before November 2005. Researchers looked at 13 treatment arms consisting of 41,173 patients.

They found no relationship between either the percentage change in LDL level, or the absolute reduction, and cancer risk. However, they observed higher rates of newly-diagnosed cancer among patients with lower LDL levels. The new cancers were not of any specific type or location. 'The cardiovascular benefits of low achieved levels of LDL-C may in part be offset by an increased risk of cancer,' the researchers concluded.

Recent data from large-scale statin trials have shown that more intensive LDL lowering can provide significant cardiovascular benefits to higher-risk patients. In response to these findings, recent guidelines have advocated lower LDL goals and higher doses of statins to reach them. However, informal observations linking intensive LDL lowering and higher incidence of reported health problems, including liver and muscle toxicity and cancer, has led to concerns about the safety of such treatments.

These concerns prompted the current study. The findings, though, are not definitive. The analysis was based on summary data taken from published manuscripts of each trial. An analysis based on individual patient data would have yielded more specific and potentially more compelling results.

'The present observation is exploratory and hypothesis-generating. In addition, the current findings do not demonstrate causality between low achieved LDL-C levels or statin use and cancer. However, it is also important to note that the primary end point utilised in the large-scale statin trials demonstrating benefit is typically a combined cardiovascular end point and not total mortality', the researchers write.

One potential explanation is that low cholesterol levels are the effect of the disease rather than the cause: occult malignancy causes low cholesterol levels which are then associated with cancer when it becomes clinically manifest. The researchers say, though, that this possibility is inconsistent with the persistence of the statistical association between cancer and low cholesterol after excluding early deaths (within 5 years of the study baseline) in epidemiological studies.

'A concerning inverse relationship between achieved LDL-C levels in statin-treated patients and risk of cancer was observed, and requires further investigation,' the study concludes.

In an accompanying editorial, Dr John LaRosa (SUNY Downstate Medical Center, Brooklyn New York) says that, because no single form of cancer predominates, 'the effect of low-achieved LDL would have to have

'LOW LDL WOULD HAVE TO STIMULATE NEOPLASIA IN A VARIETY OF TISSUES'

been one that stimulated neoplasia in a variety of tissues. Although not impossible, such a universal trigger mechanism would have to involve some change in cell biology or immunity not yet described or related to cholesterol metabolism.

'In addition, because these trials generally lasted 5 years or less, such an effect of low LDL would have to be unusually rapid, particularly in producing new cancer cases.'

He concludes: 'These current findings provide insufficient evidence that there is any problem with LDL lowering that outweighs its significant benefits on vascular disease.'

Group therapy 'does not improve survival'

Group therapy did not improve survival among women with metastatic breast cancer, American researchers said. The group, led by Dr David Spiegel (Stanford University, Palo Alto, California, USA) were seeking to replicate their earlier work, which suggested that group psychotherapy conferred a survival advantage.

In 1989, Dr Spiegel found that women with metastatic breast cancer who received group therapy for a year were more likely to be alive 18 months after diagnosis than patients who received no therapy. Subsequent studies had mixed results.

In the current study, 125 women all received educational literature. Half also received weekly group psychotherapy. Group therapy improved quality of life, but not survival.

The researchers maintain that the psychotherapy has associated with a clear psychological benefit. 'Being confronted with their worst fears as they see others die of the same illness, with help in managing the strong emotions that understandably arise, is emotionally helpful for patients, and not physically harmful,' they conclude.

Why is progress in treatment of cancer cachexia so slow?

A pilot trial involving 11 patients with head and neck cancer who have cachexia showed that the cyclooxygenase-2 (COX-2) inhibitor celecoxib produces a significant increase in weight and body mass index (*Head and Neck 2007, doi:10.1002/hed.20662*).

Even such a small and preliminary study is seen as important because of the rarity of trials into cachexia (typified by uncontrollable weight loss, muscle wasting, and an increase in general metabolism leading to extreme thinness, fatigue, pain, and lowered activity and quality of life). 'In the last decade, very little progress has been made towards treating a condition that leads directly to 30% of cancer deaths and affects half of all cancer patients during the course of their disease,' comments Thomas Adrian (United Arab Emirates University, Al Ain, UAE).

'At present there is no agreed management for cachexia... indeed there is no internationally agreed definition of cachexia', says Ken Fearon (University of Edinburgh, UK). 'Extraordinary, isn't it?' comments Neil MacDonald (McGill University, Montreal, Quebec, Canada). 'Although patients and families care a great deal about the impact of cachexia, the oncology profession seemingly does not respond.'

Beyond dietary advice and oral nutritional supplements, treatment options for the management of patients with cachexia are currently 'non-existent', according to Fearon. Lead author of the celecoxib trial, Marion Couch (Johns Hopkins Medical Center, Baltimore, MD, USA) agrees: 'I do not know of any FDA [Food and Drug Administration] approved drugs for cancer cachexia,' she says.

Nutrition alone is not sufficient to treat or prevent cachexia, which is a different process to starvation. 'One of the main effects of cachexia is the specific depletion of skeletal muscle mass, which leads to a general muscle weakness and which ends with death when the respiratory muscles atrophy', says Mike Tisdale Aston University, Birmingham, UK).

The drugs currently used do not address this problem but merely stimulate increased food intake. Megestrol acetate and glucocorticoids improve appetite and energy intake but have severe toxic effects, and both increase muscle proteolysis, so any weight gain is caused by accumulation of fat or oedema. As Tisdale observes, 'Megestrol acetate is the most used approach to clinical management and therapy for cachexia, not because it works, but because there is nothing else.'

Trials of thalidomide, cannabis, non-specific inhibitors of the ubiquitin-proteasome pathway, and various monoclonal antibodies have shown little benefit, but a vast amount of exciting molecular biology is unfolding in the literature. Candidates for intervention include proteins in the dystrophin glycoprotein complex (DGC), and specific targets on the complex ubiquitin-proteasome pathway. But, Fearon says, 'very few potential drugs are making it through to clinical trials and treatment.'

'TREATMENT OPTIONS ARE CURRENTLY NON-EXISTENT'

One reason for this, as Adrian says, is that so far, 'a lot of effort has been expended with little to show for it.' This is because animal and cellular models do not mimic the spectrum of clinical disease: 'Preclinical research in rodents either investigates a single pathway, or looks at cachexia induced by a single tumour-cell line. In this situation, a given therapeutic agent may be effective. However, in humans we are dealing with a very complex process involving multiple pathways'.

There is also a false perception of cachexia by funding decision-makers. 'Clinicians involved in clinical trials and on the grant committees of charities never see cachexia, since it often appears later in the course of the disease. They therefore regard it as unimportant and not worth investigating,' comments Tisdale. Other clinicians accept it as an untreatable symptom of late-stage cancer. Funding from large pharmaceutical firms, who control the clinical cancer research agenda, is also almost impossible to obtain. 'Only the nutritional arm of pharmaceutical companies show an interest,' says Tisdale.

MacDonald sees the rules that govern entry into trials as a major stumbling block since they often limit simultaneous participation in another trial. 'Newly diagnosed cancer patients are commonly restricted from participation in a cachexia trial. Then, after 2 or 3 lines of failed chemotherapy, frail, exhausted patients with limited life expectancy might, finally be offered participation', he explains. Showing the benefit of any treatment is difficult because cachexia trials need to be done for at least 3 months: 'you can not expect trial participants to have successful outcomes when death is imminent'.

MacDonald highlights the need for infrastructure to deal with cachexia as a multifactorial problem. The Cancer Nutrition and Rehabilitation Programme at McGill University is one of the few that provide a multiple approach: nutritional counselling, a tailored exercise programme, selected nutritional supplements, omega-3 fatty acids to combat inflammation, assessment and treatment for the myriad problems that contribute to anorexia (eg anxiety, depression, pain, dyspnoea, constipation), and, not least, the opportunity to take part in clinical trials.

Fearon says, 'we need to develop early biomarkers of the cachectic process and the medical oncology community must accept that precachexia intervention trials may impinge on a period of a patient's cancer journey that has traditionally been reserved for adjuvant or palliative chemotherapy studies'.

But there is some positive news on the celecoxib trial, which may be extended. 'We aim to add a protein supplement to one arm of the study, in the hope of increasing lean body mass in the patients taking the COX-2 inhibitors', says Couch.

Kathryn Senior

The full version of this story appears in Lancet Oncol 2007;**8**:671–2

Delaying radiotherapy in children

Using chemotherapy to delay or avoid radiotherapy in young children with ependymoma may reduce potentially damaging long term side effects, researchers found. Study author Professor Richard Grundy (University of Nottingham, UK) said: 'We know radiotherapy can be harmful to the developing brain, so avoiding it or using it at an older age if needed will hopefully reduce any learning difficulties these children may develop as a result of this treatment without compromising their chance of a cure.'

The study included 89 children with newly-diagnosed ependymoma in the UK, Scandinavia and the Netherlands. They all underwent surgery followed by an intensive course of chemotherapy. Radiation therapy was reserved only for those children whose disease had spread or progressed. This compares with the standard approach, which has been to give radiotherapy as first-line treatment on diagnosis. The children in the study were followed for 12 years (*Lancet Oncol 2007 doi: 10.1016/S1470-2045(07)70208-5*).

Overall, 42 percent of the children were spared radiotherapy altogether. Of those who received it, use of chemotherapy delayed the radiotherapy by more than 18 months, so that they received treatment at a slightly older age, 3.6 years of age on average, when their brains were more developed.

Almost two-thirds of the children – 64 percent – were still alive 5 years after diagnosis. The 3-year survival rate was equal to the best published radiotherapy results, and the 5-year survival is better than previous trials that have used radiotherapy as a matter of course.

The majority of long-term survivors of ependymomas who are treated with radiotherapy experience reduced IQ and short term memory loss. Professor Grundy: 'It's clear from this study that a significant proportion of children can be spared, or have delayed, the effects of radiotherapy by using chemotherapy.'

Positive opinion for trabectedin

The European Medicines Agency (EMEA) has issued a positive opinion on the use of trabectedin (Yondelis) for the treatment of advanced soft tissue sarcoma. The Committee for Medicinal Products for Human Use (CHMP) announced that the drug may be given after failure of anthracyclines and ifosfamide, or to patients who are unsuited to receive these agents.

Trabectedin was originally isolated from the marine tunicate *Ecteinascidia turbinate*, and is now produced semi-synthetically. It binds to the minor groove of the DNA and interacts with DNA repair enzymes and transcription factors, interfering with different cell cycle processes.

Manufacturer PharmaMar, a subsidiary of the Zeltia group, says it is the first anticancer drug to be developed and produced by a Spanish biopharmaceutical company. The company's president, José Maria Fernández Sousa said the positive opinion is excellent news for patients and their families: 'It is also excellent news for Spanish science as well as for the investigators from all over the world who have participated in the clinical trials and believed in the therapeutic potential of compounds of marine origin.'

The opinion was based on a randomised trial comparing 2 different schedules of trabectedin in patients, most of whom had been diagnosed with either liposarcoma or leimyosarcoma. The primary endpoint was risk of disease progression.

Common side effects include a decrease in white blood cell, platelet and red blood cell count and an increase in bilirubin and liver enzymes in the blood.

Trabectedin is also being studied in a phase III trial in ovarian cancer and a phase II trail in prostate and breast cancers. It received orphan drug status for soft tissue sarcomas from the European Commission (EC) in 2001, and from the US' Food and Drug Administration (FDA) in 2004; and for ovarian cancer by the EC in 2003, and the FDA in 2005.

New indication for bevacizumab

CHMP also issued a positive opinion on a new indication for Roche's bevacizumab (Avastin). It recommended use of the drug, in addition to platinum-based chemotherapy, as first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.

The opinion was based on phase III data: the US' E4599 and the Avastin in Lung (AVAiL) studies. The E4599 randomised controlled trial included 878 patients; median survival of those receiving bevacizumab plus chemotherapy was 12.3 months, compared to 10.3 months for those treated with chemotherapy alone. Overall survival was 25% higher in the bevacizumab group. The AVAiL study included more than 1000 patients in centres worldwide. Results showed that the addition of bevacizumab to a cisplatin/gemcitabine regimen significantly prolonged progression-free survival by 20 to 30%. Side effects were generally manageable, Roche said.

Professor Christian Manegold (Heidelberg University, Germany), principal investigator of the AVAiL study, said: 'I believe that Avastin is such an innovative treatment that it will change not only the current standard of care in NSCLC, but it will also re-write our expectations for patient outcomes.'

Bevacizumab is an angiogenesis inhibitor which targets the vascular endothelial growth factor (VEGF) protein. Its use is being studied in colorectal, breast, lung, pancreatic, ovarian and renal cell carcinoma, among others, and as both adjuvant therapy and in advanced cancers.

The drug received approval for first-line treatment of patients with metastatic colorectal cancer in the US in 2004, and in Europe in 2005. It was further approved in the US as second-line treatment for patients with this indication. It is approved in the US for the treatment of NSCLC, in Europe for the first-line treatment of women with metastatic breast cancer, and in Japan for use in advanced or recurrent colorectal cancer.

PODIUM

Quality of life in Spain

Dr. Juan Ignacio Arraras (Servicio Navarro de Salud, Pamplona, Spain) is a clinical psychologist with a special interest in quality of life. He has been a member of the EORTC Quality of Life Group since 1992. He has participated in the development of various EORTC questionnaires and validated some of them for Spain.

Why do the EORTC quality of life questionnaires need validating?

We need to know how the EORTC questionnaires work in this country; whether people understand the questions and think they address important issues. We need to establish typical values for Spanish-speaking patients for professionals to use as a reference. We are collecting patients' views, not oncologists'.

How are the EORTC questionnaires structured?

There is a general core questionnaire common to different tumours. It is supplemented by different modules which evaluate in more detail the features of different tumours, treatments, or other aspects; there is a breast module, a fatigue module, and so on.

How widely used are the questionnaires?

Most oncologists consider that quality of life is one of the key elements of their work. The assessment tells them how patients feel about their disease and the treatment. The quality of life status of elderly patients, or those with advanced cancer, may determine treatment choices. The questionnaires are useful in clinical trials, other research, and in clinical work.

Are there particular issues that vary a lot between countries?

EORTC questionnaires cover, among other areas, emotional and social life. Some issues – body image, sex life or family relationships, for example – do not mean the same in every country. In Spain, for example, the role of the family is particularly important. Here, family members come to outpatient clinics with patients; they spend a lot of time in the hospital and in the patient's room and expect to be included in consultations with the oncologists. Spain is culturally different from the UK, for example, where patients may not rely as heavily on their family for support.

What changes are made to questionnaires during development?

The original questionnaires are created by EORTC with input from professionals (oncologists, nurses, psychologists) and patients from different countries. Cultural and societal characteristics are taken into account during several phases of development and are reflected in the final common EORTC questionnaires. We were able to include the experience of Spanish patients and professionals during development.

How similar are Spain and South America?

We receive requests from elsewhere in Spain and from South America about using the questionnaires, what values to expect, and how to include them in clinical trials. The language is similar, though some words and expressions differ and there may be differences in the way people to refer to their disease and experience. But people in South America understand the questionnaires.

How does the validation process work?

Validation studies take place in each country after development. The process evaluates the questionnaires in more detail for use in a specific country, in another language and culture. For example, validation of a breast cancer questionnaire involved 170 patients who were interviewed 3 times: once before treatment, once during and once a month afterwards. This gives us information on how the patient was at those three points and how their quality of life changed; the answers are then evaluated using statistical techniques. Patients are also asked directly what they thought of the questionnaire; whether it covered their concerns or if there was something missing.

We validated the general core questionnaire EORTC QLQ-C30 for use with Spanish patients and the specific modules for those with breast, lung, head and neck, or colorectal cancer. The oncology departments in the Hospital of Navarra are involved and the studies are funded by the Servicio Navarro de Salud.

How seriously is quality of life taken?

Protocols now aim to include evaluation of quality of life; the information may be crucial in making clinical decisions. For example, patients with advanced lung cancer have a short life expectancy, which may be increased by giving chemotherapy or radiotherapy. But we need scientific evidence on the impact on quality of life.

Quality of life may be particularly important when treating elderly patients. Having cancer when you are over 65 is not the same as when you are younger. Older people may have done in life what they wanted to, have had experience in facing difficulties and be better able to face their disease than younger people. These factors can be crucial for their quality of life.

How cooperative are patients with these assessments?

Patients have helped during the questionnaires development processes to choose the key aspects of quality of life – the aspects important to them. For patients with advanced cancer, there are brief versions of the EORTC general questionnaire. In our experience, they appreciate someone asking about their physical, social and emotional state, and like talking about it.