EUROPEAN JOURNAL OF CANCER 43 (2007) 2019–2023

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

NEWS. . .NEWS. . .NEWS

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.'

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

doi:10.1016/j.ejca.2007.08.007

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.