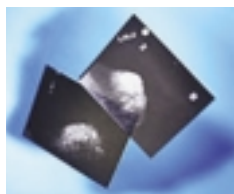


# Common *VEGF* polymorphism could reduce breast-cancer risk

Vicki Brower, BMN News



Austrian researchers have identified a common polymorphism of the gene

encoding vascular endothelial growth factor (VEGF) that both reduces levels of the growth factor in the body and lowers the risk of developing breast cancer.

VEGF is reported to be an important regulator of angiogenesis, regulating the growth of new blood vessels that support the development, growth and metastasis of tumours. The growth factor has been found to be expressed at higher levels in certain tumour types.

## Low-penetrance gene polymorphisms

The Austrian team, led by Peter Krippel of the Division of Oncology at Karl-Franzens University in Graz, Austria (<http://www.kfunigraz.ac.at>), report that only a small number of cases of breast cancer can be explained by inherited genetic mutations, and that the majority are 'most probably explained by a combination of common low-penetrance gene polymorphisms.'

The researchers hypothesized that a common gene variation, the 936C/T polymorphism, which is associated with lower VEGF plasma levels in healthy men, might also be associated with the VEGF plasma levels in women and the risk of developing breast cancer.

Krippel and team carried out genetic analysis on blood samples from 500 post-menopausal Caucasian women with confirmed breast cancer and

compared them against age-matched healthy controls [1].

'We found that carriers of the VEGF 936T polymorphism were less frequent in breast cancer patients than in healthy subjects, indicating that this genetic variant may be protective against breast cancer,' said Krippel. Interestingly, the team did not see a stronger protective effect in homozygous 936T carriers. He and his colleagues believe that in a prospective study, there might be an even stronger protective effect of the VEGF 936T allele, and further studies should be done to determine whether that is true.

The researchers do not know how the polymorphism affects VEGF levels or how it might relate to reduced risk of breast cancer. They note that the observed association of the *VEGF* genotype with breast cancer could also be confounded by other risk factors such as obesity, which might also be linked to breast cancer. Theoretically, higher levels of VEGF could encourage abnormal angiogenesis.

'Further studies are needed to investigate the potential pharmacogenetic role of the VEGF 936C/T polymorphism for antiangiogenesis approaches,' say the researchers. 'Additionally, it might be interesting to analyze the implications of VEGF polymorphism for other malignant diseases.'

## VEGF and ALS

Interestingly, another VEGF study [2] found an inverse relationship in humans and mice between VEGF and neurodegenerative diseases like amyotrophic lateral sclerosis (ALS).

Discovered by angiogenesis researcher Peter Carmeliet of the Flanders Interuniversity Institute for Biotechnology in Leuven, Belgium (<http://www.vib.be>) while studying 1900 patients, Carmeliet found three 'at risk' genetic variations that gave individuals almost twice the risk of developing ALS. Those with the at-risk polymorphisms had lower levels of circulating VEGF and reduced VEGF gene transcription. Carmeliet and colleagues believe that the lower levels of VEGF protect motor neurons against ischaemic death.

Although levels of VEGF in humans are normally variable, says Carmeliet, lower levels of VEGF might be related to ALS, and other neurodegenerative diseases might be related to lower levels of oxygen, which upregulates VEGF.

In cancer, as well as in neurological disorders, VEGF is related to perfusion of blood and oxygen: if blood vessels are not functioning properly, there might be a chronic perfusion problem, or ischaemia, which in turn upregulates VEGF. But if there are low VEGF levels to begin with, 'such a feedback loop may not work,' said Carmeliet. More research is needed to understand the role of VEGF in health and disease, both teams would agree.

## References

- 1 Krippel, P. *et al.* (2003) A common 936 C/T gene polymorphism of vascular endothelial growth factor is associated with decreased breast cancer risk. *Int. J. Cancer* 106, 468-471
- 2 Lambrechts, D. *et al.* (2003) VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death. *Nat. Genet.* 34, 383-394