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Genetic marker in vitamin D receptor gene associated with increased pancreatic cancer survival

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Pancreatic cancer patients with a genetic marker linked to increased expression of the receptor for vitamin D have higher rates of overall survival, according to findings presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held here June 18-21.

"Based on these findings, we should refocus our attention on the role of the vitamin D pathway in pancreatic cancer because it may have an impact on the survival of patients," said Federico Innocenti, M.D., Ph.D., associate professor of pharmacy at the University of North Carolina at Chapel Hill Eshelman School of Pharmacy.

In a previous study, Innocenti and his colleagues prospectively collected DNA from 365 patients enrolled in the CALGB 80303 randomized phase III clinical trial testing two treatments for advanced pancreatic cancer. A genome-wide association study (GWAS) was conducted using these DNA samples to identify genetic variations known as single-nucleotide polymorphisms (SNPs) associated with better or worse patient outcome. In the new study, the 300 SNPs previously shown to be most strongly associated with overall survival were tested for their association with overall survival in 408 patients of European descent with advanced pancreatic cancer treated at the Mayo Clinic.

Among the SNPs with concordant effects on overall survival of patients

in the CALGB 80303 clinical trial and treated at the Mayo Clinic was a SNP in the gene coding for the vitamin D receptor. This SNP, known as rs2853564 in the VDR gene, was associated with better overall survival.

Patients with two copies of rs2853564 in VDR had a median overall survival of 10.5 months in the Mayo Clinic group and 8.9 months in the CALGB 80303 study. Patients with one copy had a median overall survival of 8.34 months in the Mayo Clinic group and 5.9 months in the CALGB 80303 study. Patients with no copies of the variant allele had a median overall survival of 6.6 months in the Mayo Clinic group and 4.7 months in the CALGB 80303 study.

While Innocenti does not see this study having any immediate clinical implications, he believes it provides more information about the link between vitamin D biology and pancreatic cancer.

More information:

Abstract

Role of vitamin D receptor (VDR) gene polymorphisms for overall survival in pancreatic cancer: Genome-wide association and functional mechanistic studies. Federico Innocenti1, Alan P. Venook2, Howard L. McLeod1, Yusuke Nakamura3, Mark J. Ratain4, Gloria M. Petersen5, William R. Bamlet5, Robert R. McWilliams5, Kouros Owzar6, Dylan M. Glubb1, Chen Jiang6, Nancy J. Cox4, Michiaki Kubo3, Hitoshi Zembutsu3, Taisei Mushiroda3, Hedy L. Kindler4. 1University of North Carolina, Chapel Hill, 2University of California at San Francisco, San Francisco, CA, 3RIKEN, Yokohama, Japan, 4University of Chicago, Chicago, IL, 5Mayo Clinic, Rochester, MN, 6Duke University Medical Center, Durham, NC.

Background: Genome-wide association studies (GWAS) are designed to

provide novel insights on candidate genes involved in the pathophysiology of cancer and outcome of therapy. We have previously conducted a GWAS in 294 genetic European advanced pancreatic cancer patients treated with gemcitabine in CALGB80303, a phase III randomized clinical trial (Innocenti et al., Clin Cancer Res, 2012;18:577). In the present study, we aim to identify novel genes associated with overall survival (OS) by replicating the most significant single-nucleotide polymorphisms (SNPs) for OS in CALGB80303 in a cohort of pancreatic cancer patients from the Mayo Clinic. We also aim to provide the mechanistic basis for the replicated associations.

Methods: We have selected the top 300 most statistically significant SNPs for OS in CALGB 80303, and tested their association in 408 genetic European advanced pancreatic cancer patients from the Mayo Clinic. The characteristics of the patients in CALGB 80303 are described in our previous publication. Half of the Mayo Clinic patients had locally advanced disease (and half with metastatic disease), about 30% received prior radiation, and about 60% received gemcitabine. They have been genotyped for about 550,000 SNPs using the same Illumina platform of CALGB80303, and the association with OS was tested using a Cox proportional hazard regression model from date of diagnosis to death or last-follow-up.

Results: In the Mayo Clinic patients, we selected 10 SNPs with an effect on OS concordant with CALGB80303 (p