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Five inherited genetic variants linked to the most lethal prostate cancers

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An international team of researchers led by Fred Hutchinson Cancer Research Center has identified five inherited genetic variants that are strongly associated with aggressive, lethal prostate cancer. The discovery ultimately could lead to the development of a simple blood test that could be given upon diagnosis to determine which men should receive aggressive treatment versus a more conservative "watchful waiting" approach.

The findings, by Janet L. Stanford, Ph.D., co-director of the Hutchinson Center's Program in Prostate Cancer Research and a member of its Public Health Sciences Division, are published online Aug. 16 ahead of the September issue of *Cancer Epidemiology, Biomarkers and Prevention*.

A substantial number of men with indolent tumors – which have a low probability of progressing to clinically significant, lethal prostate cancer – are overtreated and, as a result, suffer side effects such as sexual impotence and urinary incontinence. In addition to its personal toll, overtreatment of indolent prostate cancer also carries a substantial economic burden, with an average of $2 billion to $3 billion spent annually in the U.S. on initial therapy alone.

"Biomarkers that could distinguish between patients with indolent versus more-aggressive tumors are urgently needed," Stanford said. "The panel of markers we've identified provides the first validated evidence that inherited genetic variants play a role in prostate cancer progression and mortality. Ultimately these markers could be used in the clinic, along

with other known predictors that are used to assess tumor aggressiveness, such as a high Gleason score, to identify men with a high-risk profile."

The Hutchinson Center has filed a patent on the panel of five single-nucleotide polymorphisms, or SNPs (pronounced "snips"), which are single-letter variations within the four-letter DNA alphabet that serve as markers of genetic variation across the genome which may play a role in the development or progression of disease. "We chose to study SNPs in genes that potentially play a key role in biological pathways that may contribute to prostate cancer progression such as inflammation, steroid-hormone production and metabolism, DNA repair, circadian rhythm and vitamin D activity," Stanford said.

For the study, the researchers analyzed DNA in blood samples taken from a population-based group of 1,309 Seattle-area prostate cancer patients who were age 35 to 74 at the time of diagnosis. They evaluated 937 SNPs in 156 candidate genes and, of these, 22 SNPs emerged as being significantly associated with prostate cancer-specific mortality.

A subsequent validation study of these 22 SNPs was conducted in another population-based group of 2,875 prostate cancer patients in Sweden who were age 35 to 74 at diagnosis. Upon genotyping DNA from their blood, five of the 22 SNPs emerged as being significantly associated with death from prostate cancer. A higher proportion of patients from Sweden (17.4 percent) had died of prostate cancer relative to those from Seattle (4.6 percent) during a median follow-up period of 6.5 years, which is consistent with the higher prostate cancer mortality rate in Sweden relative to the U.S.

The five SNPs were located in or tagged, one each, to five genes that may affect prostate cancer progression:

- LEPR – The strongest marker associated with prostate cancer mortality in the study was the leptin receptor gene, which helps control tissue growth, inflammation, blood-vessel development and bone density. The latter effect makes LEPR an interesting candidate for understanding disease progression, since the primary metastatic site for prostate cancer is bone, and such metastases are predictive of fatal disease.
- RNASEL – This gene is associated with hereditary prostate cancer and is associated with apoptosis (programmed cell death), inflammation and the ability of cells to proliferate and stick to each other (hallmarks of cancer growth).
- IL4 – This Interleukin 4 gene is associated with tumor growth, blood vessel development and cancer cell migration.
- CRY1 – Cytochrome 1 is a gene that impacts the circadian rhythm and thereby may affect androgen levels, which are known to be involved in prostate cancer progression.
- ARVCF – This gene is a member of the catenin family of proteins, which help the inside and outside of cells "talk" to each other. Increased expression of ARVCF has been shown to disrupt cell adhesion, which may facilitate cancer progression.

Patients who carried four or all five of these genetic markers had a 50 percent higher risk of dying from their prostate cancer than patients who had two or fewer. The risk of dying from prostate cancer increased with the number of SNP genetic variants a patient carried.

"While previous studies have suggested that genetic background influences prostate cancer outcomes, this is the first study to validate genetic markers associated with lethal disease," Stanford said.

"The ability to distinguish patients at elevated risk for having aggressive, life-threatening prostate cancer at the time of diagnosis could improve care for the subset of cases most likely to benefit from aggressive

therapy and help avoid overtreatment of patients whose tumors are likely to remain indolent," the authors wrote.

The potential usefulness of the panel of five SNPs in the clinic to stratify patients at higher risk for disease progression now needs to be evaluated in other patient populations. Stanford and colleagues are also planning additional studies of this set of genetic markers to predict adverse prostate cancer outcomes.

Provided by Fred Hutchinson Cancer Research Center