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Inherited mutations in three genes predict for aggressive prostate cancer

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A study of three genes associated with the development of prostate cancer found that men with inherited mutations in these genes are more likely to develop aggressive forms of the disease and die from prostate cancer at an earlier age than those without the mutations. The study to be published in the journal *European Urology* looked at germline mutations in the ATM and BRCA1/2 genes and represents important progress on the goal of being able to predict which men are more likely to develop a lethal form of prostate cancer versus an indolent one.

"The study results have an important translational impact because they clearly demonstrate germline mutations in these three well-established genes can be used to predict risk for lethal prostate cancer and time to death," said Jianfeng Xu, MD, DrPH, Vice President of Translational Research at NorthShore University HealthSystem (NorthShore) and Director of the Program for Personalized Cancer Care. "This confirms major findings from previous studies and provides further direct evidence of the important role of genetic testing in prostate cancer screening and treatment."

The study was a collaboration of NorthShore, the John Hopkins University School of Medicine (William Isaacs, PhD, et al.), and Fudan Institute of Urology, Fudan University (Qiang Ding, MD, et al.), in Shanghai, China. It is a retrospective case study of 313 patients with lethal prostate cancer and 486 with indolent prostate cancer in men of European American, African American and Chinese ancestry.

"Our aim is to find genetic markers among men who are at high risk of developing an aggressive prostate cancer," said Dr. Isaacs, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology at the Johns Hopkins Brady Urological Institute and member of the Johns Hopkins Kimmel Cancer Center. "Mutations in these genes, particularly BRCA2 and ATM, have been linked to aggressive prostate cancer, and this study provides important estimates of the frequency of mutations in men dying at different age ranges."

The study found the frequency of gene mutations in lethal prostate cancer patients (6.07%) was significantly higher than that observed in localized cancer patients (1.23%). Mutation carrier status was also significantly associated with more advanced prostate cancer at time of diagnosis, and among lethal prostate cancer patients an earlier death (67 years vs. 72 years in non-carriers). In addition, the median survival time after diagnosis was significantly shorter in carriers (four years) than the non-carriers (eight years). In contrast, no mutations were observed in 49 men dying from prostate cancer over the age of 80.

Study authors say the results have important clinical implications, and recommend that mutation carrier status be included as an important factor as clinicians make treatment decisions. Men who have their prostates removed may experience significant side effects, including incontinence and erectile dysfunction.

"We have made great progress in identifying molecular factors in the development of prostate cancer in recent years but what remains elusive is being able to distinguish cancers that are particularly aggressive versus ones that are likely to remain indolent, maybe for years," said Brian Helfand, MD, a NorthShore urologist and an author of the study. "This is absolutely vital information to have when considering whether to aggressively treat a patient's cancer or take an approach of active surveillance."

Authors acknowledged the rate of mutations in these three genes in men with lethal prostate cancer is relatively low, pointing to the need for further studies that investigate other DNA repair genes. Members of this same research group have conducted similar such studies and recently had a letter published in the *New England Journal of Medicine* about the potential role of the DNA repair gene CHEK2 in prostate cancer and lethal prostate cancer.

Provided by NorthShore University