Testing for inherited mutations could benefit men with advanced prostate cancer

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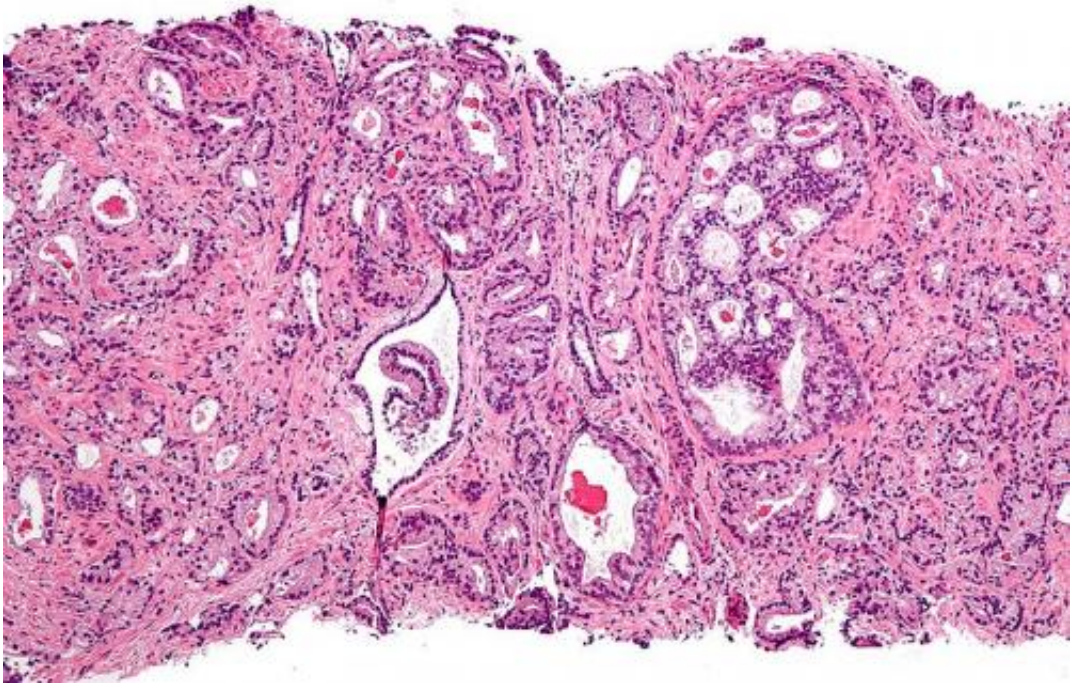

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Inherited mutations in genes that function to repair DNA may contribute to metastatic prostate cancer more than previously recognized, according to a study out today in the *New England Journal of Medicine*. Though infrequent in the general population, inherited mutations in specific types of DNA repair genes, such as BRCA1 and BRCA2, are known to predispose to prostate cancer. However, the rate of such mutations in

men with metastatic prostate cancer previously was unknown.

This groundbreaking study revealed that more than 10 percent of men with aggressive prostate cancer that has spread outside of the prostate have inherited mutations in DNA repair genes—more than four times the rate of the general population and more than twice the rate of men with localized prostate cancer. Men with such mutations could benefit from targeted treatment already approved for ovarian cancer patients with these mutations, such as PARP inhibitors or platinum drugs.

Dr. Peter Nelson, a Member of the Human Biology, Clinical Research and Public Health Sciences divisions at Fred Hutchinson Cancer Research Center and senior and corresponding author of the study commented: "The result is surprising and important for men with prostate cancer as this information may prioritize certain therapies. It is also important for family members as they may have inherited a gene that predisposes them to developing one of several types of cancer and heightened awareness could enhance early detection and treatment. These findings present a compelling argument for updating prostate cancer screening guidelines to include germline DNA testing as a part of standard care for men with metastatic prostate cancer." Dr. Nelson is also a professor of medical oncology at the University of Washington School of Medicine and an oncologist specializing in therapies for early- and late-stage prostate cancer, pathology and genome sciences at Seattle Cancer Care Alliance.

Key results of the study found that 11.8 percent of men with metastatic prostate cancer, regardless of age or family history of prostate cancer, have deleterious germline mutations in one of 20 DNA repair genes surveyed. Men with metastatic prostate cancer were five times as likely to have these inherited mutations in DNA repair genes as the general population. In particular, men with advanced prostate cancer had an 18 times higher risk of carrying a BRCA2 mutation than men without

prostate cancer.

Dr. Colin C. Pritchard, Associate Professor in the Department of Laboratory Medicine, and Associate Director of the Genetics and Solid Tumors Laboratory at the University of Washington School of Medicine is the first author of the study. "We were excited to learn how high the percentage of inherited DNA repair gene mutations is in men with metastatic prostate cancer because of the potential benefits of genetic testing. We already know a lot about some DNA repair genes such as BRCA2, but for others we are just beginning to understand how germline mutations contribute to prostate cancer risk and selection of optimal therapy. As these men consider getting tested it is important to note that not all DNA repair genes are the same, and clinical genetic testing requires specialists to ensure appropriate counseling, accurate mutation detection, and results that are correctly interpreted and communicated."

The project pooled results from 692 men with metastatic prostate cancer included in seven case series across several institutions, including the Fred Hutchinson Cancer Research Center and the University of Washington through support from StandUp2Cancer and the Prostate Cancer Foundation. Each site conducted independent screening of mutations in 20 DNA repair genes using next-generation sequencing assays.

As mutations in some DNA repair genes predispose to other types of cancer, including breast, ovarian and pancreatic, family members of metastatic prostate cancer patients with inherited mutations may be offered genetic testing, counseling and enrollment in research studies, if appropriate.

Dr. Heather H. Cheng, Assistant Professor of Medical Oncology at University of Washington and Assistant Member in the Clinical

Research Division at Fred Hutchinson Cancer Research Center is also a coauthor on the study, and is leading a new Prostate Cancer Genetics Clinic at the SCCA to advise men with prostate cancer about genetic testing and how results may help tailor their treatment options.

An important strength of these findings is that men included in the study were not chosen due to family history of prostate cancer or age, and different genetic screening assays produced the same percentage of men with inherited mutations.

More information: *New England Journal of Medicine*, DOI: 10.1056/NEJMoa1603144

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