Genetic Risk Scores and Prostate Cancer

New research shows polygenic risk scores could help distinguish who with prostate cancer can cut back on “active surveillance.”

January 6, 2025 By Fred Hutch News Service and Diane Mapes

Not all cancers are alike, especially when it comes to prostate cancer.

“Most patients are diagnosed with a low- or favorable intermediate-risk prostate cancer,” said Fred Hutch Cancer Center genetic epidemiologist Burcu Darst, PhD, who collaborated with Daniel Lin, MD; Louisa Goss, MS; Lisa F. Newcomb, PhD; Yingye Zheng, PhD, and others on new research published December 12 in JAMA Oncology. Lin holds the Pritt Family Endowed Chair in Prostate Cancer Research at UW Medicine.

“The guidelines recommend they go on active surveillance rather than getting treated. For many of them, it’s really unlikely they’ll later be diagnosed with aggressive disease.”

The problem — for patients, clinicians and researchers — is figuring out who will develop an aggressive form of the disease and who will not.

According to the American Cancer Society, around one in eight men are diagnosed with prostate cancer and one in 44 men die of it. Most diagnosed with the disease do not die; there are currently 3.3 million prostate cancer survivors in the U.S. As one cancer center director put it, most men diagnosed with the disease “die with prostate cancer, not of prostate cancer.”

Now, research by Darst and scientists from the Canary Prostate Active Surveillance Study (PASS), suggests that a patient’s polygenic risk score, or PRS, may be able to help clinicians differentiate the more dangerous prostate cancers from those that will never cause an issue.

What’s a polygenic risk score?

People being screened for prostate cancer usually receive a blood test known as a PSA or prostate-specific antigen test. A higher than usual PSA warrants evaluation, usually via biopsy; high PSAs could be the result of infection, inflammation, prostate enlargement or cancer.

If a patient receives a cancer diagnosis, they either go on to treatment (if the cancer appears to be

aggressive) or they go into “active surveillance,” where they are regularly monitored by a care team. The person’s Gleason score, established by analyzing prostate tissue gathered via biopsy or surgery, determines what clinical pathway they take. Before researchers could distinguish the nature of the cancer, most patients went into treatment, which can include surgery, chemotherapy, radiation and androgen-deprivation therapy (also known as “chemical castration”).

“Over the years, many men have been overtreated for prostate cancer that was unlikely to ever become aggressive,” Darst said. “And these can be treatments with serious side effects, like incontinence and impotence.”

A polygenic risk score (or PRS) is determined by identifying the germline genetic variants associated with a cancer risk through a GWAS or genome-wide association study, then analyzing those individual patient “scores” to determine who is at high risk and who is not.

In the study, prostate cancer patients with high PRS were more likely to have tumor features that were characteristic of risk of aggressive disease. Notably, in the years following their initial diagnosis, they had a higher risk of their prostate cancer being reclassified to a higher Gleason grade, commonly referred to as “upgrading.”

“Gleason grade is one of the strongest predictors of developing a more aggressive disease or potentially metastatic disease down the line,” Darst said.

Darst used the signatures of 451 germline genetic variants (or mutations) associated with prostate cancer risk to create the PRS used in the study, which was then compared with the patients within the Canary Foundation’s PASS cohort.

“The patients receiving active surveillance via the PASS study follow a strict protocol,” Darst said. “They have needle biopsies at diagnosis and then again at six months, 12 months and 24 months. Active surveillance can involve going in pretty often for biopsies, blood draws and MRIs, which can be costly and burdensome, both mentally and physically.”

Cutting back on surveillance

Darst, who works with patient advocates within the Pacific Northwest Prostate Cancer SPORE, said the aim of the research is to allow “some of these patients to safely de-intensify the active surveillance.”

But it may do more.

The association of higher PRS with higher grade prostate cancer could potentially carve out a clinical pathway for “incorporating genetic susceptibility into disease management,” Darst wrote. Doing so “could help identify patients receiving active surveillance who may benefit from intensive versus passive surveillance, reducing burdens for patients with lower risk of disease progression.”

The next step for this research, she said, is to try to create an even more accurate polygenic risk score for prostate cancer patients.

“Right now, this could be meaningful for some people but it’s hard to know how clinically useful it could be,” she said, emphasizing that more research is needed before clinically implementing PRS for active surveillance patients.

“We need to do more research to try to improve the models to be more specific to disease progression on active surveillance,” she said. “And we also need to look at rare variants, which can be very important in prostate cancer.”

Darst also highlighted the importance of working with cancer patients when designing and launching studies.

“It’s been really helpful to meet with patients,” she said. “Up until recently, I’ve been doing research on specific diseases but not getting to know the people who are impacted by these diseases. Working with patients has provided a very helpful perspective, and it personalizes and humanizes everything. It also helps me to hear when I’m on the right track and when I can make improvements.”

In other prostate cancer news …

Fred Hutch faculty also published new research in the Journal of the National Cancer Institute last November that found that Black patients were less likely to receive certain prostate cancer treatments, even though they’re more than twice as likely to die from the disease as patients who are white.

The research team, which included urologic oncologist Yaw A. Nyame, MD, MS, found “neighborhood-level social determinants of health contribute to barriers in prostate cancer treatment for Black individuals,” but these social determinants of health didn’t account for all treatment inequities. Black patients, they discovered, were “less likely to receive radical prostatectomy” and also “less likely to receive radiation” than other patients.

“Physicians treat Black individuals differently than they do white individuals, even when compared to that physician’s average behavior,” they wrote, adding that their findings “underscore the need for lasting, community-driven interventions to address treatment inequities facing Black individuals with prostate cancer.”

Fred Hutch medical oncologist Robert B. Montgomery, MD, also contributed to a recent editorial in European Urology that proposes a reexamination of the language used to describe prostate cancer, particularly with regard to descriptive disease states like “metastatic castration-sensitive prostate cancer” or “castration-resistant prostate cancer.”

“Words matter,” the team wrote. “We believe that the word ‘castration’ is difficult for patients,

partners and families to hear and should be avoided when we describe this advanced prostate cancer disease state."

Instead, they recommend using newly coined terms including "metastatic hormone-sensitive prostate cancer" and "androgen deprivation–resistant prostate cancer," along with other, less-alarming terms, to "minimize confusion and allow for better communication and greater accuracy and less fear of therapy in the advanced prostate cancer state."

Burcu's work was supported by the National Cancer Institute at the NIH, an award from the Andy Hill Cancer Research Endowment Distinguished Researchers Program, a Fred Hutch/University of Washington SPORE Cancer Enhancement Program award, the Prostate Cancer Foundation and the Institute for Prostate Cancer Research.

Nyame's work was supported by the Andy Hill CARE Fund and the National Cancer Institute at the National Institutes of Health SPORE.

This article was originally published December 12, 2024, by Fred Hutch News Service. It is republished with permission.
