Study finds what could be a key to prostate cancer progression

William Check, PhD

October 2016—The Gleason classification for prostate cancer is by no means going away. But within the Gleason grade, the presence or absence of a DNA-repair gene mutation may signal who is likely to proceed to invasive cancer, says Colin C. Pritchard, MD, PhD, lead author of a study published Aug. 4 in the *New England Journal of Medicine.*

In the multicenter study (2016;375[5]:443–453), inherited mutations in DNA-repair genes were found at a significantly higher frequency in men with metastatic prostate cancer (11.8 percent) than in men with localized disease (4.6 percent).

“The biology of these mutations suggests that they are important drivers of prostate cancer progression and important contributors to hereditary components of this disease,” says Arul Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology at the University of Michigan Comprehensive Cancer Center and a participant in the study.

The results point to the benefit of testing all men with metastatic prostate cancer for these genetic variants, says Dr. Pritchard, an associate professor of laboratory medicine and associate director of the genetics and solid tumors laboratory at the University of Washington. Identifying the mutations associated in this study with metastatic prostate cancer will aid in managing risk for individual patients, he says, and prompt counseling for family members who may be at risk.

“Especially exciting,” Dr. Pritchard adds, “is the therapeutic implication, which is promising in metastatic prostate cancer.” Indeed, the finding published last year that treatment with the PARP inhibitor olaparib led to a high response rate in men whose prostate cancers had stopped responding to standard treatments and who had defects in DNA-repair genes “provides a clear treatment pathway in accordance with precision medicine strategies,” write the authors of the latest study.

Overall, “We believe this is really a very important study that will change clinical practice” for clinicians and molecular laboratories, study participant Mark A. Rubin, MD, Homer T. Hirst professor of oncology in pathology and director of the Englander Institute for Precision Medicine at Weill Cornell Medicine and NewYork-Presbyterian Hospital, told CAP TODAY.

In the study, physicians at four medical centers in the United States and one in England enrolled 692 men with metastatic prostate cancer. Using next-generation sequencing techniques, participating laboratories analyzed the sequences of 20 genes associated with autosomal dominant cancer-predisposition syndromes in both tumor and matched normal tissue. Dr. Pritchard’s laboratory used a targeted panel called BROCA. The laboratories of Dr. Chinnaiyan and Dr. Rubin used whole exome sequencing.

All 20 genes are responsible for DNA repair and maintenance of DNA integrity. “We selected genes that are already known to be part of clinical genetic testing for some cancers,” Dr. Pritchard explains, though prostate cancer was not known to be part of the spectrum for every gene.

Among the 692 patients, 84 germline mutations were found in 82 patients (11.8 percent). Mutations were found in 16 of the 20 genes. The highest frequency of mutations was found in the *BRCA2* gene, followed by *ATM, CHEK2,* and *BRCA1.*

Dr. Pritchard

“The fact that the prevalence and frequency were so high was a surprise to us,” Dr. Pritchard says. “We thought these mutations were rarer.” Questions about guidance and screening are fairly new in this setting. “Some people are working on that,” Dr. Pritchard says. “Now we can begin to set screening guidelines.”

The difference in frequency of repair-gene mutations between localized and metastatic prostate cancer is not only statistically significant but also clinically meaningful. “To some extent we could ask what is the threshold that should prompt testing,” Dr. Pritchard says. “We can learn from the breast and ovarian cancer community, where testing for *BRCA1* and *BRCA2* is the standard of care among women who meet certain criteria and have breast or ovarian cancer.” In that situation, he notes, testing anyone in a risk group in which the prevalence of inherited mutations rises above 10 percent is strongly recommended and generally accepted. “So at 12 percent the frequency of mutations in DNA-repair genes may justify routine testing among men with metastatic prostate cancer.”

In this study, DNA was taken from white cells in peripheral blood. Strong evidence supports the interpretation that identified variants were inherited or germline mutations. “We can look at the fraction of variants detected in the white blood cells. If they are found in half of sequences, they are usually heterozygous inherited variants,” Dr. Pritchard explains. “Also, a lot of these mutations, maybe most, have already been described as inherited mutations.” While circulating tumor cells and circulating DNA can be found in peripheral blood, Dr. Pritchard adds, “they only constitute a tiny fraction of cells or DNA in the blood.” Of course, patients were selected to have no evidence of blood cancers.

Among the seven cohorts included in the work (three from the University of Washington and four from other institutions), mutation frequency was similar across individual case series. “This was one of the most encouraging things to us,” Dr. Pritchard says. Groups of patients were accrued for different reasons and none were based on a known family history. “So the result was very convincing and reproducible,” he says. One question that remains to be addressed is whether the result applies to those who are not of European descent, in particular African-Americans, who, Dr. Pritchard notes, have a higher rate of prostate cancer and more aggressive disease.

After identifying patients who had a germline mutation in one of the 20 DNA-repair genes, study investigators went back and analyzed tumor tissue from those men. They found that almost 60 percent of them also had an inactivating mutation in the other allele of that gene in the tumor. Finding that both alleles were mutated in tumor tissue supports the notion that the defects found in those genes were related to tumor biology. “Loss of the second allele is important,” Dr. Pritchard points out. “We can make pathogenic inferences.”

Dr. Chinnaiyan

Where both alleles were defective, it presumably represented the germline mutation plus a second, somatic

mutation, says Dr. Chinnaiyan, who is the S. P. Hicks endowed professor of pathology at Michigan. “One allele was defective at the germline level,” he explains, “and in many cases the matched tumor tissue had the germline mutation plus a hit in the second allele, suggesting that that gene was the driver in that tumor.” (If both mutations had been present in the germline, the fetus would have been an embryonic lethal.) One would expect this sequence from the multi-hit hypothesis for cancer (https://en.wikipedia.org/wiki/Knudson_hypothesis).

This study was an extension of earlier work in which most of the same investigators examined the integrative genomics of castration-resistant prostate cancer in 150 patients in what Dr. Chinnaiyan says was “an unbiased way.” (That work and the most recent research were supported in part by a grant from the Stand Up to Cancer–Prostate Cancer Foundation to a consortium Dr. Chinnaiyan leads.) In the earlier study it was observed that the frequency of mutations in BRCA1 and 2 and ATM was much higher in castrate-resistant prostate cancer (Robinson D, et al. Cell. 2015;161:1215–1228). Dr. Chinnaiyan called that group the discovery cohort. In the more recent publication, which he called the validation cohort, that finding was verified.

Of the finding’s therapeutic implications, Dr. Pritchard says that in other cancers, the types of mutations in DNA-repair genes seen in this study have been strongly predicted to respond to platinum-based chemotherapy and PARP inhibitors. Platinum therapy is fairly new in prostate cancer and has been used previously only rarely—and as a last step.

“PARP” refers to the DNA-repair enzyme poly-ADP ribose polymerase. Says Weill Cornell’s Dr. Rubin, “It has been known for many years in hereditary cases of breast cancer with a BRCA mutation, where homologous DNA repair is lost, that tumor cells can repair through non-homologous enzymes in another pathway.” That makes them extremely vulnerable to drugs that target that pathway, which PARP inhibitors do. “The combination of a mutation in a DNA-repair enzyme plus a drug that blocks the alternate pathway creates what is called a synthetic lethal,” Dr. Rubin explains. “Cells can no longer repair DNA mistakes, and they die. It is very important that this option adds one more drug that patients can consider for controlling advanced prostate cancer.”

Inhibitors of the PARP enzyme are now used in patients who have defects in DNA repair due to mutations in BRCA1 and 2, Dr. Chinnaiyan says, adding, “These tumors preferentially respond to PARP inhibitors.” He cites the clinical study he conducted with others that found that patients with metastatic prostate cancer that was no longer responding to standard treatments and who had defects in genes for DNA-repair enzymes preferentially responded to a PARP inhibitor (Mateo J, et al. *N Engl J Med.* 2015;373[18]:1697–1708).

“Based on those results, earlier this year FDA provided breakthrough status for PARP inhibitors for patients with metastatic prostate cancer who have germline defects in DNA-repair genes *BRCA1* and *2* and *ATM*,” Dr. Chinnaiyan says.

Beyond screening patients who have metastatic prostate cancer for mutations in DNA-repair genes, the findings of the latest study suggest analysis also of family members. “Finding a germline mutation in one of these DNA-repair genes suggests a higher risk in family members to have defects in repair genes that could lead to a predisposition to other cancer types,” Dr. Chinnaiyan says.

In the study, 71 percent of patients with a germline mutation in one of the 20 DNA-repair genes had a first-degree relative with a cancer other than prostate cancer, a significant increase over metastatic prostate cancer patients who did not have a germline mutation in a DNA-repair gene. This information can be used not only for risk management of the patient and for his own therapy but also for family counseling. “We are optimistic that this could be incorporated into practice soon,” Dr. Pritchard says. “Men will be motivated to get tested for their own treatment as well as for the potential benefit of family members.”

This fall, the Seattle Cancer Care Alliance will open a cancer genetics clinic dedicated to prostate cancer. (The Seattle Cancer Care Alliance provides clinical cancer care as a consortium of the University of Washington, Fred Hutchinson Cancer Research Center, and Seattle Children’s Hospital.) “It may be the first of its kind or one of the first,” Dr. Pritchard says. Men with prostate cancer can go in for counseling and find out whether genetic testing is

right for them. “It will have experts at all levels and oncologists who can make treatment decisions,” he says.

At a more complex level, how will next-generation sequencing analysis for inherited mutations in DNA-repair genes interact with prostate-specific antigen testing? An ongoing European study has already found a lower PSA threshold to proceed to biopsy if a patient has an inherited mutation in *BRCA1* or *2*, Dr. Pritchard says. “If I had one of these mutations, I would start PSA screening early. However, we need evidence to make screening recommendations,” he adds.

Dr. Rubin

Weill Cornell Medical College is also poised to act on the findings. “We are very much convinced that this is important,” Dr. Rubin says. “As an academic institution we are doing several prospective studies to evaluate what is the best policy for performing germline testing.” One approach is to do homegrown whole exome sequencing to try to identify mutated DNA-repair genes. Then, too, there are companies that offer inexpensive tests directly to patients or with an oncologist’s order, Dr. Rubin says, and at least one of the tests looks robust and has a rapid turnaround time. “That wouldn’t stop us from performing NGS in the future,” he says, “but it would be a way to get testing done rapidly right now.”

More broadly, Dr. Rubin says, the results of this study are going to require a re-evaluation of germline testing. “We know there is a strong call for women with breast cancer to have germline testing. These results will very much open the question as to which men should be tested and which family members. We need to decide how we are going to handle this.”

He cautions against underestimating the complexity of germline testing. “Although there are some very well-known predisposition genes and mutations defined, there are still many that are not clearly understood as to their significance,” Dr. Rubin says. “So there is still a lot of work to be done when results come back.”
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