

Discussing the predictive, prognostic, and therapeutic value of germline DNA-repair gene mutations in metastatic prostate cancer patients

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ABSTRACT

Recent trends in cancer therapy have begun emphasizing the use of precision medicine, especially genetic tools, in the evaluation of malignancies and decision-making. Prostate cancer is a malignancy where the benefits and utility of screening and early treatment are still heavily controversial. A recent paper in the *New England Journal of Medicine* found that patients with metastatic prostate cancer presented germline mutations in DNA-repair genes at a significantly higher incidence than those with localized prostate cancer. These findings indicate the need for further research in this field as genetic differences between metastatic and localized prostate cancer could have great clinical value.

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Prostate cancer is the most commonly diagnosed form of non-cutaneous cancer among males.¹ Although much progress has been made toward understanding the biologic foundations of this malignancy resulting in improved clinical therapies, it remains a lethal disease when metastatic castration resistant prostate cancer (mCRPC) develops. The benefits of prostate cancer screening have recently been challenged. While this can result in early detection of aggressive malignancies, some patients are best managed conservatively and physicians often recommend such paths as active surveillance.² Difficulty remains in management of treatment strategies due to the low availability of predictive and prognostic markers that more accurately inform treatment. One possible avenue has been to investigate genetic markers and mutations. Genetics have been shown to heavily affect prostate cancer risk, with one study ascribing as much as 57% of risk variability to genetic factors.³

While genome-wide association studies have identified genes influencing prostate cancer risk, few have suggested associations with an increased risk of progression or negative outcomes. One recent study investigated the presence of various genetic alterations in tumor samples from 150 patients with mCRPC.⁴ These genetic alterations were organized by pathway to better understand how they contribute to cancer progression. The study also found that germline mutations in DNA-repair genes such as *BRCA1* and *BRCA2* could have a significant impact on prostate cancer. These genes were studied in localized prostate cancer but showed a low prevalence and thus yielded little clinical significance. Genetic alterations in these genes were more prevalent in metastatic prostate cancer, a finding that warranted further investigation.⁵

In their recent publication in the *New England Journal of Medicine*, Pritchard et al. investigate such genetic mutations in

patients with metastatic prostate cancer. Building on the earlier findings showing that 8% of 150 men with metastatic prostate cancer carried pathogenic germline mutations in DNA-repair genes, the authors expanded their analysis to include an additional 542 subjects with metastatic prostate cancer from 6 different case series. They sequenced germline DNA in search of mutations within 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes. Their analysis found that 82 out of the 692 patients (11.8%) displayed at least one mutation in 16 unique DNA-repair genes, with the majority of mutations within *BRCA2*, *ATM*, *CHEK2*, and *BRCA1*. The prevalence of these mutations was surprising when compared with other populations. An analysis of 499 patients with localized prostate cancer from the Cancer Genome Atlas yielded only 23 men (4.6%) with germline mutations in DNA-repair genes ($p < 0.001$). A much larger analysis of the general population from the Exome Aggregation Consortium revealed only 2.7% of 53,105 healthy males carried such a mutation ($p < 0.001$). This stark contrast between groups provides compelling evidence that these mutations could be used to better understand disease progression, improve prognosis formulation, and identify therapeutic targets.

Some interesting associations were noted. Gleason scores were available for 73 of the 82 patients. Germline DNA-repair gene mutations were associated with a higher Gleason score with 56 of 73 (77%) having Gleason 8 or higher disease while 15 men (21%) had a Gleason score of 7. This resulted in a significant difference between the presence of a germline DNA-repair gene mutation and a Gleason score of 8–10 as opposed to 7 or less ($p = 0.04$). Family history of cancer was found to have correlation although in an unexpected manner. Seventy-two of the 82 metastatic prostate cancer patients with

germline DNA-repair gene mutations and 537 of 692 without mutations had family history available. Having a first degree relative with prostate cancer was not statistically significant between those groups. A family history of cancer other than prostate was significantly correlated (71% to 50%, $p = 0.001$). Cancers found in family members included a wide variety indicating that such mutations are relevant to both male and female family members. Further study in this area could lead to screening patients with metastatic prostate cancer for germline DNA-repair gene mutations. The group found no difference in the incidence of germline mutations in DNA-repair genes between men younger or older than 60 ($p = 0.90$) or non-Hispanic white men and non-white men diagnosed with prostate cancer ($p = 0.84$).

This study may also aid in the future analysis of tumor tissue. Analysis of genetic mutations could potentially reveal considerable tumor differences depending on both the site of the biopsy and exposure to therapies. Pritchard et al. were able to sequence tumor DNA in 61 of the 82 patients with mutations, noting that 36 (59%) contained a mutation in the second allele of that gene. This appeared to concur with a previous study describing how patients exhibited a somatic mutation at a second allele in addition to an initial germline one in advanced cancers.⁶ Tumor heterogeneity has been demonstrated in other tumor types with variations both in the same tumor as well as among different tumors within the same individual.⁷ In contrast, another study investigating the genetic characteristics of different metastases within the same metastatic prostate cancer patients found limited variation. They then proposed that a biopsy from a single site could provide information applicable to all the tumor sites.⁸ Similarities and differences in tumors within the same patient have important clinical significance and must be further explored. A somatic mutation in a second allele in metastases combined with potentially limited metastatic variability within an individual suggests an understanding of these germline mutations could elicit a better understanding of metastatic progression.

The findings of an increased prevalence in germline DNA-repair gene mutations in patients with metastatic prostate cancer could directly influence treatment options. Recent studies have shown encouraging evidence that DNA-repair mutations can be used as therapeutic targets. This could be of special importance for men with metastatic castration-resistant prostate cancer (mCRPC) who may not respond to standard therapies. One case series found that patients with mCRPC with mutations in the *BRCA2* DNA-repair gene showed an excellent response to platinum chemotherapy.⁹ A different study described the benefit of treatment with the poly(adenosine diphosphate [ADP])-ribose polymerase (PARP) inhibitor olaparib in men with mCRPC with DNA-repair gene mutations.¹⁰ Therefore, the findings from the Pritchard study may prove important as a higher incidence of these mutations in metastatic prostate cancer patients could open the door to these therapies.

The knowledge provided by genomic analysis of cancers has already benefitted our understanding of the biology of tumors, many resulting in clinical benefit to patients. The article by

Pritchard et al. builds upon and contributes to this knowledge base. The identification of an increased prevalence of germline DNA-repair gene mutations in metastatic prostate cancer patients has many avenues of relevance. Such information could be used to better understand metastatic progression as well as prognosis formulation in newly diagnosed patients. Screening for these mutations could lead to new therapeutic strategies in metastatic castration-resistant prostate cancer patients. Evidence of these mutations could help predict potential risks of breast, ovarian, pancreatic, and other cancers in family members. Overall, the findings by Pritchard et al. are highly encouraging and could prove to have great clinical significance.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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