Germline contributions to metastatic prostate cancer

Heather H. Cheng, MD, PhD[1,2]

[1]Department of Medicine, University of Washington, Seattle, Washington, USA

[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

CHENG HH. Germline contributions to metastatic prostate cancer. *Can J Urol* 2019;26(Suppl 2):19-21.

Recent studies demonstrate that the prevalence of germline mutations in DNA repair genes in metastatic prostate cancer is higher than previously recognized, and is higher than in localized disease and in unaffected men. This is compelling evidence that specific gene dysfunction is critical in prostate cancer initiation and/or evolution to metastases. Applications to treatment in advanced disease are imminent, and further investigation in early-stage disease, as well as in diverse and at-risk populations will help maximize clinical benefit.

Key Words: *BRCA2*, *BRCA1*, prostate cancer, cancer predisposition, DNA repair, germline, metastases

Introduction

Prostate cancer is recognized to have a heritable component but incorporation of genetic and genomic testing has not yet become widespread. In 2015 and 2016, two landmark papers led to a dramatic shift in understanding and now practice. Other articles in this issue will review therapeutic implications, genetic predisposition syndromes, multigene testing and polygenic risk scores. This brief article reviews germline genetic contributions to development of metastatic prostate cancer and how these genetic factors may inform management of prostate cancer early detection and early stage prostate cancer.

Early sequencing discoveries in prostate metastases involve DNA repair genes

Prior to 2015, understanding about molecular features of prostate cancer came largely from prostatectomies and biopsies. With the exception of a few select rapid autopsy programs, metastatic disease was understudied. Support from SU2C and PCF enabled an international, multi-institutional study to obtain metastatic biopsies and characterize mutational spectra. Results from the first 150 metastatic biopsies identified a high proportion of actionable mutations—including 23% with mutations in DNA repair genes such as *BRCA2*, *ATM* and *BRCA1*.[1] Evidence was also mounting that prostate cancers with *BRCA2* inactivation were highly susceptible to platinum chemotherapy,[2,3] and the TOPARP-A study reported early compelling evidence that PARP inhibitors held similar promise.[4] Notably, about half of the DNA repair mutations were germline, thus representing known or suspected autosomal dominant cancer predisposition syndromes.

Germline DNA repair gene mutations in metastatic prostate cancer patients

In 2016, a definitive study of 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, was conducted with targeted germline sequencing. Remarkably, 11.8% (82/692) had germline mutations in DNA repair genes—most frequently *BRCA2*, *ATM*, *CHEK2* and *BRCA1*.[5] Presence of germline mutation was not correlated with family history of prostate cancer or age at diagnosis. In the tumors available for sequencing, 67% (36/61) had evidence of second allele inactivation, evidence that germline alterations were biologically relevant rather than simply bystanders. These findings have been born out in other studies with largely similar, albeit population-specific, proportions.[6,7]

Address correspondence to Dr. Heather H. Cheng, Seattle Cancer Care, 825 Eastlake Avenue East, Seattle, WA 98109 USA

Individuality of DNA repair genes

DNA repair genes require further individual characterization. Key differences are already apparent in estimated cancer risk in germline carriers and as predictive biomarkers of treatment response. For example, germline mutations seen in metastatic disease are observed most commonly in *BRCA2*, which confers the highest prostate cancer risk, poor outcomes, and observed best responses to platinum and PARP inhibitors.

In comparison, germline *BRCA1* mutations are also associated with elevated risk of prostate cancer, aggressive disease and response to DNA damaging agents, but less common and appears to confer attenuated risk of prostate cancer. Germline *ATM* pathogenic variants are more common in the general population yet are enriched in metastatic prostate cancer setting, this raises some uncertainty as to whether absence of function contributes to cancer initiation or to metastatic potential. Early data on response to PARP is in the setting of *ATM* inactivation suggests differences, not surprising due to different functions of *BRCA2* and *ATM* proteins. Other genes are newly implicated with prostate cancer risk and still less characterized due to rarity, e.g. *FANCA* or *RAD51C*.

Collective registries and databases of rare variants in population-based and in metastatic settings will be essential. Table 1 summarizes current reported data, although additional data is emerging. For the sake of clinical trial enrollment, it is reasonable to take a more permissive approach in the metastatic setting,

TABLE 1. **Genes with potential clinical actionability**

Gene	Association with ↑ prostate cancer risk	Prevalence of germline mutations in metastatic prostate cancer[5]	Prevalence of germline mutations in prostate cancer with fam hx[6]	DNA damaging agents: PARPI, platinum[4]	Immune checkpoint inhibitors: PD-1 inhibitors
ATM	X	1.6%	2.0%	X	
ATR		0.3%	Not evaluated		
BRCA1	X	0.9%	0.7%	X	
BRCA2	X	5.4%	4.7%	X	
BRIP1		0.2%	0.3%		
CDK12 (somatic only)		-			X
CHEK2	X	1.9%	2.9%	X	
FAM175A		0.2%	Not evaluated		
FANCA		-	Not evaluated	X	
HOXB13 (germline only)	X	Not evaluated	1.1%		
MLH1	X	-	0.06%		X
MRE11A		0.14%	Not evaluated		
MSH2	X	0.14%	0.69%		X
MSH6	X	0.14%	0.45%		X
NBN	*	0.3%	0.32%	X	
PALB2	*	0.4%	0.56%	X	
PMS2	X	0.3%	0.54%		X
RAD51C		0.14%	0.21%		
RAD51D		0.4%	0.15%		

*emerging/limited data
*adapted from Cheng, et al 2019 JNCCN[8]

especially if standard treatment options have been exhausted, and patients should be encouraged to participate in clinical trials and/or variant/mutation registries whenever possible.

Lack of diversity in data sets perpetuates health disparities

A notable health disparity in the USA is the fact that African American (AA) men are at higher risk for prostate cancer while also experiencing worse cancer outcomes. Causes are multifactorial, but likely include genetic factors. Since AA men and other racial/ethnic subgroups are underrepresented in genetic studies to date, there are fewer examples of affected and unaffected individuals contributing to higher rates of variants of uncertain significance (VUS). A recent report found similar rates of pathogenic variants in known cancer risk genes among AA men with prostate cancer,[6,7] and prioritization of diverse representation in research efforts will help address gaps in knowledge and practice.

Incorporating emerging data into earlier disease state management and clinical research

The opportunities for more complete understanding of rare gene variants and VUS in underrepresented populations poses challenges, albeit surmountable, around best clinical practices. For localized disease management and/or early cancer detection approaches in germline carriers, clinical trials and variant registries should be encouraged whenever possible. There may be an increasing role for specialized cancer genetics clinics and tumor boards to synthesize available data (family history and somatic sequencing) and promote clinical and research advances.

Disclosures

HHC receives research funding from the Institute for Prostate Cancer Research, the Pacific Northwest Prostate Cancer SPORE CA097186, Prostate Cancer Foundation, NIH/NCI P30 CA015704, Clovis Oncology, Janssen, Medivation and Sanofi. □

References

1. Robinson D, Van Allen EM, Wu YM et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015;161:1215-1228.
2. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. *Eur Urol* 2016;69(6):992-995.
3. Pomerantz MM, Spisak S, Jia L et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer* 2017;123(18):3532-3539.
4. Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373(18):1697-1708.
5. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375(5):443-453.
6. Nicolosi P, Ledet E, Yang S et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol* 2019;5(4):523-528
7. Castro E, Romero-Laorden N, Del Pozo A et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2019;37(6):490-503.
8. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw* 2019;17(5):515-521.
9. Petrovics G, Price DK, Lou H et al. Increased frequency of germline BRCA2 mutations associates with prostate cancer metastasis in a racially diverse patient population. *Prostate Cancer Prostatic Dis* 2019;22(3):406-410.
10. Chandrasekar T, Gross L, Gomella LG, Hegarty SE, Leong JY, Giri VN. Prevalence of suspected hereditary cancer syndromes and germline mutations among a diverse cohort of probands reporting a family history of prostate cancer: toward informing cascade testing for men. *Eur Urol Oncol* 2019. Epub ahead of print.