Natural history and imaging in men with high genetic risk for developing prostate cancer

William L. Dahut, MD,[1] Anna Couvillon, CRNP,[1] Peter A. Pinto, MD,[2] Baris Turkbey, MD,[3] Fatima Karzai, MD[1]

[1]Genitourinary Malignancies Branch, National Cancer Institute, NIH, Bethesda, Maryland, USA
[2]Urologic Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland, USA
[3]Molecular Imaging Program, National Cancer Institute, NIH, Bethesda, Maryland, USA

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Prostate cancer is the most common malignancy and the second leading cause of cancer related deaths in the United States. Established risk factors for prostate cancer incidence include older age, African-American race, and positive family history. Prostate cancer has substantial inherited predisposition and certain genetic variants are associated with increased risk of disease. Screening and imaging should target high-risk populations based on their genetic predisposition.

Key Words: multiparametric MRI, prostate cancer, genetic risk, germline, pathogenic variants, natural history, *BRCA1/2*, MMR genes, Lynch syndrome

Introduction

Prostate cancer is the most common malignancy and the second leading cause of death in men in the United States. In 2019, an estimated 174,650 new cases were diagnosed and an estimated 31,620 men die from the disease.[1] As such, established risk factors, particularly genetic contribution to prostate cancer risk, are of particular importance. An evolving approach to prostate cancer screening is to target populations of men at risk of developing prostate cancer based on known germline or likely pathogenic variants. Genome-wide association studies (GWAS) have provided evidence of genetic predisposition to the disease.[2,3] Factors which contributed to this genetic predisposition include 1) early onset of disease (age ≤ 55 years); 2) multiple first-degree relatives with prostate cancer; and 3) prostate cancer with a family history of other cancers including breast, ovarian or pancreatic. GWAS studies and linkage analyses have identified several genes and chromosomal regions associated with prostate cancer. Pathogenic variants in genes such as *BRCA1* and *BRCA2* and *HOXB13* confer modest to high lifetime risk of prostate cancer.[4-6] There is also evidence of the link between prostate cancer and DNA mismatch repair (MMR) gene variants associated with Lynch syndrome.[7] Recommendations for genetic counseling referrals are based on prostate cancer age at diagnosis, stage, and specific family cancer history patterns.

The IMPACT study (Identification of Men with genetic predisposition to Prostate Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) is evaluating the role of targeted prostate-specific antigen (PSA) screening in men with *BRCA1/2* variants.[8] Preliminary results support the use of targeted PSA screening and show that screening yields a high proportion of aggressive disease. These rates on based on non-image guided biopsies and may underestimate the true prevalence of disease in these high-risk patients.

Magnetic resonance imaging (MRI) of the prostate is an emerging method for detection and diagnosis of prostate cancer. Multiparametric MRI (mpMRI) has shown advantages in detection and characterization of prostate cancer. MpMRI and MRI-targeted fusion biopsies have the potential to assist clinical decision-making and recent studies have reported mpMRI as a useful modality for predicting pathological outcomes in participants with high-risk prostate cancer.[9] However, little is known about the role of mpMRI in high-risk participants as a tool for monitoring disease progression which remains to be further investigated.

In this study, we identify this targeted, high-risk population and follow the natural history of these men with known germline variants that put them at risk for developing prostate cancer. A practical approach

Address correspondence to Dr. William L. Dahut, National Cancer Institute, 9000 Rockville Pike, Building 10, Room 3-2571, Bethesda, MD 20892 USA

to prostate cancer screening for men is taken with a documented pathogenic/likely pathogenic germline variant in a known/suspected high-penetrance cancer predisposition gene (ie: *BRCA1/2*).

Materials and methods

Participants are men between the ages of 30-75 years old, who must have documented germline or likely pathogenic variants in prostate cancer-related risk gene(s): *BRCA1/2*, MMR genes associated with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), *HOXB13*, *ATM*, *NBN*, *TP53*, *CHEK2*, *PALB2*, *RAD51D*, or *FANCA*). Up to 500 participants will be enrolled and all patients are initially evaluated with a complete history and physical and family history questionnaire. Participating investigators and sites include Dr. Heather Cheng at the University of Washington and Fred Hutchinson Cancer Research Center, Dr. Todd Morgan at the University of Michigan Medical School, and Dr. Veda Giri at the Sidney Kimmel Cancer Center at Thomas Jefferson University. Study schema is shown in Figure 1. Blood sampling for PSA and digital rectal exam (DRE) are performed and participants undergo a baseline mpMRI evaluation with follow up scans every 2 years as clinically indicated. Following initial evaluation, participants will be followed as clinically indicated, at 12 month intervals, to determine PSA level, prostate cancer treatment (if relevant), and/or disease/survival status until death. The indication for prostate biopsies may include: abnormal DRE, PSA > 2.0 ng/mL or > 2.5 ng/mL for ages 30-49 and 50-70 years respectively, Prostate Imaging-Reporting and Diagnosis System (PIRADS) 3+ MRI lesion(s) or clinical discretion. If a biopsy is indicated, an extended mpMRI-transrectal ultrasound guided biopsy will be performed as per standard procedures. The primary objective of the study is to follow the natural history of men with known germline pathogenic or likely pathogenic variants that put them at risk for developing prostate cancer. Secondary objectives include utilizing mpMRI for the localization and detection of local prostate cancer and examining the role of mpMRI in monitoring participants on active surveillance and as a tool for monitoring local disease progression. PSA, MRI, and biopsy data including stage and Gleason score obtained over time will be recorded and reported descriptively. Multiple correlative studies for research are collected including analyses on biopsy specimens, circulating cell-free DNA, plasma biomarkers, serum biomarkers, and peripheral blood mononuclear cells (PBMCs). PBMCs will be used for future retrospective biomarker validation studies.

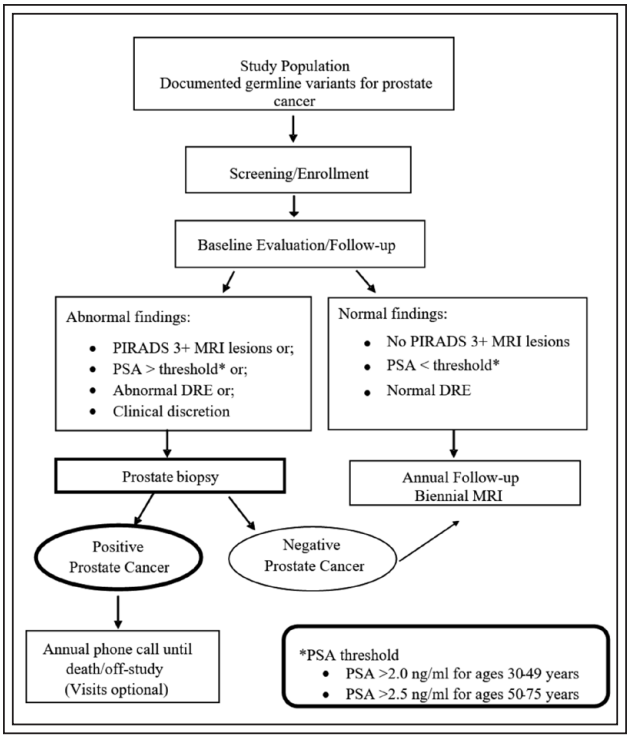

Figure 1. Study schema.

Disclosures

The authors have no disclosures. □

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69(1):7-34.
2. Al Olama AA, Kote-Jarai Z, Berndt SI et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet* 2014;46(10):1103-1109.
3. Eeles RA, Olama AA, Benlloch S et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet* 2013;45(4):385-391, 91e1-2.
4. Kote-Jarai Z, Leongamornlert D, Saunders E et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer* 2011;105(8):1230-1234.
5. Mersch J, Jackson MA, Park M et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. *Cancer* 2015;121(2):269-275.
6. Ewing CM, Ray AM, Lange EM et al. Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med* 2012;366(2): 141-149.
7. Haraldsdottir S, Hampel H, Wei L et al. Prostate cancer incidence in males with Lynch syndrome. *Genet Med* 2014;16(7):553-557.
8. Bancroft EK, Page EC, Castro E et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. *Eur Urol* 2014;66(3):489-499.
9. Jeong IG, Lim JH, You D et al. Incremental value of magnetic resonance imaging for clinically high risk prostate cancer in 922 radical prostatectomies. *J Urol* 2013;190(6):2054-2060.