Prostate Cancer Predisposition

Yasin Bhanji, MD[a], William B. Isaacs, PhD[b,*], Jianfeng Xu, MD, DrPH[c], Kathleen A. Cooney, MD[d]

KEYWORDS

• Prostate cancer • Hereditary cancer syndrome • Cancer susceptibility gene • Polygenic risk score

KEY POINTS

- Three risk factors for prostate cancer (PCa), namely family history, increasing age, and African ancestry, have been consistently recognized.
- Recently, rare pathogenic variants/mutations (RPMs) in several genes with moderate to high penetrance, such as *BRCA2*, *ATM*, *PALB2*, *CHEK2*, and *HOXB13*, and more than 160 common single nucleotide polymorphisms (SNPs), have been associated with PCa risk.
- The 3 inherited risk factors (family history, RPMs, and polygenic risk score) each affect the risk for PCa and may act independently. For example, most men carrying RPMs and high polygenic risk score in the general population do not have positive family history. Although family history and RPMs can identify 11% of men at higher PCa risk in the general population, adding polygenic risk score can identify an additional 22% of men at increased PCa risk.
- Although pathogenic mutations in *BRCA2*, *ATM*, and *PALB2* are associated with more aggressive PCa, the roles of mutations in other candidate PCa genes and SNP-based polygenic risk scores in PCa aggressiveness and progression is unclear.
- Pathogenic mutations in genes responsible for several hereditary cancer syndromes are likely relevant for PCa.
- For largely unexplained reasons, men of African ancestry are affected disproportionately by PCa; mutations in rare cancer susceptibility genes may contribute but cannot account for this disparity. Ancestry-specific risk SNPs may be more important.
- Two clinical strategies for germline testing in the setting of PCa are supported by available evidence: (1) testing RPMs in several genes (eg, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, and *HOXB13*) and race-specific polygenic risk score among unaffected men to identify men at increased risk for early PCa development; and (2) testing RPMs in a subset of genes (eg, *BRCA2*, *ATM*, and *PALB2*) at time of diagnosis of high-grade and/or metastatic PCa for developing personalized treatment approaches.

INTRODUCTION

The 3 most important recognized risks for prostate cancer (PCa) are increasing age, ancestry, and family history of the disease. The clustering of PCa within families can be attributed to genetic factors, environmental factors, and/or random chance. Multiple lines of evidence support the hypothesis that genetic factors underlie much of the inherited predisposition to PCa. In a recent report

[a] Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Marburg 134, 600 North Wolfe Street, Baltimore, MD 21287, USA; [b] Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Marburg 115, 600 North Wolfe Street, Baltimore, MD 21287, USA; [c] Program for Personalized Cancer Care, NorthShore University HealthSystem, 1001 University Place, Evanston, IL 60201, USA; [d] Department of Medicine, Duke University School of Medicine and the Duke Cancer Institute, 2301 Erwin Road, DUH 1102, Durham, NC 27710-3703, USA
* Corresponding author.
E-mail address: wisaacs1@jh.edu

Urol Clin N Am 48 (2021) 283–296
https://doi.org/10.1016/j.ucl.2021.03.001

from the Nordic Twin Study of Cancer (NorTwinCan) comparing cancer risks between monozygotic and dizygotic twins, PCa showed one of the highest estimates of heritability and no measurable contribution of environmental factors.[1] Over the last 30 years, significant progress has been made in defining the genetic factors that contribute to PCa risk and aggressiveness. This article focuses on describing the impact of family history, rare pathogenic mutations (RPMs), and single nucleotide polymorphisms (SNPs) on the understanding of inherited forms of PCa.

EPIDEMIOLOGY OF PROSTATE CANCER RISK

PCa is the most common noncutaneous malignancy in the United States among men, and an estimated 13% of all men alive now can expect to be diagnosed with the disease, with approximately 2.5% expected to die of the disease. The incidence of PCa varies by ancestry and ethnicity, with African Americans experiencing a 73% higher incidence than European Americans. According to the American Cancer Society, for 2020, an estimated 191,930 new cases of PCa will be diagnosed in the United States, and the age-adjusted incidence rate is 104.2 per 100,000 men per year. The average age at diagnosis is 66 years, with 55% of all deaths occurring after the age of 65 years.[2,3] A detailed review of the incidence and mortality patterns, lifestyle, and dietary factors for PCa has been recently presented by Pernar and colleagues.[4]

The observation that the number of men dying of PCa is less than one-fifth the number of diagnosed cases emphasizes the low malignant potential of most PCa cancers. This situation creates significant challenges for optimal patient management. This problem is compounded by the observations made at autopsy that between 30% and 70% of men more than 70 years of age have lesions that, if detected by biopsy, result in a cancer diagnosis.[5] Most of these lesions, often termed latent cancers, are small-volume, low-grade tumors that do not become clinically manifest. Knowing which men are more likely to develop a high-risk, potentially lethal PCa that requires early detection and aggressive treatment versus more ubiquitous latent cancers, which can be safely monitored by active surveillance, is a critical goal that can be reached through better identification and understanding of molecular risk factors associated with tumor progression to lethal disease.

IMPLICATION OF GENETIC RISK FACTORS

Increasing age, family history, and ancestry/ethnicity are 3 of the most important factors associated with risk of PCa. Increasing age, although associated with risk of virtually all common human cancers, is perhaps the strongest risk factor for PCa, because the exponential rate at which both diagnosis and mortality increase for PCa far exceeds that of virtually all other cancers.[6] Although several hypotheses have been put forth, including prostate-specific deficiencies in DNA damage response, the underlying mechanistic basis for the age-related basis for PCa is unknown.[7]

Several different epidemiologic approaches have been used to detect and understand the genetic contribution to PCa risk. Investigations of family history and twin studies have been particularly informative in providing data consistent with a genetic cause for PCa. Twin studies of cancer in a population can provide valuable inferences regarding the variable contributions of inherited factors to a particular disease cause by taking advantage of the increased genetic likeness of monozygotic versus dizygotic pairs of twins. In NorTwinCan, time-to-event analyses were used to estimate familial risk of cancer given a twin's development of cancer as well as heritability or the proportion of variance in cancer risk caused by interindividual genetic differences.[1] A total of 27,156 cancers were diagnosed in 23,980 individuals who were included in the study, of which PCa had the highest estimated cumulative incidence (10.5%) with a heritability estimate of nearly 57%. This percentage was substantially higher than the corresponding estimates for other common cancers, including those of the breast, colon, and kidney, 3 types of cancers with multiple, known, well-established genetic risk factors.

Relatedly, family history was one of the first risk factors identified for PCa, and remains a consistent and robust marker of increased risk.[8] In general, the relative risk of developing PCa increases as (1) the number of affected family members increases, (2) the closer in relatedness the affected relatives are, and (3) the age of diagnosis of the affected decreases.[9] The recognition of the importance of these 3 characteristics led to the first operational definition of hereditary PCa (HPC), which was defined as a family with (1) 3 generations affected with PCa, and/or (2) 3 first-degree relatives affected, and/or (3) 2 relatives affected before age 55 years.[10]

Although all professional screening guidelines, including the National Comprehensive Cancer Network (NCCN), recommend an assessment of family history, family history used by itself has important limitations for assessing PCa risk.[11] Family history is based on the current disease status of related family members and not on the

individual's genetic makeup. Furthermore, it is limited by recall and screening bias.[12] Although having an affected first-degree relative is consistently associated with increased risk for PCa, the magnitude of this increase varies substantially, ranging from less than 1.5 to more than 2, depending largely on the intensity of disease screening in the population studied, and the extent to which a positive family history increases this screening.[10] Differential screening intensity for PCa in different settings and populations likely plays an important role in shaping many of the demographic characteristics of PCa. Although the operational definition of HPC has been useful for framing gene mapping studies and other investigations of familial clustering, the lack of inclusion of any clinical variable to assess tumor aggressiveness has diluted its translational utility. As an example of this, a comparison of 324 patients with PCa with HPC, who fit the operational definition of HPC listed earlier, with 1664 patients with sporadic PCa (ie, with no family history) was performed using the Netherlands Cancer Registry. Patients with HPC were on average 3 years younger at diagnosis, had lower prostate-specific antigen (PSA) values, lower Gleason scores, and more often had locally confined disease, with 35% having high-risk disease compared with 51% of patients with sporadic PCa. Despite the favorable clinical phenotype in patients with HPC, they were less likely to receive active surveillance, and instead were more likely to receive radical treatment.[13]

Familial Prostate Cancer versus Hereditary Prostate Cancer

Familial PCa (FPC) and HPC both imply a heightened risk for development of the disease, but these two terms carry very different implications. FPC refers to a constellation of disease within families, whereas HPC implies a familial inheritance pattern consistent with the passage of a major susceptibility gene in a mendelian fashion. An early segregation analysis of patterns of familial clustering of PCa provided evidence in support of the existence of 1 or more rare (mutation allele frequency of 0.30%), high-penetrance mutations in genes inherited in an autosomal dominant, mendelian fashion.[14] These alleles were proposed to account for only 9% of PCa overall but had penetrance of 88% by age 85 years. Presciently, these numbers are strikingly similar to the characteristics of *HOXB13*, *ATM*, and *BRCA2* described later.

Regarding epidemiologic studies of risk for more aggressive disease, there are data to suggest that patients with PCa are more likely to die of the disease if their fathers died of PCa.[15] Using a population-based database that includes approximately 3 million families to analyze the relationship of survival between sons and their fathers, Lindström and colleagues[16] found the hazard ratio (HR) for PCa death in an affected son was 2.1 (95% confidence interval [CI], 1.1–3.8) if there was poor survival in the father. In addition, when a father's survival was categorized as good, intermediate, or poor, a significant trend of increasing HR estimates for death of affected sons with a worsening survival outcome in fathers was observed. Furthermore, Albright and colleagues[17] provided population-based estimates of lethal PCa risk based on lethal PCa family history. Many family history constellations associated with 2 to greater than 5 times increased risk for lethal PCa were identified. These results support a genetic susceptibility to lethal PCa.

Although many genetic factors, including the large number of common SNPs discussed later, contribute to familial clustering, in PCa, like other cancers, mutations in a very small number of major genes have been identified that have the degree of penetrance required to generate strict mendelian inheritance patterns in PCa families. This feature is compounded by the high prevalence (and thus high phenocopy rate) of PCa, particularly low-grade disease, and the heterogeneous genetic influences that contribute to this common disease. As the genetics underlying familial clustering and inheritance of PCa in general become more well elucidated, the further refinement of the terms sporadic, familial, and hereditary with respect to PCa, and their relevance in terms of clinical application and utility, might be expected. Furthermore, by having a better genetics-based definition of HPC that incorporates a clinicopathologic component to address disease aggressiveness, it may be possible to reduce the overdiagnosis and overtreatment among men with a family history of the disease.

LINKAGE ANALYSIS, *HOXB13*

Providing evidence through segregation analysis for the possible existence of a large-effect PCa susceptibility allele set the stage for PCa family collection and linkage-based gene mapping efforts. The International Consortium for Prostate Cancer Genetics (ICPCG) was formed in 1996 to address this question. This group performed a genome-wide linkage scan of 1233 families that fit HPC criteria.[18] Although suggestive, 5 moderate linkage signals were observed, including 1 at 17q21. Sequencing candidate genes under this linkage peak led to the identification of a recurrent but rare missense change, G84E, in *HOXB13*, a

gene highly expressed and intimately involved in prostate biology. In an analysis of germline DNA from more than 5000 patients with PCa and controls, our group reported that the frequency of the G84E allele was significantly higher in patients with PCa (1.4%) than controls (0.1%–0.4%).[19] An enrichment of G84E was found in patients with PCa who were diagnosed at early age (eg, <55 years) and with a positive family history of PCa. These finding have been consistently confirmed by many laboratories around the world, with odds ratios for PCa varying from 2-fold to 15-fold. Through combined analyses of international study populations by the ICPCG, the most common mutation in *HOXB13* in US men, G84E, had the highest frequency in individuals of Nordic descent.[20] As many as 8% to 10% of Swedish and Finnish men with family history positive for PCa diagnosed at an early age carry a G84E *HOXB13* mutation, compared with ~1% or less in unaffected men.[21,22] A critical additional finding was that nearly all G84E mutation carriers shared a common haplotype, meaning they are all descended from a common founder, presumably of Nordic ancestry.[20] Potential founder mutations in *HOXB13* have subsequently been found to be associated with PCa risk in other distinct populations, including the G132E mutation in Japanese, and the G135E mutation in Chinese.[23,24] Along with G84E, these 3 changes, substituting a glutamic acid for glycine at amino acid positions 84, 132, and 135, respectively, lie in 1 of 2 highly conserved domains in the *HOXB13* protein that are responsible for binding to the homeobox cofactor, *MEIS*, suggesting an alteration of this binding as a mechanistic feature of the cancer-promoting action of these variants.[25,26] More recently, a rare (minor allele frequency 0.2%) but recurrent stop loss mutation in *HOXB13* (Ter285-Lys, c.853delT) has been found in a collection of PCa cases of African ancestry in Martinique.[27] In ClinVar, this change is listed as a variant of unknown significance.[28]

HOXB13 is a prostate-specific homeobox transcription factor that plays a crucial role in the normal embryonic development of the prostate through its modulation of the prostate transcriptome via interaction with other key prostate transcription factors, including the androgen receptor (AR), FOXA1, and NKX3.1.[29–31] *HOXB13* expression is maintained through adulthood and is generally maintained throughout initiation and progression of PCa. As indicated earlier, 3 critical factors affect the frequency, and thus importance, of G84E as a susceptibility gene: (1) early age of PCa diagnosis, with men diagnosed before age 55 years having the highest frequency of G84E; (2) family history, with the frequency of G84E increased in men with first-degree relatives affected with PCa; and (3) ancestry, with individuals of Nordic ancestry having the highest population frequencies of G84E (as mentioned earlier). In men of African and eastern European descent, G84E is extremely rare. Although not uniform, most studies do not find any differences in PCa clinicopathologic variables between carriers and noncarriers of G84E. The association of G84E and PCa seems to be equally strong in men with high-risk and low-risk PCa (ie, carriers of G84E are at increased risk of the full spectrum of PCa, including high-risk, lethal disease). The G84E mutation can be highly penetrant and the penetrance seems to vary with ancestry, age at diagnosis, family history, and year of birth.[32] Penetrance estimates range from 40% to 60% by age 80 years, and almost complete penetrance in men who have a strong family history of early-onset PCa.[21,32] Penetrance of G84E may also be modified by genetic risk score (GRS) derived from multiple PCa risk-associated SNPs. In a large Swedish population-based study, the cumulative PCa risk by age 80 years was 33% for G84E carriers. This risk increased to 48% if carriers also had higher polygenic risk score (top quartile).[21,33] In addition, recent analyses of other cancers have implicated G84E as a risk factor for both rectosigmoid cancer (odds ratio [OR] = 2.25 [1.05–4.15]; P = .05) and nonmelanoma skin cancer (OR = 1.40 [1.12–1.74]; P = .01). Curiously, these findings were only observed in men.[34]

INHERITED DNA-REPAIR GENE MUTATIONS IN MEN WITH AGGRESSIVE PROSTATE CANCER

It has been widely established that germline mutations in DNA-repair genes (DRGs) are major contributors to the inherited risk for multiple common human cancers, including those of the breast and colon. However, until approximately 5 years ago, the frequencies of pathogenic DRG mutations in PCa were uncertain or reported to be low, leading to a poor appreciation of the potential importance of this class of genes to PCa genetic risk. The understanding of the contribution of DRGs in PCa susceptibility changed dramatically when next-generation sequencing studies began to focus on men with metastatic disease with the goal of identifying therapeutic targets. In 2015, Robinson and colleagues[35] analyzed 150 patients with metastatic, castration resistant PCa by whole-exome sequencing. Eight percent of these patients were found to have rare pathogenic germline mutations in DRGs such as *BRCA2*, a frequency 4 to 5 times higher than observed in

previous studies of patients with PCa. These findings were expanded on in another critical article, by Pritchard and colleagues,[36] who showed that the incidence of germline mutations in genes mediating DNA-repair processes in men with metastatic PCa was 11.8%, much higher than the incidence among men with localized disease. Mutations were identified in 16 different genes, with the most frequent in *BRCA2* (44% of total mutations), *ATM* (13%), and *CHEK2* (12%). **Table 1** shows the relative risk for metastatic PCa in 8 DRGs by comparing the mutation frequency in the Pritchard report with control data from the Exome Aggregation Consortium. Interestingly, the frequency of germline mutations in DRGs in men with metastatic PCa did not vary significantly when stratified by age at diagnosis or based on a positive family history of the disease.

To directly compare the ability of mutations in *BRCA* genes and *ATM* to distinguish risk for lethal disease, Na and colleagues[37] sequenced *BRCA1*, *BRCA2*, and *ATM* in a set of men who died of PCa and a set of men who had radical prostatectomy and had Gleason grade group (GG) 1, pathologically localized, low-risk disease. The rate of pathogenic mutations in these 3 genes was found to be 4-fold higher in men who had died of PCa. In addition, mutations in these genes, in particular *BRCA2*, were associated with decreased age at death, and decreased time to death from the time of diagnosis. Carter and colleagues[38] further showed the association of mutations in these 3 genes with more aggressive disease in an analysis of more than 1200 men undergoing active surveillance for PCa. Although the frequency was low, men who carried mutations in these genes were significantly more likely to undergo grade reclassification, with the OR for grade reclassification from GG1 to GG3 being more than 4.

CHEK2 is among the DRGs that are most commonly found to harbor germline loss-of-function mutations in PCa, although the association of these mutations with increased risk of high-risk disease is less consistent.[39] Likewise, *NBN*, along with *BRCA2* and *ATM*, was reported to be associated with high-risk disease in a recent study of Polish men, although this result is also less consistent in other populations.[40]

Because not all DRGs are associated with aggressive PCa risk, when interpreting panel testing in the PCa realm, it is important to understand which genes harbor mutations that are associated with tumor aggressiveness and which do not. Results from a study of 1694 radical prostatectomy patients with pathologically verified tumor grade indicate the strong association of mutations in 3 genes, *ATM*, *BRCA2*, and *MSH2*, and high risk as assessed by tumor grade.[41]

For example, men carrying a loss-of-function *BRCA2* or *ATM* mutation were more than 5 times more likely to have GG4 or GG5 tumors than GG1. *MSH2* showed a significant association as well. Although multiple other genes showed higher mutation rates in GG5 versus GG1 disease, including *BRCA1*, *CHEK2*, *MSH6*, *NBN*, *PALB2*, and *TP53*, none of the other genes tested showed a significant association with tumor grade. These results must be tempered by the rarity of mutations and thus power to detect association. Although none of the non-*ATM*/*BRCA2*/*MSH2* genes showed significant evidence of association with high tumor grade, it should be pointed out

Table 1
Genes associated with metastatic prostate cancer

	Metastatic Prostate Cancer(N = 692)		Exome Aggregation Consortium (N=53,105)				
Gene	Carriers (N)	%	Carriers (N)	%	Relative Risk	95% CI	*P* Value
ATM	11	1.59	133	0.25	6.3	3.2–11.3	<.001
BRCA1	6	0.87	104	0.22	3.9	1.4–8.5	.005
BRCA2	37	5.35	153	0.29	18.6	13.2–25.3	<.001
CHEK2	10	1.87	314	0.61	3.1	1.5–5.6	.002
MSH2	1	0.14	23	0.04	3.3	0.1–18.5	.26
MSH6	1	0.14	41	0.08	1.9	0.05–10.4	.41
NBN	2	0.29	61	0.11	2.5	0.3–9.1	.19
PALB2	3	0.43	65	0.12	2.7	0.3–6.6	.17

Data from 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. https://doi.org/10.1056/NEJMoa1603144.

that, in a combined analysis with all genes other than these 3, a significant association was still observed. This signal suggests that other genes in this panel may associate with tumor grade, but larger studies are needed to detect this effect. **Table 2** presents a summary of estimates of the importance of various DRGs as risk-affecting genes for both PCa diagnosis and advanced cancer development.

To further understand and explain the hereditary risk of PCa, the identification of additional genetic variants associated with PCa risk could be very helpful in the identification of at-risk individuals and provide more insight into the mechanisms of aggressive disease and potentially, novel targeted therapies. In a unique, 2-stage study of affected men who had a strong family history of disease or more aggressive disease, Schaid and colleagues[42] identified genes in stage 1 and screened them in stage 2 using a custom-capture design among 2917 cases and 1899 controls. In addition to *HOXB13* and several other previously identified genes including *BRCA2* and *ATM*, 10 novel genes, including *MYCBP2* and *RNASEH2B*, were implicated as prostate cancer associated genes in this study.[42] Confirmatory studies are needed to address the significance of these novel candidates.[42]

Germline testing is recommended by the NCCN for the subset of patients with PCa with high-risk, very-high-risk, regional, or metastatic disease, or with a family history of hereditary breast and ovarian cancer and Lynch syndrome (discussed later). Beyond the substantial screening value that the identification of specific germline variants has on identifying disease early and predicting its course, this type of knowledge also has profound therapeutic implications. For example, treatment with olaparib, a poly-(ADP-ribose) polymerase (PARP) inhibitor, in patients who had highly pretreated PCa and who had defects in DRGs had high response rates to therapy. Mateo and colleagues[43] performed next-generation sequencing in a cohort of these patients and 33% had mutations in *BRCA1/2*, *ATM*, or *CHEK2* and, of these, 88% had a response to olaparib, including 100% of patients with *BRCA2* loss, and 4 of 5 with *ATM* mutations.

Most cancer susceptibility genes function as tumor suppressors and are active as such as long as at least 1 of the 2 inherited copies of the gene are intact and expressed. Referring to the 2-hit hypothesis, inheriting 1 copy of a mutated *ATM*, for example, does not elicit a phenotype unless the remaining copy becomes inactive through deletion, mutation, or gene expression silencing. Correspondingly, this second hit, which can be difficult to discern in some clinical settings, can determine whether or not a mutation in a gene such as *ATM*, *BRCA2*, and most other genes that act in a tumor-suppressing manner contribute causally to tumor formation or, in the case of PARP inhibitor treatment, to treatment response.[44]

AFRICAN AMERICAN GERMLINE PREDISPOSITION TO PROSTATE CANCER

As described earlier, there is substantial evidence regarding the role of high-penetrance genes and

Table 2
Estimates of DNA-repair gene importance in susceptibility for all prostate cancer and for more aggressive disease

Gene	PCa Susceptibility	Risk for Aggressive/ Metastatic/Lethal Disease
ATM	++	++++
BRCA1	+	+
BRCA2	+++	++++
HOXB13	++++	+/–
CHEK2	+	+/–
MSH2	+	+++
MSH6	+	++
NBN	+	+/–
PALB2	+	++
RAD51C-D/	+/–	+/–
BRIP/ other Fanconi Anemia genes	—	—

Increasing numbers of plus signs indicates increasingly strong evidence as a risk factor; +/– indicates no significance evidence to support a role as a risk factor.

their significance in the increased risk of disease and as drivers of lethality. However, most of the studies documenting these findings have largely focused on men of European ancestry. This point is against the backdrop that African American men have the highest incidence and mortality from PCa in the world. Although several factors are likely contributing to the excess PCa mortality in African American men, some studies show that the difference in clinical outcomes continues to persist for African American men even after controlling for socioeconomic differences, suggesting the presence of biological factors driving this disparity.[45]

In a large recent study of African American and Ugandan PCa patients and controls, pathogenic variants of DRGs were found in 3.6% of patients compared with 2.1% in controls, and the highest risk of aggressive disease was seen in men with variants in *ATM*, *BRCA2*, *PALB2*, and *NBN* genes.[46] For single genes, significant results were seen for *BRCA2* and *ATM* mutation frequencies in patients versus controls, with ORs of 3.92 and 3.83, respectively, for the combined group of Ugandan and African American patients. The combined frequencies of pathogenic mutations in *BRCA2* and *ATM* in metastatic disease were 1.4% and 4.8% for African American and Ugandan patients, respectively. These results indicate that *BRCA2* and *ATM* mutations are significant risk factors for high-risk disease in men of African descent, although the frequencies of mutation in both genes are lower than has been observed in European Americans with high-risk disease. This finding suggests that, as in men of European ancestry, the prevalence of DNA-repair mutations remains low. An increased frequency of these potent, high-risk-inducing genes in African American men does not seem to explain the increased mortalities observed in men of African descent.

PROSTATE CANCER AS PART OF KNOWN CANCER SYNDROMES

PCa risk can be increased in men who carry a mutation in genes related to several known cancer syndromes. This finding is expected because cancer gene mutations typically increase the risk of more than 1 type of cancer in a family.

Hereditary breast and ovarian cancer

Several studies of families with hereditary breast and ovarian cancer (HBOC) conducted in the 1990s revealed that this syndrome can be attributed in some families to deleterious mutations in one of the 2 genes, namely *BRCA1* on chromosome 17 and *BRCA2* on chromosome 13.[47,48] Studies of HBOC families segregating *BRCA1* or *BRCA2* mutations confirm that there is an increased risk of male *BRCA1* and *BRCA2* mutation carriers compared with non–mutation carriers within HBOC families and compared with the general population (data from the Breast Cancer Linkage Consortium).[49,50] In these studies, the overall relative risk (RR) of PCa in men with *BRCA1* mutations was 1.07 (95% CI, 0.75–1.54) and the RR of PCa in men with *BRCA1* mutations younger than 65 years was 1.82 (95% CI, 1.01–3.29). In comparison, men with *BRCA2* mutations had a higher RR of PCa (4.65; 95% CI, 3.48–6.22) as well as a higher RR of PCa for male mutations carriers younger than 65 years (7.33; 95% CI, 4.66–11.52). Note that these risk estimates may be inflated because they are based on information from highly selected HBOC families and may not apply to the general population. Furthermore, studies of PC-only families have not found a significant number of *BRCA1/2* pathogenic mutations, indicating that these mutations likely contribute to a small portion of hereditary PC defined as families with multiple cases of PCa.[51,52]

Studies of the Icelandic founder *BRCA2* mutation, which is a 5-bp deletion beginning at nucleotide 999 (999del5), provided the initial insights into the relationship between mutations in genes associated with HBOC and aggressive and/or lethal PC.[53] Sigurdsson and colleagues[54] described PCa cases from known Icelandic HBOC families each caused by the *BRCA2* 999del5 mutation. Of the 12 patients with PCa that were available for genetic testing, 9 of the men inherited the *BRCA2* 999del5 allele and the remaining 3 men did not carry the allele. Interesting, all 9 mutation carriers died of PCa compared with only 1 of the noncarriers, suggesting that *BRCA2* mutation status correlates with a poorer prognosis from the disease. In a larger study of 527 Icelandic men with PCa, including 30 men who were carriers of the *BRCA2* 999del5 allele, carriers were shown to have a significantly earlier age at diagnosis, more advanced tumor stage and grade, and shorter survival time.[55] After adjusting for year of diagnosis and birth, mutation carriers were also shown to be at increased risk of dying of PCa, and this association remained after adjusting for stage and grade. The role of *BRCA1* and *BRCA2* in clinically aggressive PCa has been strengthened from studies of both men known to carry *BRCA1/2* germline mutations and also men discovered to have *BRCA1/2* germline mutations through clinical studies of metastatic PCa tissue.[35,56,57]

LYNCH SYNDROME FAMILIES

In addition to colorectal cancer, there are several cancers that occur with increased frequency in individuals carrying a pathogenic germline mutation in a Lynch syndrome (LS)–associated mismatch repair (MMR) gene (most commonly *MLH1*, *MSH2*, *MSH6*, and *PMS2*). These LS-associated cancers occur in the endometrium, ovary, stomach, small bowel, and ureter, but data supporting an LS-PCa correlation have been conflicting. In 2014, Raymond and colleagues, Han and colleagues[58,59] reported an overall HR for PCa of 1.99 (95% CI, 1.34–4.59; $P = .0038$) across 2 large familial LS cancer registries, whereas an independent meta-analysis identified a risk increase of 2.28-fold (95% CI, 2.32–6.67) for men with MMR mutations in LS families. Interestingly, PCa tumors sequenced from individuals with LS carry classic microsatellite instability signatures, an uncommon observation in PCa.[60] In light of this new information, there is general consensus among experts that men harboring MMR mutations are at an increased risk for PCa, but the magnitude of the risk increase is not fully defined.

USE OF SINGLE GENE POLYMORPHISMS IN RISK ASSESSMENT

To date, more than 160 inherited PCa risk–associated SNPs have been identified through genome-wide association studies (GWASs).[61] Because of stringent criteria used for declaring statistically significant risk SNPs, including multiple-stage study design, large sample size of cases and controls, and a minimum requirement of $P<5 \times 10E\text{-}8$ to account for multiple testing, most of these risk SNPs can be replicated in independent study populations. Compared with rare monogenic mutations, SNPs are more common, and each has a modest individual effect on PCa risk. However, SNPs have a stronger cumulative effect that can be measured by a polygenic risk score.

VARIOUS POLYGENIC RISK SCORE METHODS

Polygenic risk score is a generic term for statistical methods that measure the cumulative effect of multiple risk-associated SNPs. Several polygenic risk score methods have been commonly used in the last 10 years, including a direct risk allele count, an OR-weighted risk allele count (often specifically referred to as polygenic risk score), or an OR-weighted and population-standardization method, typically termed GRS.[62] A common feature of these methods is that they are based on well-established risk-associated SNPs. Recently, a novel polygenic risk score method based on millions of SNPs in the genome (not limited to the well-established risk-associated SNPs), called genome-wide polygenic score (GPS), was proposed.[63–65] In addition, a polygenic hazard score that is based on a set of SNPs that are associated with age at diagnosis of aggressive PCa has also been developed.[66]

Except for the weaker performance of the direct risk allele count method, which does not take the effect (OR) of risk allele into account, the performance of other polygenic risk score methods in risk stratification is similar. Specifically, the performance and percentile of polygenic risk score and GRS is exactly the same if the same SNPs and OR of risk alleles are used.[62] The only difference is that GRS is population standardized and can be interpreted as RR to the general population regardless of numbers of SNPs used in the calculation (therefore, the mean GRS in the population is always 1). In contrast, the values of polygenic risk score increase with the number of SNPs used in the calculation. Although many more SNPs are used in the GPS, its performance is similar to GRS,[64,67] likely because most of the risk stratification signals in GPS come from well-established risk-associated SNPs that have already been accounted for in GRS.

POLYGENIC RISK SCORE FOR PROSTATE CANCER RISK

Since the first demonstration of the cumulative effect of the first 5 established risk-associated SNPs on PCa risk in 2008 by our research group,[68] published studies to date consistently show associations between polygenic risk score and PCa risk, including those from large case-control studies,[61,69] retrospective analysis of prospective studies,[70,71] prostate biopsy cohorts,[72,73] and population-based prospective studies.[74] A dose-response association between higher percentile of polygenic risk scores and higher PCa risk is observed in all published studies. For example, using a large prospective cohort derived from the UK Biobank, where 208,685 PCa diagnosis–free participants at recruitment were followed via the UK cancer and death registries, we found that a GRS based on 130 known risk-associated SNPs significantly predicted risk and mortality for PCa.[75] Men in higher GRS deciles had significantly higher PCa incidence and PCa mortality, both P trend less than .001. Furthermore, a head-to-head comparison showed that GRS was more informative for stratifying inherited PCa risk than family history and RPMs. In addition, this study revealed that the association between GRS and

PCa incidence was independent of family history and RPMs and can therefore complement family history and RPMs for inherited risk assessment. Although family history and RPMs identified 11% of men at higher PCa risk, adding GRS (>1.5) identified an additional 15% of men at higher PCa risk with comparable PCa incidence and mortality.

Higher polygenic risk scores are also consistently associated with an earlier age of PCa diagnosis.[66,76,77] Based on a retrospective analysis of The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) chemoprevention trial, men in higher GRS risk groups (based on 110 known PCa risk-associated SNPs) were shown to have worse PCa diagnosis–free survival compared with the entire cohort (*P* trend <.0001).[76]

POLYGENIC RISK SCORE FOR DIFFERENTIATING AGGRESSIVENESS OF PROSTATE CANCER

Despite the consistent finding that polygenic risk score can effectively stratify disease risk, its association with disease is inconsistent and generally negative.[78–81] For example, in a study of 5895 surgically treated PCa cases in which each tumor was uniformly graded and staged using the same protocol, there were no statistically significant differences (*P*>.05) in risk allele frequencies between patients with more aggressive or less aggressive disease for 18 of the 20 reported PCa risk–associated SNPs.[78] In another recently published study on European men from the Prostate Cancer Prevention Trial (PCPT) (N = 2434) and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (N = 4885), a higher polygenic score based on 98 known risk-associated SNPs was associated with PCa risk in both trials but did not predict other outcomes.[79] These studies suggest that almost all PCa risk–associated SNPs are not associated with aggressiveness and currently have minimal utility in predicting the risk for developing more or less aggressive forms of PCa.

Lack of association between polygenic risk score and aggressiveness of PCa in case-case studies is not contradictory to its association with PCa mortality found in case-control studies. Because of the association of polygenic risk score and PCa risk, more men with higher polygenic risk score are expected to develop PCa (both indolent and aggressive PCa) compared with men in the general population. However, once diagnosed with PCa, polygenic risk score does not differentiate which patients are more likely to die from the disease. This explanation is supported by data from the large prospective cohort derived from the UK Biobank, with 209,588 men at risk for PCa. After approximately 10 years' follow-up, 10,203 (4.87%) men developed PCa, and 695 died of the disease. The mortality was 0.33% (695 out of 209,588) among men at risk for PCa, and the mortality ratio was 6.81% (695 out of 10,203) among men diagnosed with PCa. The PCa incidence rate was higher in men with high GRS defined as greater than or equal to 1.5 (3615 out of 37,445 = 9.65%) than low GRS defined as less than 1.5 (6558 out of 172,143 = 3.83%; *P*<.001). The PCa-specific mortality was also higher in men with high GRS (239 out of 37,445 = 0.64%) than low GRS (456 out of 172,143 = 0.26%; *P*<.001). However, there was no significant difference in mortality ratio between patients with PCa with high GRS (239 out of 3615 = 6.61%) and low GRS (456 out of 6558 = 6.92%; *P* = .58).[75]

POTENTIAL CLINICAL UTILITY OF POLYGENIC RISK SCORE

The consistent findings of associations for polygenic risk score with PCa risk and also early age of diagnosis provide a basis for its use in PCa risk stratification. Furthermore, because the associations of polygenic risk score with PCa risk and age at diagnosis are independent of family history and RPMs, polygenic risk score can be used to supplement family history and RPMs to better stratify inherited risk.[12] At present, recommendations for inherited PCa risk assessment from the US Preventive Services Task Force and the European Association of Urology rely primarily on family history only, whereas the NCCN also recommends incorporation of RPMs.[82–84] In the future, incorporation of information regarding inherited risk based on family history, RPMs, and GRS may be considered in the discussion of potential benefits and harms for baseline PSA screening at an early age.

Polygenic risk scores may be useful in the clinic to refine estimates of disease penetrance for carriers of RPMs. As mentioned above, several studies have shown significantly higher penetrance between high and low polygenic risk score among men with RPMs of *BRCA2* and *HOXB13*.[21,33,85]

Inherited risk assessment may also have potential clinical utility in decision making of prostate biopsy. Results from the REDUCE study,[70] several prostate biopsy cohorts,[72,73] and a study of Finnish men with and without PCa[86] suggest polygenic risk scores provide added value compared with PSA levels to improve the detection rate of PCa.

In contrast, the clinical utility of polygenic risk scores in differentiating aggressive from indolent PCa and in predicting prognosis of PCa is

currently unclear. However, encouraging preliminary findings are emerging on the use of polygenic risk scores for predicting tumor upgrading in 2 active surveillance (AS) cohorts, as discussed by Helfand and Xu.[87] The prognostic value of polygenic risk scores may be unique for use in AS and this observation awaits confirmation in additional studies.

IMPORTANT CONSIDERATIONS FOR IMPLEMENTING POLYGENIC RISK SCORE IN THE CLINIC

Based on the consistent association between polygenic risk score percentile and PCa risk,[61,66,68–77,88] polygenic risk scores have been proposed and recently adopted by several genetic testing companies to estimate an individual's risks for common diseases, including PCa. However, the important and consistent trend between percentiles of polygenic risk score and disease risk in study populations is not sufficient to support their clinical use for risk assessment at the individual patient level. There are 2 major considerations for this statement. First, although an informative risk measurement, the percentile of risk only ranks an individual's probability of disease risk within a population. It does not specify the quantity of risk, and individuals with the same percentile may have different quantities of risks for different diseases and in different populations. Second, percentiles per se are not commonly used in current clinical guidelines for risk assessment. Instead, absolute risk, such as lifetime risk, is routinely used in clinical guidelines. Lifetime risk is calculated from an individual's RR derived from various risk factors (including polygenic risk) and population-based incidence and mortality.

Another important factor for translating polygenic risk score is the need to develop race-specific scores. This factor is critical because the effect size (OR) and allele frequency of risk-associated SNPs differ among racial populations.[59,89] To date, most GWASs and polygenic risk scores were based on white populations. As such, the validity and calibration of polygenic risk score for other minority racial groups are not well developed. This status quo may exacerbate existing racial disparities in PCa care. Substantial efforts should be devoted to address this need in order to fully realize the potential of polygenic risk scores for use in the clinical management of PCa.

SUMMARY

PCa remains a leading cause of cancer death among American men. Genetic testing to assess mutational status of DRGs is a noninvasive, reproducible means of identifying men at increased risk of lethal disease at a time when cure is still possible. Unaffected carriers of DRG and *HOXB13* mutations should managed with earlier and more intensive disease screening, whereas DRG mutation carrier status in men diagnosed with PCa should be used in both surgical and systemic treatment decision making. Although the data supporting the role of *BRCA2* and *ATM* in aggressive PCa seem unequivocal, some data also exist to support a role for mutations in other DRGs, including *BRCA1*, *MSH2*, *PALB2*, *CHEK2*, and *NBN*, as risk factors for aggressive disease, but larger studies are needed before these genes become actionable in terms of clinical decision making. The use of polygenic risk score to stratify risk of PCa diagnosis is highly effective, inexpensive, and informative, but currently underused. Future studies should focus on combining family history, RPMs, and polygenic risk score to more accurately define PCa risk in unaffected men.

CLINICS CARE POINTS

- PCa has a strong inherited component and having a family history of clinically significant PCa or other cancers, such as breast, colon, ovarian, or pancreatic cancer, particularly when diagnosed at an early age, increases the risk of developing clinically significant PCa ~1.5-fold to 3-fold.
- The NCCN recommends offering genetic testing to men who are diagnosed with high-risk or very-high-risk PCa and if the patient has a family history of *BRCA1* or *BRCA2* mutations, LS, or comes from a high-risk ancestry group such as the Ashkenazi Jewish.
- Pathogenic mutations in *BRCA2* and *ATM* are the most consistent and reproducible genetic risk factors for aggressive, potentially lethal PCa. *MSH2* mutations, although much less common, seem to be associated with high-risk disease as well. Because of their rarity, further studies are necessary to more fully determine the prognostic importance of mutations in *PALB2*, *NBN*, *CHEK2*, *BRCA1*, *HOXB13*, and most other putative PCa risk genes tested on most cancer gene panels. *HOXB13* G84E continues to be a reproducible and informative risk factor for all PCa risk.
- Polygenic risk scores determined using well-characterized common genetic factors are powerful and informative predictors of PCa

risk in Americans of both European and African descent. However, there are important differences in the panel of SNPs that stratify risk most effectively in these 2 groups.

- Increased use of combined, ancestry-optimized polygenic risk score and genetic testing for *BRCA2*, *ATM*, and *MSH2* should be strongly considered for inclusion in routine disease screening paradigms to optimize patient management in the era of precision medicine.

DISCLOSURE

The generous support from the Patrick C Walsh Hereditary Prostate Cancer program is gratefully acknowledged. This study was supported by grants from Department of Defense (W81XWH-16-1-0764, W81XWH-16-1-0765, and W81XWH-16-1-0766).

REFERENCES

1. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in nordic countries. JAMA 2016;315(1):68–76.
2. NVSS - Mortality Data. Available at: https://www.cdc.gov/nchs/nvss/deaths.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fnchs%2Fdeaths.htm. Accessed October 23, 2020.
3. About Prostate Cancer. Available at: www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/how-. Accessed October 23, 2020.
4. Pernar CH, Ebot EM, Wilson KM, et al. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med 2018;8(12). https://doi.org/10.1101/cshperspect.a030361.
5. Sandhu GS, Andriole GL. Overdiagnosis of prostate cancer. J Natl Cancer Inst Monogr 2012;2012(45):146–51.
6. Prostate cancer statistics | Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed October 23, 2020.
7. Kiviharju-af Hällström TM, Jäämaa S, Mönkkönen M, et al. Human prostate epithelium lacks Wee1A-mediated DNA damage-induced checkpoint enforcement. Proc Natl Acad Sci U S A 2007;104(17):7211–6.
8. Woolf CM. An investigation of the familial aspects of carcinoma of the prostate. Cancer 1960;13:739–44.
9. Nelson Q, Agarwal N, Stephenson R, et al. A population-based analysis of clustering identifies a strong genetic contribution to lethal prostate cancer. Front Genet 2013;4:152.
10. Steinberg GD, Carter BS, Beaty TH, et al. Family history and the risk of prostate cancer. Prostate 1990;17(4):337–47.
11. Carlsson S, Castle EP, Catalona WJ, et al. NCCN guidelines version 2.2020 prostate cancer early detection. Plymouth Meeting: National Comprehensive Cancer Network; 2020.
12. Xu J, Labbate CV, Isaacs WB, et al. Inherited risk assessment of prostate cancer: it takes three to do it right. Prostate Cancer Prostatic Dis 2020;23(1):59–61.
13. Cremers RG, Aben KK, van Oort IM, et al. The clinical phenotype of hereditary versus sporadic prostate cancer: HPC definition revisited. Prostate 2016;76(10):897–904.
14. Carter BS, Ewing CM, Ward WS, et al. Allelic loss of chromosomes 16q and 10q in human prostate cancer. Proc Natl Acad Sci U S A 1990;87(22):8751–5.
15. Hemminki K, Ji A, Försti A, et al. Concordance of survival in family members with prostate cancer. J Clin Oncol 2008;26(10):1705–9.
16. Lindström LS, Hall P, Hartman M, et al. Familial concordance in cancer survival: a Swedish population-based study. Lancet Oncol 2007;8(11):1001–6.
17. Albright FS, Stephenson RA, Agarwal N, et al. Relative risks for lethal prostate cancer based on complete family history of prostate cancer death. Prostate 2017;77(1):41–8.
18. Xu J, Dimitrov L, Chang BL, et al. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. Am J Hum Genet 2005;77(2):219–29.
19. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366(2):141–9.
20. Xu J, Lange EM, Lu L, et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 2013;132(1):5–14.
21. Karlsson R, Aly M, Clements M, et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol 2014;65(1):169–76.
22. Laitinen VH, Wahlfors T, Saaristo L, et al. HOXB13 G84E mutation in Finland: population-based analysis of prostate, breast, and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2013;22(3):452–60.
23. Momozawa Y, Iwasaki Y, Hirata M, et al. Germline pathogenic variants in 7636 Japanese patients with prostate cancer and 12 366 controls. J Natl Cancer Inst 2020;112(4):369–76.
24. Lin X, Qu L, Chen Z, et al. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. Prostate 2013;73(2):169–75.
25. Bhanvadia RR, Van Opstall C, Brechka H, et al. MEIS1 and MEIS2 expression and prostate cancer

progression: a role for HOXB13 binding partners in metastatic disease. Clin Cancer Res 2018;24(15):3668–80.
26. Johng D, Torga G, Ewing CM, et al. HOXB13 interaction with MEIS1 modifies proliferation and gene expression in prostate cancer. Prostate 2019;79(4):414–24.
27. Marlin R, Créoff M, Merle S, et al. Mutation HOXB13 c.853delT in Martinican prostate cancer patients. Prostate 2020;80(6):463–70.
28. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res 2018;46(D1):D1062–7.
29. Economides KD, Capecchi MR. Hoxb13 is required for normal differentiation and secretory function of the ventral prostate. Development 2003;130(10):2061–9.
30. Norris JD, Chang CY, Wittmann BM, et al. The homeodomain protein HOXB13 regulates the cellular response to androgens. Mol Cell 2009;36(3):405–16.
31. Luo Z, Farnham PJ. Genome-wide analysis of HOXC4 and HOXC6 regulated genes and binding sites in prostate cancer cells. PLoS One 2020;15(2). https://doi.org/10.1371/journal.pone.0228590.
32. Nyberg T, Govindasami K, Leslie G, et al. Homeobox B13 G84E mutation and prostate cancer risk. Eur Urol 2019;75:834–45.
33. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Ann Oncol 2015;26(4):756–61.
34. Wei J, Shi Z, Na R, et al. Germline HOXB13 G84E mutation carriers and risk to twenty common types of cancer: results from the UK Biobank. Br J Cancer 2020;123(9). https://doi.org/10.1038/s41416-020-01036-8.
35. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;162(2):454.
36. 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):443–53.
37. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death [figure presented]. Eur Urol 2017;71:740–7.
38. Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer (figure presented.). Eur Urol 2019;75(5):743–9.
39. Wu Y, Yu H, Zheng SL, et al. A comprehensive evaluation of CHEK2 germline mutations in men with prostate cancer. Prostate 2018;78(8):607–15.
40. Wokołorczyk D, Kluźniak W, Huzarski T, et al. Mutations in ATM, NBN and BRCA2 predispose to aggressive prostate cancer in Poland. Int J Cancer 2020;147(10):2793–800.
41. Wu Y, Yu H, Li S, et al. Rare germline pathogenic mutations of DNA repair genes are most strongly associated with grade group 5 prostate cancer. Eur Urol Oncol 2020;3:224–30.
42. Schaid DJ, McDonnell SK, FitzGerald LM, et al. Two-stage study of familial prostate cancer by whole-exome sequencing and custom capture identifies 10 novel genes associated with the risk of prostate cancer. Eur Urol 2020. https://doi.org/10.1016/j.eururo.2020.07.038.
43. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373(18):1697–708.
44. Hughley R, Karlic R, Joshi H, et al. Etiologic index — A case-only measure of BRCA1/2–associated cancer risk. N Engl J Med 2020;383(3):286–8.
45. Hoffman RM, Gilliland FD, Eley JW, et al. Racial and ethnic differences in advanced-stage prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 2001;93(5):388–95.
46. Matejcic M, Patel Y, Lilyquist J, et al. Pathogenic variants in cancer predisposition genes and prostate cancer risk in men of African ancestry. JCO Precis Oncol 2020;4(4):32–43.
47. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71.
48. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–91.
49. Thompson D, Easton DF. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94(18):1358–65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12237281.
50. The Breast Cancer Linkage C. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91(15):1310–6.
51. Wilkens EP, Freije D, Xu J, et al. No evidence for a role of BRCA1 or BRCA2 mutations in Ashkenazi Jewish families with hereditary prostate cancer. Prostate 1999;39(4):280–4.
52. Zuhlke KA, Madeoy JJ, Beebe-Dimmer J, et al. Truncating BRCA1 mutations are uncommon in a cohort of hereditary prostate cancer families with evidence of linkage to 17q markers. Clin Cancer Res 2004;10(18 Pt 1):5975–80.
53. Thorlacius S, Olafsdottir G, Tryggvadottir L, et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 1996;13:117–9.
54. Sigurdsson S, Thorlacius S, Tomasson J, et al. BRCA2 mutation in Icelandic prostate cancer patients. J Mol Med 1997;75(10):758–61.

55. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99(12): 929–35.
56. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013; 31(14):1748–57.
57. Mateo J, Cheng HH, Beltran H, et al. Clinical outcome of prostate cancer patients with germline DNA repair mutations: retrospective analysis from an international study. Eur Urol 2018;73(5):687–93.
58. Raymond VM, Mukherjee B, Wang F, et al. Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 2013;31(14):1713–8.
59. Han Y, Signorello LB, Strom SS, et al. Generalizability of established prostate cancer risk variants in men of African ancestry. Int J Cancer 2015; 136(5):1210–7.
60. Bauer CM, Ray AM, Halstead-Nussloch BA, et al. Hereditary prostate cancer as a feature of Lynch syndrome. Fam Cancer 2011;10(1):37–42.
61. Schumacher FR, Al Olama AA, Berndt SI, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet 2018;50(7):928–36.
62. Conran CA, Na R, Chen H, et al. Population-standardized genetic risk score: the SNP-based method of choice for inherited risk assessment of prostate cancer. Asian J Androl 2016;18(4):520–4.
63. Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am J Hum Genet 2015; 97(4):576–92.
64. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet 2018;50(9):1219–24.
65. Ge T, Chen CY, Ni Y, et al. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 2019;10(1):1776.
66. Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. BMJ 2018;360:j5757.
67. Yu H, Shi Z, Wu Y, et al. Concept and benchmarks for assessing narrow-sense validity of genetic risk score values. Prostate 2019;79(10):1099–105.
68. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. N Engl J Med 2008;358(9):910–9.
69. Hoffmann TJ, Van Den Eeden SK, Sakoda LC, et al. A large multiethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences. Cancer Discov 2015;5(8):878–91.
70. Kader AK, Sun J, Reck BH, et al. Potential impact of adding genetic markers to clinical parameters in predicting prostate biopsy outcomes in men following an initial negative biopsy: findings from the REDUCE trial. Eur Urol 2012;62(6):953–61.
71. Chen H, Liu X, Brendler CB, et al. Adding genetic risk score to family history identifies twice as many high-risk men for prostate cancer: results from the prostate cancer prevention trial. Prostate 2016; 76(12):1120–9.
72. Ren S, Xu J, Zhou T, et al. Plateau effect of prostate cancer risk-associated SNPs in discriminating prostate biopsy outcomes. Prostate 2013;73(16): 1824–35.
73. Jiang H, Liu F, Wang Z, et al. Prediction of prostate cancer from prostate biopsy in Chinese men using a genetic score derived from 24 prostate cancer risk-associated SNPs. Prostate 2013;73(15):1651–9.
74. Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol 2015;16(16):1667–76.
75. Shi Z, Platz E, Wei J, et al. Performance of three inherited risk measures for predicting prostate cancer incidence and mortality: a population-based prospective analysis. Eur Urol 2021;79(3):419–26.
76. Na R, Labbate C, Yu H, et al. Single-nucleotide polymorphism-based genetic risk score and patient age at prostate cancer diagnosis. JAMA Netw Open 2019;2(12):e1918145.
77. Karunamuni RA, Huynh-Le MP, Fan CC, et al. African-specific improvement of a polygenic hazard score for age at diagnosis of prostate cancer. Int J Cancer 2020. https://doi.org/10.1002/ijc.33282.
78. Kader AK, Sun J, Isaacs SD, et al. Individual and cumulative effect of prostate cancer risk-associated variants on clinicopathologic variables in 5,895 prostate cancer patients. Prostate 2009;69(11): 1195–205.
79. Ahmed M, Goh C, Saunders E, et al. Germline genetic variation in prostate susceptibility does not predict outcomes in the chemoprevention trials PCPT and SELECT. Prostate Cancer Prostatic Dis 2020;23(2):333–42.
80. Helfand BT, Roehl KA, Cooper PR, et al. Associations of prostate cancer risk variants with disease aggressiveness: results of the NCI-SPORE Genetics Working Group analysis of 18,343 cases. Hum Genet 2015;134(4):439–50.
81. Pomerantz MM, Werner L, Xie W, et al. Association of prostate cancer risk Loci with disease aggressiveness and prostate cancer-specific mortality. Cancer Prev Res (Phila) 2011;4(5):719–28.
82. Force USPST, Grossman DC, Curry SJ, et al. Screening for prostate cancer: US preventive services task force recommendation statement. JAMA 2018;319(18):1901–13.

83. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71(4):618–29.
84. Mohler JL, Higano CS, Schaeffer EM, et al. Current recommendations for prostate cancer genetic testing: NCCN prostate guideline. Can J Urol 2019; 26(5 Suppl 2):34–7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31629426.
85. Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35(20): 2240–50.
86. Li-Sheng Chen S, Ching-Yuan Fann J, Sipeky C, et al. Risk prediction of prostate cancer with single nucleotide polymorphisms and prostate specific antigen. J Urol 2019;201(3):486–95.
87. Helfand BT, Xu J. Germline testing for prostate cancer prognosis: implications for active surveillance. Can J Urol 2019;26(5 Suppl 2):48–9.
88. Yu H, Shi Z, Lin X, et al. Broad- and narrow-sense validity performance of three polygenic risk score methods for prostate cancer risk assessment. Prostate 2020;80(1):83–7.
89. Du Z, Hopp H, Ingles SA, et al. A genome-wide association study of prostate cancer in Latinos. Int J Cancer 2020;146(7):1819–26.