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Familial prostate cancer

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Abstract

Prostate cancer is the most commonly diagnosed cancer among men in the United States as well as most Western countries. A significant proportion of men report having a positive family history of prostate cancer in a first-degree relative (father, brother, son), which is important in that family history is one of the only established risk factors for the disease and plays a role in decision-making for prostate cancer screening. Familial aggregation of prostate cancer is considered a surrogate marker of genetic susceptibility to developing the disease, but shared environment cannot be excluded as an explanation for clustering of cases among family members. Prostate cancer is both a clinically and genetically heterogeneous disease with inherited factors predicted to account for 40%–50% of cases, comprised of both rare highly to moderately penetrant gene variants, as well as common genetic variants of low penetrance. Most notably, *HOXB13* and *BRCA2* mutations have been consistently shown to increase prostate cancer risk, and are more commonly observed among patients diagnosed with early-onset disease. A recurrent mutation in *HOXB13* has been shown to predispose to hereditary prostate cancer (HPC), and *BRCA2* mutations to hereditary breast and ovarian cancer (HBOC). Genome-wide association studies (GWAS) have also identified approximately 100 loci that associate with modest (odds ratios < 2.0) increases in prostate cancer risk, only some of which have been replicated in subsequent studies. Despite these efforts, genetic testing in prostate cancer lags behind other common tumors like breast and colorectal cancer. To date, National Comprehensive Cancer Network (NCCN) guidelines have highly selective criteria for *BRCA1/2* testing for men with prostate cancer based on personal history and/or specific family cancer history. Tumor sequencing is also leading to the identification of germline mutations in prostate cancer patients, informing the scope of inheritance. Advances in genetic testing for inherited and familial prostate cancer (FPC) are needed to inform personalized cancer risk screening and treatment approaches.

Keywords

Genetics; Epidemiology; Hereditary prostate cancer; Genome-wide association; *HOXB13*; *BRCA1/2*

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1. Introduction

Familial clustering of prostate cancer has been a long-standing observation [1–3], with concentrated clustering or young-onset of disease indicating a strong predisposition to hereditary prostate cancer [2,4]. Over time, the link of prostate cancer to other cancers in families has also been observed [5–9], potentially expanding the scope of family cancer history when considering the diagnosis of hereditary prostate cancer (HPC). Several factors have been associated with familial prostate cancer (FPC), including genetic variants, family cancer history, race/ethnicity, and diet/environmental factors. This brief review will discuss the risk factors for prostate cancer, current knowledge of the genetic basis for inherited predisposition to prostate cancer, and emerging developments in clinical translation relevant to FPC.

2. The epidemiology of familial prostate cancer

Prostate cancer is the most common cancer diagnosed among men in the United States and most of the Western world [10,11]. In the United States, an estimated 220,800 new cases of prostate cancer were diagnosed in 2015, representing over one quarter of all new invasive cancers among men [11]. Prostate cancer is also the second leading cause of cancer death with an estimated 27,500 deaths in the United States attributed to the disease in 2015 [11]. Prostate cancer is a heterogeneous disease, with a wide spectrum of age of onset and clinical severity, which complicates the study of epidemiologic risk factors. Established risk factors include older age, African American race, and a positive family history of prostate cancer [12]. Other factors with inconsistent associations include energy intake, diet, obesity and metabolic syndrome, physical inactivity, and environmental exposure to heavy metals such as cadmium [13,14] and herbicides such as Agent Orange [15].

A positive family history of prostate cancer, particularly when diagnosed in a first-degree relative, has been associated with an approximate two- to threefold increase in the risk of prostate cancer [16]. Risk generally increases with the number of affected relatives and the specific relatives (affected brothers as opposed to father and sons), and it is inversely related to the age at diagnosis among affected relatives [3]. FPC has been defined as families with either: (1) two first-degree relatives diagnosed with prostate cancer at any age, or (2) one first-degree relative and two or more second-degree relatives diagnosed at any age [17]. A more stringent definition of HPC has been used to characterize families with a particularly strong history of prostate cancer and includes those families with either: (1) three or more affected first-degree relatives, (2) prostate cancer diagnosed in three successive generations of the same lineage (paternal or maternal), or (3) two first-degree relatives both diagnosed with early-onset disease (age < 55 years) [4]. It has been estimated that 5%–10% of prostate cancer cases may be considered hereditary.

Study results have been mixed with respect to the clinicopathologic characteristics and short-term and long-term outcomes of patients diagnosed with FPC or HPC. These studies are also likely confounded by enhanced prostate-specific antigen (PSA) screening among those with a family history of disease. Among 16,472 radical prostatectomy patients treated

at the Mayo Clinic, patients with a family history were more likely to be diagnosed with organ-confined disease, lower pathologic Gleason score, and higher 10-year cancer-specific and overall survival compared with sporadic cases [18]. These findings are inconsistent with those of an earlier study by Kupelian et al, which observed a greater risk of biochemical recurrence after surgery among patients with a family history of prostate cancer where the period of study (1987–1996) was less likely influenced by screening history and intensity [19]. Findings from the prostate arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial also indicate the prostate cancer death rate was significantly higher among men with a positive family history of prostate cancer; however, age and PSA at diagnosis and Gleason score were similar between those with and without a family history. Notably, comparison of the usual care versus screening arms of the PLCO trial among patients with a positive family history indicate the potential benefit of screening on cancer-specific mortality (hazard ratio [HR] = 0.49; 95% confidence interval [CI] 0.22–1.1) that was not observed in men with no family history [20]. It should be noted that the vast majority of studies have been conducted among patients almost, if not entirely, exclusively European descent and further investigation is required among minorities diagnosed with prostate cancer.

Though family history is often considered an indicator of genetic susceptibility, one cannot exclude the possibility of shared environmental exposures, particularly exposures in the environment occurring early in life, as well as the interaction between gene(s) and environment in explaining aggregation of prostate cancer within families. A recently published study of more than 80,000 adoptees and their adoptive parents identified from the Swedish Register and linked to the Swedish Cancer Registry suggested that 5% of prostate cancers diagnosed among family members are attributed to shared environmental factors and not genetics [21].

3. Genetic contribution to inherited prostate cancer

Prostate cancer has a substantial inherited component estimated at 40%–50% [22]. This genetic contribution is made up of a combination of rare variants in genes of high- to moderate-penetrance and common, low-penetrance genes. However, the identification of susceptibility genes in prostate cancer has been challenging due to both the clinical and genetic heterogeneity of the disease.

3.1. Rare gene mutations of high- to moderate-penetrance

Genetic mutations that impact cancer risk management typically have been rare (< 5% of the population) and highly penetrant (80%–100% likelihood of expressing the phenotype), and have usually been associated with hereditary cancer syndrome phenotypes. Numerous studies have focused specifically on identifying these variants in HPC, while others have observed prostate cancers diagnosed in hereditary cancer syndromes notably linked to other solid tumors including hereditary breast and ovarian cancer (HBOC) and Lynch syndrome. Table 1 shows the range of risk for prostate cancer, aggressive prostate cancer, risk for early-onset prostate cancer, and outcomes from selected studies by genes associated with hereditary cancer syndromes. HBOC syndrome is a hereditary cancer syndrome associated with a significantly increased lifetime risk for breast and ovarian cancers in families, most

commonly caused by mutations in *BRCA1* or *BRCA2* [23–25]. Other cancers implicated in HBOC caused by *BRCA* mutations include prostate cancer [5,26], pancreatic cancer, and melanoma [26–28]. *BRCA2* mutation carriers have been reported to have more aggressive prostate cancer and decreased cause-specific survival [29–31]. Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes and is associated with increased risks for cancers of the colon, uterus, ovaries, upper urologic tract, stomach, small bowel, biliary tract, and brain in addition to predisposing to sebaceous adenomas [32]. Germline mutations/alterations in DNA MMR genes accounting for Lynch syndrome include *MLH1*, *MSH2*, *MSH6*, and *PMS2* [33–35]. Furthermore, deletions in *EPCAM* have also been implicated in Lynch syndrome [36,37]. Prostate cancer incidence has been reported at higher rates in Lynch syndrome families and in male carriers of mutations in the DNA MMR genes [9,38]. Prostate tumor testing among male MMR gene mutation carriers displayed microsatellite instability and loss of MMR gene expression in one study implicating this pathway in prostate cancer formation in those with germline MMR mutations [39].

Next-generation sequencing (NGS) technology has ushered in an era of new genetic testing approaches, such as germline multigene panel testing and somatic multigene/genomic testing, which have led to the identification of rare variants in genes of moderate penetrance [40]. These moderately penetrant gene mutations typically lead to a 35%–60% lifetime risk of manifesting the disease phenotype, and several of these genes have been identified in prostate cancer populations. Most notably, in 2012, a rare, recurrent mutation in the homeobox transcription factor *HOXB13* gene was identified in a subset of HPC and early-onset cases and has been consistently replicated in numerous independent populations (Table 1) [41–50]. The reported penetrance estimates of prostate cancer associated with the *HOXB13* G84E mutation have ranged from 33%–60%. [51,52]

Overall, studies have consistently demonstrated the role of *BRCA2* and *HOXB13* mutations in prostate cancer risk. However, these genes account for a small fraction of inherited predisposition to prostate cancer. The reported frequency of *BRCA2* mutations ranges from 1.3%–3.2% depending on the study design and population [53–57], with some smaller studies reporting frequencies of < 1% among cases. The carrier frequency of *HOXB13* mutations has been reported at 0.66%–6.25% from studies of cases and controls encompassing a variety of geographic regions [45]. A large pooled analysis including 9,016 prostate cancer cases reported a carrier frequency of 1.34% among cases [47]. Mutations in *CHEK2*, *PALB2*, and *NBS1* have also been reported in prostate cancer with less consistency in replicative studies. Mutations in *CHEK2* (checkpoint kinase 2) have been reported to confer an approximate 2.0- to 2.7-fold increased risk for prostate cancer in a Polish population [58]. This study also reported an odds ratio (OR) of 2.3 (95% CI 1.8–3.1) for prostate cancer diagnosis at age < 60 years. In a Finnish study, a truncating mutation in *PALB2* was observed among multiple family members affected with prostate cancer [59]. This gene is of particular interest due to its reported association with breast cancer and the encoded protein's ability to bind with BRCA2. Findings from a subsequent study of 95 University of Michigan HPC families did not support a role for this mutation in HPC [60]. Mutations in *NBS1* (Nijmegen breakage syndrome 1) have also been reported to associate

with prostate cancer risk (OR 2.5, 95% CI 1.5–4.0), age at diagnosis < 60 (OR 3.1, 95% CI 1.5–6.4), and FPC (OR 4.3, 95% CI 2.0–9.0) [58,61]. Additional germline mutations in moderately penetrant genes are being reported from studies of somatic sequencing of prostate tumors aimed at identifying treatment targets [62,63].

3.2. Common variants

With the growing knowledge of the human genome, common genetic variation has been able to be exploited to identify new loci associated with a multitude of diseases, including prostate cancer risk. Genome-wide association studies (GWAS) have identified multiple loci that explain an estimated 33% of FPC risk [64,65]. Figure 1 depicts a subset of those loci identified for association to prostate cancer achieving variant-trait associations with $P < 5.0 \times 10^{-8}$ [66]. Overall, approximately 100 loci have been reported to associate with prostate cancer with validation in independent cohorts [67]. While these loci have associations to prostate cancer with a high level of statistical significance, the magnitude of risk remains modest with typical ORs of < 2.0 [68]. Furthermore, the functional significance of identified variants remains unclear, with ongoing efforts at functional annotation of variants identified from GWAS [69]. Finally, no common variants have been consistently associated with prostate cancer-specific survival [70], which is an important factor regarding the clinical utility of germline variants in informing management. While studies are reporting the cumulative risk for prostate cancer associated with carrying multiple GWAS-identified variants [71,72], the clinical utility remains uncertain. Taken together, while multiple genetic variants have been identified from GWAS with strong statistical associations to prostate cancer, the discriminative ability to identify individuals at risk for developing prostate cancer remains modest and therefore these variants are not advocated for clinical use at the present time [73,74].

4. Clinical translation

4.1. Genetic testing for inherited prostate cancer

Genetic counseling and genetic testing for inherited prostate cancer has been a more slowly evolving field when compared to other common cancers such as breast cancer or colon cancer. Of all of the genetic determinants of prostate cancer identified so far, genetic testing for *BRCA1* and *BRCA2* mutations in the context of prostate cancer is now emerging from national organizations [75]. The National Comprehensive Cancer Network (2015) guidelines incorporate prostate cancer for genetic counseling and potential genetic testing for the following: personal history of breast cancer and two or more close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age. “Close blood relatives” include first-degree, second-degree, or third-degree relatives on the same side of the family per the guideline. An additional criterion for genetic counseling/testing includes personal history of prostate cancer (Gleason score ≥ 7) at any age with one or more close blood relatives with breast cancer (age ≥ 50 years) and/or invasive ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age [76]. These criteria highlight the importance of obtaining a detailed and thorough family cancer history on the maternal and paternal sides of the family for an individual presenting for prostate cancer risk evaluation. Furthermore, genetic counseling remains vital in order to provide patients with pre-test

information regarding potential additional cancer risks for the proband and their blood relatives that could be identified from genetic testing for *BRCA1/2* gene mutations, such as risk for breast and ovarian cancers, male breast cancer, pancreatic cancer, and melanoma.

Histopathologic features can also be indicative of underlying germline predisposition to prostate cancer [77]. Approximately 42% of *BRCA2* mutation carriers with prostate cancer have been reported to have intraductal carcinoma on pathology, while approximately 45% of prostate cancer patients harboring a *HOXB13* mutation have been reported to have “pseudohyperplastic” features [77]. Furthermore, prostate cancers of these individuals with the *HOXB13* G84E mutation have been reported to have lower prevalence of ERG expression compared to unselected cases, pointing to a potential underlying molecular phenotype of *HOXB13*-associated prostate cancer [78]. Unique histopathologic and molecular features of prostate cancer tissues may prove useful in identifying individuals for referral to genetic counseling.

4.2. Prostate cancer screening

The use of PSA in screening for prostate cancer in the general population remains controversial. Current US Preventive Services Task Force recommends against the use of PSA screening in asymptomatic men [79]. However, both the American Urologic Association (AUA) and the American Cancer Society (ACS) suggest that clinicians consider patient age, life expectancy, family history and race in making decisions about recommendations for screening [80,81]. Family history of prostate cancer is factored into ACS guidelines for recommendation of when to begin the discussion of PSA-based prostate cancer screening. The ACS recommends that men with a first-degree relative diagnosed with prostate cancer younger than age 65 should have a discussion of PSA screening starting at age 45. Those with an even stronger family history, such as more than one first-degree relative with prostate cancer at a young age, should have this screening discussion at age 40 [82]. Current NCCN guidelines support discussion of baseline PSA testing for all men beginning at age 45 with the frequency of testing post-baseline dependent on the baseline PSA concentration. Despite the fact that African Americans and men with a positive family history have a greater risk of being diagnosed, NCCN guidelines do not suggest separate screening guidelines for these high-risk groups. NCCN does recommend that *BRCA2* mutation carriers begin prostate cancer screening at age 40 and suggest the same for *BRCA1* cancers [83]. These recommendations are partly in response to early findings from the IMPACT screening trial, which reported a significantly higher positive predictive value (PPV) for prostate cancer detected upon subsequent biopsy among *BRCA2* carriers compared with related non-carriers (48.0% v 33.3%) [84]. Current NCCN guidelines do not comment on prostate cancer screening for men with Lynch syndrome [83].

4.3. Prostate cancer treatment

One important goal of genetic information is to provide individualized estimates of disease prognosis and severity in order to tailor management. An example of this approach for germline genetic testing is in relapsed/refractory ovarian cancer, where women are tested for *BRCA* mutations, and if positive, can be treated with a poly(ADP-ribose) polymerase (PARP) inhibitor where there has been demonstrated improvement in progression-free

survival [85,86]. In prostate cancer treatment, data regarding *BRCA* mutations is informing expert opinion about potential individualized management. Prostate cancer patients with *BRCA* mutations have been reported to have higher rates of metastatic disease and prostate cancer-specific death after localized treatment with radical prostatectomy or radiotherapy [31]. Prostate cancer-specific survival has also been reported to be lower among screen-detected prostate cancer for individuals carrying a *BRCA2* mutation compared to non-carriers (61.8% v 94.3%, $P < 10^{-4}$) [30]. Another study reported no significant difference in response of castrate-resistant prostate cancer to taxane-based therapy between *BRCA* mutation carriers versus non-carriers in an Ashkenazi Jewish population [87], providing further insight into potential systemic treatment for prostate cancer patients carrying *BRCA* mutations. While genetically-based treatment guidelines do not currently exist for prostate cancer, expert opinion is emerging regarding how to consider individualizing management [88]. Suggestions include combining local therapy with systemic approaches in *BRCA* mutation carriers, particularly for *BRCA2* carriers, due to the poorer prognosis in these patients. Furthermore, PARP inhibition may play more of a role in the metastatic, castrate-resistant setting based on emerging data [62,63,88].

As precision medicine efforts launch forward, somatic sequencing of prostate tumor tissues is also identifying potential targets for treatment. The goal of somatic sequencing is to identify tumor-specific genetic alterations in specific genes for which there are treatments available or clinical trial options for patients. A recent study reported that patients with metastatic, castrate-resistant prostate cancer with DNA repair defects (as defined by a homozygous deletion or deleterious mutation in the tumor in a gene reported to be involved either in DNA damage repair or sensitivity to PARP inhibition) had significantly improved radiologic progression-free survival and overall survival compared to those without evidence of DNA repair defects [62]. This study also reported a prevalence of *BRCA2* germline mutations of 6% in the cohort. Another report of precision oncology that integrated somatic sequencing with multidisciplinary management recommendations for patients reported a rate of 8% clinically actionable germline pathogenic mutations in metastatic castrate-resistant individuals [63]. Furthermore, another study assessing germline inherited DNA-repair mutations in men with metastatic, castrate-resistant prostate cancer reported 11.2% rate of mutations in DNA-repair genes, and 5.3% were in *BRCA2* [100]. Thus sequencing efforts will likely expand the knowledge of prevalence and scope of germline mutations identified in prostate cancer patient populations, and inform treatment options for these patients.

5. Conclusion

FPC remains an important clinical entity, with a spectrum of epidemiologic and genetic risk factors. Advances in DNA sequencing technologies will lead to new discoveries of the genetic predisposition to this disease, and potential gene-environment contribution to FPC. Insight into the predisposition to FPC is expected to further inform individualized prostate cancer screening and treatment.

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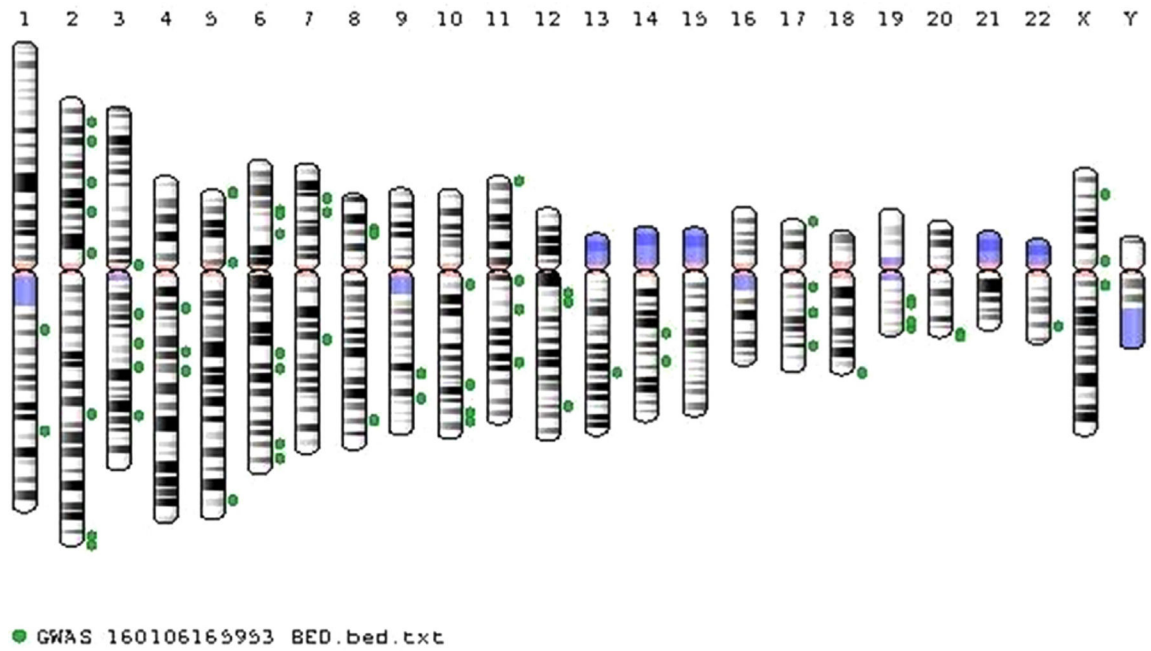
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Selected Prostate Cancer-Associated Loci Identified from GWAS ($p\text{-value} \leq 5 \times 10^{-8}$)



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Fig. 1.
Selected prostate cancer associated loci identified from GWAS ($P = 5 \times 10^{-8}$).

Table 1

Risk estimates for prostate cancer (PCA) by genes associated with hereditary cancer syndromes.

Gene	Risk for PCA *	Risk for aggressive PCA features †	**Risk for early-onset PCA (age at diagnosis < 65) ‡	§ PCA-specific outcomes †
<i>BRCA1</i>	1.07–3.81 [26,53,89–92]	--	1.82 [90]	5.16 [56]
<i>BRCA2</i>	3.18–8.6 [26,56,57,89,93–95]	3.18–4.38 [30,55,96]	7.33 [89]	HR for death 2.4–5.48 [56,96–98], decreased survival [31]
Mismatch repair genes	1.99–3.67 [38,99]	--	2.48 [38]	--
<i>HOXB13</i>	2.8–8.47 [41,44,47,50]	--	2.7–10.11 [41,44,47,50,100]	--

* Risks are a combination of odds ratios, relative risks, hazard ratios, or standardized incidence ratios depending on the study. Risks vary based on strength of family history reported.

† Outcomes are a combination of survival estimates or mortality depending on the study.

‡ Definition of aggressive prostate cancer features include Gleason score 7, depending on the study. Additional studies have described an association of *BRCA1* and *BRCA2* in particular to features of aggressiveness. The table highlights those studies with reported risk estimates.

§ While definitions for early-onset prostate cancer can vary, risks are reported for age at diagnosis < 65 years to encompass the majority of studies with an age-related focus.