The Epidemiology and Clinical Implications of Genetic Variation in Prostate Cancer

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KEYWORDS

• Prostate cancer • Genetic variants • Susceptibility • Tumor aggressiveness

KEY POINTS

- There is a strong genetic predisposition to prostate cancer.
- Studies have identified rare, highly penetrant genetic variants that significantly increase the risk of prostate cancer and the aggressive forms of the disease.
- Genome-wide association studies have identified common widely validated genetic variations within the population that increase the risk of prostate cancer in a cumulative fashion.
- Genetic mutations within tumors have also been found that contribute to disease risk and aggressiveness; some have been incorporated into commercial assays.
- The mechanisms by which genetic variations influence the risk and progression of prostate cancer and their clinical application are under investigation; however, these variants hold potential to improve and personalize current screening and treatment algorithms.

INTRODUCTION

Prostate cancer (PC) is the second most common visceral malignancy in men worldwide, with approximately 900,000 new cases being diagnosed annually.[1] However, there is substantial variation in disease incidence based on geographic region. This situation is partly due to the influence and variability in the implementation of routine testing for PC with serum prostate-specific antigen (PSA) measurement and digital rectal examination. As such, geographic regions with the highest rates of testing, such as the United States and Western and Northern Europe, have the highest reported rates of PC, whereas regions with low rates of testing, such as some Asian and African countries, have the lowest incidence rates.[2] In addition, in countries with high PC incidence rates, there is a significant discrepancy between PC incidence and mortality. For example, there are almost 240,000 new PC diagnoses annually in the United States, but fewer than 15% of these men ultimately die of PC.[3] This low mortality-to-incidence ratio is largely attributed to the widespread implementation of PSA testing and effective treatment of early-stage disease throughout the United States.[4–7]

Since its introduction as an aid to the early detection of PC in the 1990s, PSA testing has influenced the diagnosis and treatment of PC.[7] Routine PSA testing has been associated with a stage migration toward increased diagnoses of organ-confined, low-grade PC.[4–7] The result has been a significant decrease in both the percentage and absolute number of men presenting with metastatic disease as well as a 45% reduction in the age-adjusted PC-specific mortality rate.[8] Despite these improvements, PSA testing has negatively

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affected some men. It is likely that some have been subject to risks secondary to potentially unnecessary biopsies and the overtreatment of a non–life-threatening PC that may not have been diagnosed without PSA testing. Furthermore, unnecessary treatment is costly and may be associated with side effects.[9–11] Thus, there is an urgent need for new biomarkers to distinguish aggressive from indolent PC and to improve current early detection strategies and clinical treatment decisions.

The strongest risk factor for PC, other than advanced age and race (eg, African American ancestry), is family history of the disease.[12–14] In fact, it has been shown that PC is one of the most heritable of cancers, as studies of twins have shown that up to 42% of the risk can be explained by genetic factors.[15] Epidemiologic data provide further support for a hereditary component. For example, data derived from a Swedish population-based study suggested that 11.6% of PC cases can be accounted for by familial factors alone.[16] In addition, a meta-analysis investigating familial clustering suggested that risk was greater for men with affected brothers (relative risk [RR] = 3.4) than for men with affected fathers (RR = 2.2). Second-degree relatives conferred a lower risk (RR = 1.7) than fathers or brothers, and having 2 or more first-degree relatives conferred the highest risk (RR = 5.1).[17] The risk also appears to be greater among probands with first-degree relatives who are diagnosed with PC at younger ages.[18]

Until recently, the study of cancer genetics has focused on identifying a few genes with high penetrance.[14,19] Despite strong evidence for the existence of PC susceptibility genes, family-based linkage studies have largely failed to reproducibly identify mutations within genes that can explain most PC cases. This is believed to be due to the high incidence of nonfamilial PC and the lack of statistical power in familial (segregation) studies. However, over the past several decades, PC genetics has been revolutionized by increasing genetic technologies at significantly decreasing costs. Specifically, the field witnessed a progression from these early linkage studies involving families of PC patients using microsatellite markers, to loss-of-heterozygosity studies using a more targeted approach with candidate genes (eg, BRCA and retinoblastoma genes), to genome-wide association studies (GWAS) of genetic variants (called single-nucleotide polymorphisms [SNPs]), to expression profiling studies to copy number variation studies, to whole exome sequencing, and now to entire genome-sequencing studies. These advances have allowed for the identification of genetic variants in both germline and tumor DNA that increase a man's risk for PC and aggressive disease (eg, Refs.[20–22]). This review discusses the potential use of genetic markers as a way to identify groups of men at high risk of developing PC, improve screening practices, discriminate aggressive from indolent disease, and, potentially, personalize therapeutic strategies.

USEFULNESS OF RARE GENOMIC VARIATION IN SCREENING FOR AND TREATMENT OF PROSTATE CANCER

As previously mentioned, many prior genetic studies have failed to identify a highly prevalent and penetrant gene or mutation associated with PC susceptibility. Linkage studies have identified PC-risk loci on several chromosomes, with the strongest linkage being to chromosome 1. Notable candidate genes include HPC1 on chromosome 1q23-35, PCAP on chromosome 1q42-43, and CAPB on chromosome 1p36.[23] In addition, data from the International Consortium for Prostate Cancer Genetics (ICPCG) has identified 12 additional regions associated with PC risk, including 1q23, 5q11, 5q35, 6p21, 8q12, 11q13, and 20p11-q11.[24]

Many studies have revealed an association between rare mutations in the breast cancer predisposition genes (*BRCA1* and *BRCA2*) and PC risk.[25–27] *BRCA1* and *BRCA2* are tumor-suppressor genes, located on chromosomes 17q21 and 13q12, respectively, that are inherited in an autosomal dominant fashion. In healthy individuals, the *BRCA1* and *BRCA2* genes function within the DNA repair pathway, and help regulate transcription and chromatin remodeling. However, in patients with germline mutations in one of the BRCA genes, acquired inactivated or mutation of the remaining wild-type allele is associated with tumorigenesis. This loss of function is associated with loss of DNA repair mechanisms (eg, double-strand breaks by homologous recombination) and genomic instability, which often results in tumors within breast, ovarian, pancreatic, and prostate tissue.[28–31]

One of the major challenges to studying the role of BRCA mutations in PC susceptibility is the relatively low incidence of germline mutations in those genes.[32–35] Although present in less than 0.3% of sporadic PC cases, germline mutations within the BRCA genes have been associated with a significantly increased risk of PC (for *BRCA1* it is increased up to 3.5-fold, and for *BRCA2* it is increased up to 8.6-fold in men $\leq$65 years).[33] In addition, it has been estimated that the lifetime risk of developing PC in *BRCA1* or *BRCA2*