https://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq

Genetics of Prostate Cancer (PDQ®)–Health Professional Version

Executive Summary

This executive summary reviews the topics covered in this PDQ summary on the genetics of prostate cancer, with hyperlinks to detailed sections below that describe the evidence on each topic.

- **Inheritance and Risk**
  A genetic contribution to prostate cancer risk has been documented, and knowledge about the molecular genetics of the disease is increasing. Clinical management based on knowledge of inherited pathogenic variants is emerging. Factors suggestive of a genetic contribution to prostate cancer include the following: 1) multiple affected first-degree relatives (FDRs) with prostate cancer, including three successive generations with prostate cancer in the maternal or paternal lineage; 2) early-onset prostate cancer (age ≤55 years); and 3) prostate cancer with a family history of other cancers (e.g., breast, ovarian, pancreatic).
- **Associated Genes and Single-Nucleotide Polymorphisms (SNPs)**
  Several genes and chromosomal regions have been found to be associated with prostate cancer in various linkage analyses, case-control studies, genome-wide association studies (GWAS), and admixture mapping studies. Pathogenic variants in genes of high and moderate penetrance, such as *BRCA1*, *BRCA2*, the mismatch repair genes, and *HOXB13* confer modest to high lifetime risk of prostate cancer. Some, such as *BRCA2*, have emerging clinical relevance in the treatment and screening for prostate cancer. In addition, GWAS have identified more than 100 SNPs associated with the development of prostate cancer, but the clinical utility of these findings remains uncertain. Studies are ongoing to assess whether combinations of these SNPs may have clinical relevance in identifying individuals at increased risk of the disease. Studies analyzing the association between variants and aggressive disease are also ongoing.

- **Clinical Management**
  Information is limited about the efficacy of commonly available screening tests such as the digital rectal exam and serum prostate-specific antigen (PSA) levels in men genetically predisposed to developing prostate cancer. Initial reports of targeted PSA screening of carriers of BRCA pathogenic variants has yielded a higher proportion of aggressive disease. On the basis of the available data, most professional societies and organizations recommend that high-risk men engage in shared decision-making with their health care providers and develop individualized plans for prostate cancer screening based on their risk factors. For example, some experts suggest initiating prostate cancer screening at age 45 years in carriers of *BRCA2* pathogenic variants and consideration of screening in *BRCA1* carriers. Inherited variants may influence treatment decisions, particularly for males with pathogenic variants in DNA repair genes. Studies have reported improved response rates to PARP inhibition among males with metastatic, castrate-resistant prostate cancer carrying germline pathogenic variants in *BRCA2* and other DNA repair genes.
- **Psychosocial and Behavioral Issues**
  Psychosocial research in men at increased hereditary risk of prostate cancer has focused on risk perception, interest in genetic testing, and screening behaviors. Study conclusions vary regarding whether FDRs of prostate cancer patients accurately estimate their prostate cancer risk, with some studies reporting that men with a family history of prostate cancer consider their risk to be the same as or less than that of the average man. Factors such as being married and the confusion between benign prostatic hyperplasia and prostate cancer have been found to influence perceived risk of prostate cancer. Studies conducted before the availability of genetic testing for prostate cancer susceptibility showed that factors found to positively influence men's hypothetical interest in genetic testing included the advice of their primary care physician, a combination of the emotional distress and concern about prostate cancer treatment effects, and having children. Several small studies have examined the behavioral correlates of prostate cancer screening at average and increased prostate cancer risk based on family history; in general, results appear contradictory regarding whether men with a family history are more likely to be screened than those not at risk and whether the screening is appropriate for their risk status. Research is ongoing to better understand and address psychosocial and behavioral issues in high-risk families.