



☆ Topic: Prostate cancer

☆ **Summary:** Prostate cancer is a polygenic disease. Only 5% of prostate cancer occurs in families with a hereditary prostate cancer pattern. In the past two years, genome wide association studies have identified over a dozen common single nucleotide polymorphisms (SNPs) that are each associated with a mild increase in risk of prostate cancer (OR<1.30). However, in combination, these SNPs may result in substantially higher absolute risk as well as population attributable risk.¹

☆ **Bottom line:** At present, clinical genetic testing for a single inherited prostate cancer susceptibility gene is not available. A risk profile screening test based on the common low risk SNPs detected to date will likely have low positive and negative predictive value in the general population. Risk assessment should be based on the three known risk factors of age, race and family history.

✓ The Disease

- Prostate cancer affects 1 in 7 men for an approximate 14% lifetime risk in the general population.
- Only 5% of prostate cancer occurs in “hereditary prostate families” (defined by either 3 or more affected first degree relatives, or three successive generations with disease, or 2 relatives diagnosed under 56).
- Risk factors: age, ethnicity and family history
- Highest to lowest disease incidence: African Americans> Caucasians> Asians
- First degree relatives of affected men (brothers, sons) have a 2-3 fold increased risk for the disease.
- Risk increases rapidly with each decade after the age of 40, but disease still uncommon in men under 50.

✓ The Genetic Heterogeneity of Familial Prostate Cancer

- Unlike breast cancer and colon cancer, where a very small number of highly penetrant genes account for some of the disease in high-risk families, a single high-risk prostate cancer gene will likely be very rare and account for an even smaller proportion of cases.
- Rather, many different genes are likely to be involved in prostate cancer susceptibility, each conferring a small to moderate increase in risk.
- These predisposing genetic variants are likely very common in the population and could account for a large attributable risk in specific ethnic populations.
- Genetic linkage analysis in families with multiple affected individuals helps to identify a disease susceptibility locus (the position on a chromosome occupied by a known or potential gene associated with a particular disease).
- A genome-wide association study is an approach that involves rapidly scanning markers across complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Strategically selected markers of genetic variation are called SNPs- single nucleotide polymorphisms.
- Many loci and SNPs for prostate cancer susceptibility have been identified to date.
- However, the search for a common, inherited prostate cancer susceptibility gene continues.

✓ The Genetic Variants

- Over a dozen SNPs have been identified by genome wide association studies and multiple prostate cancer studies with highly replicated results.

- The SNPs are common in the general population and associated with a mild increase in risk- odds ratios are typically <1.30.
- Research has shown a strong cumulative risk of prostate cancer with five of these SNPs, resulting in an odds ratio of 9.46.²
- Three distinct loci lie in an area of chromosome 8 (8q24) and may result in a 25% to 50% increased risk of prostate cancer. No specific genes have been identified in this region.¹

✓ **Known genes that are potential candidates**

- Mutations in the *BRCA1* or *BRCA2* genes (see Hereditary Breast/Ovarian Gene Messenger) are associated with a three to seven fold increased risk of prostate cancer by age 70 with a greater risk being associated with *BRCA2* and for cases diagnosed under age 65.
- *BRCA2* testing in one study of 263 men with prostate cancer identified a mutation in 6 (2.3% frequency).
- Genes involved in steroid hormone metabolism (e.g. Androgen receptor gene) have been proposed, but a clear association is still lacking here.
- *CHEK2* on chromosome # 22 - one study detected *CHEK2* variants in 4.8% of 578 prostate cancer patients and in no controls.

✓ **Who should be offered referral for genetic counseling?**

- At present, there is no clinical genetic test specific to prostate cancer susceptibility.
- Assess the rest of the family history carefully → prostate cancer in the presence of a history of breast and ovarian cancer (on the same side of the family) would be suggestive of a mutation in *BRCA1/2* and a referral to a clinical genetics clinic would be indicated.
- Families with three or more relatives affected with prostate cancer may be eligible for research studies.

✓ **Screening**

- The US Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate specific antigen (PSA) testing or digital rectal examination (DRE) in men younger than age 75 years.³ (*I recommendation*)*
The USPSTF recommends against screening for prostate cancer in men age 75 years or older. (*D recommendation*)**
- If early detection improves health outcomes, the population most likely to benefit from screening will be men aged 50-74, and men older than 45 who are at increased risk (African American men and men with a family history of a first-degree relative with prostate cancer).³
- In some Canadian provinces, male patients are eligible to receive insured PSA testing if they have a family history of one or two first degree relatives with prostate cancer (e.g. father or brother).
- *I recommendation: The USPSTF concludes that evidence that the service is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.
- ** D recommendation: The USPSTF notes there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

☆ **Web Resources:** National Cancer Institute: www.cancer.gov

☆ **References:**

1. Witte, JS. Prostate Cancer Genomics: Toward a New Understanding. *Nat Rev Genet.* 2009; 10(2):77-82.
2. Zhang, SL et al. Cumulative Association of Five Genetic Variants with Prostate Cancer. *N Engl J Med.* 2008;358:910-9.
3. U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2008;149:185-191.

☆ **Review Articles**

Foulkes, W.D. Inherited susceptibility to common cancers. *N Eng J Med* 2008;359:2143-53.

Gudmundsson et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nature Genetics* 2007;39:631-637.

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