

## Appendix B:

# Hereditary Prostate Cancer

Of the 1 in 6 American men who will develop prostate cancer in their lifetime, approximately 5-10% are in Hereditary Prostate Cancer (HPC) families. An additional 20% of men with prostate cancer have a single affected family member.

Older age, being of African descent, and a positive family history of prostate cancer have long been recognized as risk factors, but understanding the complex genetic and environmental influences and mechanisms underlying this disease are at an early stage.<sup>29</sup> As a result of genetic studies to date, it may be said that genetic heterogeneity is very likely in prostate cancer as are gene-gene and gene-environment interactions.<sup>30</sup>

### Genetic Mechanisms in the development of prostate cancer

Gene mutations that play a part in the initiation or progression of prostate cancer include the following mechanisms:

- Decreased RNA degradation activity
- Increase in testosterone biosynthesis
- Increase in the conversion of testosterone to dihydrotestosterone, the more metabolically active form, which stimulates cell division in androgen dependent prostate cancers.
- Associated with inflammation
- Abnormal proliferation or a decrease in apoptosis or programmed cell death
- Decreased carcinogen detoxification<sup>31</sup>

### Hereditary Prostate Cancer

The Hopkins clinical criteria for HPC require at least one of the following:

- Three or more affected first-degree relatives
- A prostate cancer case in three generations on either the maternal or paternal side of the family
- Any two family members diagnosed before age 55<sup>32</sup>

Hereditary prostate cancer is generally inherited in an autosomal mode including BRCA1 and BRCA2 gene mutations which represent a very small fraction of hereditary prostate cancers. There is some epidemiologic evidence for X-linked and/or recessive inheritance patterns in some hereditary prostate cancer families as well; in these families men have an increased risk when a brother is affected as compared to a father.

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<sup>29</sup> Schaid, D. (2004) The complex genetic epidemiology of prostate cancer. *Human Molecular Genetics*, 13(Review Issue 1), R103-R121.

<sup>30</sup> Nelson, W.G., De Marzo, A., & Issacs, W.B. (2003) Mechanisms of Disease: Prostate Cancer. *NEJM*, (349), 366-381.

<sup>31</sup> Bock, C. The Genetics of Prostate Cancer. Wayne State University, Karmanos Cancer Institute. Presentation to MDCH Cancer Section June 10, 2005.

<sup>32</sup> Smith, J.R., Freije, D., Carpten, J.D., et al. (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science*, 274, 1371.

## **Public Health Implications**

Patient educational materials including decision aids need to be accessible to fully inform men of their personal risk status, of available screening options, and of the benefits and risks of testing and treatment options. Genetic counseling should be available regardless of insurance or financial status for men with a strong family history of prostate cancer or a family with a known BRCA1 or BRCA2 mutation.

## **Additional References**

1. Bock, C.H., Cunningham, J.M., McDonnell, S.K., Schaid, D.J., Peterson, B.J., Pavlic, R.J., Schroeder, J.J., Klein, J., French, A.J., Marks, A., Thibodeau, S.N., Lange, E.M., & Cooney, K.A. (2001) Analysis of the prostate cancer susceptibility locus HPC20 in 172 families affected by prostate cancer. *American Journal of Human Genetics*, 68(3), 795-801. NOTE: May require you to be a subscriber to AJHG.
2. Bock, C.H., Peyser, P.A., Gruber, S.B., Bonnell, S.E., Tedesco, K.L., & Cooney, K.A. (2003) Prostate cancer early detection practices among men with a family history of disease. *Urology*, 62(3), 470-475.
3. Chen, H., Griffin, A.R., Wu, Y.Q., Tomsho, L.P., Zuhlke, K.A., Lange, E.M., Gruber, S.B., & Cooney, K.A. (2003) RNASEL mutations in hereditary prostate cancer. *J Med Genet*, 40(3), e21.
4. Cooney, K.A. (2000) Advances in our understanding of the inherited predisposition to cancer. *Michigan Oncology Journal*, (Spring), 11-12.
5. Cooney, K.A., Tsou, H.C., Petty, E.M., Miesfeldt, S., Ping, X.L., Gruener, A.C., & Peacocke, M. (1999) Absence of PTEN germ-line mutations in men with a potential inherited predisposition to prostate. *Clin Cancer Res*, 5(6), 1387-1391.
6. Cooney, K.A., McCarthy, J.D., Lange, E., Huang, L., Miesfeldt, S., Montie, J.E., Oesterling, J.E., Sandler, H.M., & Lange, K. (1997) Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. *J Natl Cancer Inst*, 89(13), 955-959.
7. Gruber, S.B., Chen, H., Tomsho, L.P., Lee, N., Perrone, E.E., & Cooney, K.A. (2003) R726L androgen receptor mutation is uncommon in prostate cancer families in the United States. *Prostate*, 54(4), 306-309. NOTE: Access to this article may require membership to *The Prostate*
8. Lange, E.M., Chen, H., Brierley, K., Perrone, E.E., Bock, C.H., Gillanders, E., Ray, M.E., & Cooney, K.A. (1999) Linkage analysis of 153 prostate cancer families over a 30-cM region containing the putative susceptibility locus HPCX. *Clin Cancer Res*, 5(12), 4013-4020.
9. Lange, E.M., Chen, H., Brierley, K., Livermore, H., Wojno, K.J., Langefeld, C.D., Lange, K., Cooney, K.A. (2000) The polymorphic exon 1 androgen receptor CAG repeat in men with a potential inherited predisposition to prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 9(4), 439-442.
10. Liede, A., Karlan, B.Y., Narod, S.A. (2004) Cancer Risks for Male Carriers of Germline Mutations in BRCA1 or BRCA2: A Review of the Literature. *J of Clinical Oncology*, 22(4), 735-742.

11. Perrone, E.E., Theoharis, C., Mucci, N.R., Hayasaka, S., Taylor, J.M.G., Cooney, K.A., & Rubin, M.A. (2000) Tissue microarray assessment of prostate cancer tumor proliferation in african american and white men. *J Natl Cancer Inst*, 92(11), 937-939.
12. Wu, Y.Q., Chen, H., Rubin, M.A., Wojno, K.J., & Cooney, K.A. (2001) Loss of heterozygosity of the putative prostate cancer susceptibility gene HPC2/ELAC2 is uncommon in sporadic and familial prostate cancer. *Cancer Res*, 61(24), 8651-8653.