The present study focuses on genetic polymorphisms in androgen and carcinogen metabolism, DNA repair and apoptosis so as to propose susceptibility markers and genotype profiles attributing to increased risk.

The genetic risk factors in prostate cancer in the present investigation has been done by association study, since exploration of the genetic basis of prostate cancer susceptibility by linkage analysis is challenging due to the genetic heterogeneity and incomplete penetrance of germline mutations. Further, highly penetrant genetic factors that confer a high relative risk on the few individuals who carry them may explain only about 5-10% of the prostate cancer cases and are unlikely to explain the large ethnic differences in prostate cancer risk. In contrast, common polymorphisms account for a larger proportion of prostate cancer in the population despite having a lower penetrance and conferring a much lower prostate cancer risk on individuals.

Scientists have begun to appreciate the presence of genes exhibiting common polymorphisms that modulate physiologic and biochemical processes related to prostate cancer. The presence of both high-risk as well as low-risk markers at different loci in an individual might result in no overall difference in risk. This suggests the need to develop a polygenic model, incorporating multiple loci from the individual genes to maximize the ability to identify individuals at high risk.

The increase in incidence of prostate cancer in the Indian population stresses the need to identify genetic markers for susceptibility and prognosis. Unfortunately, studies on genetic polymorphisms and prostate cancer are scanty especially among the South Indians and hence the present work relates to South Indian men. Since prostate cancer exhibits distinct ethnic variation, the present study is concentrated in exploring and identifying susceptibility markers in the South Indians. The work has been done by collecting blood samples from 95 histologically confirmed prostate cancer patients and 120 age-matched controls. Genomic DNA was isolated and PCR based methods were adopted to detect the polymorphisms. The salient findings in the present investigation are summarized below:
In the study on androgen metabolism, ≤19 CAG repeats of AR was found to condition a significantly increased risk for prostate cancer (OR 5.90; 95% CI 3.20-11.20; P<0.001). The haplotypes ≤19 CAG and ≤21 GGN; ≤19 CAG and > 21GGN were significantly associated with an increased risk (OR-5.2 at 95% CI -2.17-12.48, P <0.001 and OR-6.9 at 95% CI-2.85-17.01, P <0.001 respectively). The CYP17 A1/A2 polymorphism has attributed to a significant protective effect in older age group (OR-0.37, 95% CI -0.16-0.89, P 0.04), while the SRD5A2 V89L, SRD5A2 (TA)n repeats and PSA A/G polymorphism were not independently associated with the risk of cancer. Certain genotype combinations were found to enhance the risk of cancer and the genetic profile, ARCAG ≤19, AR GGN >21, CYP17 A1/A1 and SRD5A2 V/L was found to significantly elevate the risk of cancer (OR-9.38, 95%CI 1.3-67.65)

In respect of carcinogen metabolism, CYP1A1 w1/m1 genotype and CYP1A1 m1/m1 were found to significantly increase the risk (OR 2.73; 95%CI 1.43-5.2, P<0.01) while GSTP1 Ile/Val had a protective effect (OR 0.39;95%CI 0.22-0.73). The GSTM1 and GSTT1 null genotypes lacked any association. However, the genetic profile CYP1A1 w1/m1, GSTT1+/+ and GSTM1+/+ was significantly associated with the increased risk for prostate cancer (OR 2.6,95%CI 1.19-5.67,P 0.02), while CYP1A1 w1/w1, GSTP1 Ile/Val and GSTM1+/+ attributed to a significant protective effect (OR 0.38; 95%CI 0.18-0.85,P 0.02)

In the DNA repair pathway analyzed in the present study, XRCC1 Arg/Gln (OR 2.02; 95% CI 1.03-3.94) and XPD Lys/Gln (OR 1.93; 95%CI 1.09-3.42, P 0.03) were found to exhibit an increased risk for prostate cancer. Arg/Gln and Lys/Gln genotype combination (OR-4.58; 95%CI-1.71-12.29; P<0.001).
Summary and Conclusions

- Though the **p53 Arg/Pro polymorphism** was not found to be associated individually with the risk of prostate cancer, in combination with carcinogen metabolism the genetic profile p53 Pro/Pro, CYP1A1 w1/m1, GSTT1+/+ (OR- 6.53; 95%CI 1.80-22.63, $P = 0.007$), and in combination with DNA repair, the genetic profile p53 Arg/Pro, XRCC1 Arg/Gln and XPD Lys/Gln were found to significantly increase the risk of prostate cancer (OR 38.33; 95% CI 1.79-820.17)

- The interaction of genes of all the pathways investigated in the present work revealed certain genetic profiles within each pathway as well as among all the pathways to attribute to a greater genetic predisposition. Among all the pathways combined, the genetic profile ARCAG $\leq$19 repeats, CYP17 A1/A1, CYP1A1 w1/m1, GSTT1 +/+, XRCC1 Arg/Gln, XPD Lys/Gln and ARCAG $\leq$19 repeats, CYP17 A1/A2, CYP1A1 w1/w1, GSTT1+/+, XRCC1 Arg/Gln and XPD Lys/Gln were found to exhibit increased risk and the combination of CYP17A1/A2 and GSTP1 Ile/Val was found to exhibit a significant protective effect.

- Of the 95 prostate cancer patients taken for the study, 28 had relapse of cancer after androgen ablation therapy. AR CAG $\leq$ 19 repeats, PSA A/G, GSTT1 +/+, GSTP1 Ile/Ile and p53 Arg/Pro genotypes have individually attributed for this risk of relapse.

- Stratified analysis of the subjects based on age at diagnosis revealed ARCAG $\leq$19 repeats (OR-6.9; 95% CI 2.80-16.95; $P < 0.001$) to be significantly associated with increased risk at early age at diagnosis, while CYP17A1/A2 (OR-0.37, 95% CI -0.16-0.89, $P = 0.04$) and GSTP1 Ile/Val genotypes (OR- 0.37; 95%CI 0.15-0.94, $P = 0.05$) were found to exhibit a significant protective association with early age at diagnosis. None of the other genotypes are significantly associated with age at diagnosis.
With respect to the association of genotypes with tumor grade, XRCC1 Gln/Gln was significantly associated with low-grade tumor (OR 0.28, 95%CI 0.07-1.08; P 0.05) and AR CAG ≤19 was predominant in high-grade tumor but not statistically significant. None of the other genotypes exhibited a significant association with tumor grade.

Except for the SRD5A2 L/L genotype, which was associated with high PSA level (>49 ng/ml) (OR 4.4; 95%CI 1.40-14.14), none of the other SNPs were associated with serum PSA levels at diagnosis.

Immunohistochemistry for p53 and bcl2 on the formalin fixed paraffin embedded tissues of patients’ revealed aberrant expression specifically in high-grade tumors and in those with relapse of cancer after androgen ablation therapy. There was no significant association between p53 expression and p53 genotype.

The study has also revealed ethnic differences in the distribution of polymorphic genes and prostate cancer susceptibility.

A summary of the genes analysed indicating the high risk genotypes for prostate cancer is depicted in Fig 8.1. An ideogram representing all the genes studied indicating the genes with susceptible, protective and non-risk genotypes is presented in Fig. 8.2.

Conclusion

The results thus propose a multigene model for prostate cancer. It substantiates the concept that no single gene is sufficient to produce a Mendelian pattern of disease segregation; rather, disease risk is influenced by several genes and possibly by several gene-gene interactions. Certain genetic profiles brought out in the present study, strongly predict the risk of cancer and these would enable identification of genetically predisposed individuals.
Summary and Conclusions

Since patients were not selected with respect to specific exposures, only genetic predisposition factors prevalent in a majority of the patients would be expected to become evident in this kind of analysis. The study involved 40 asymptomatic BPH subjects in the control group. It is important to note that the incidence of histological evidence of BPH in the 7th to 8th decade of life was 70% to 80% (394). Hence, it would be almost impossible to identify a population without BPH in this age group. By contrast, it is generally accepted that BPH is neither a premalignant lesion nor a precursor carcinoma. In addition, in all the gene polymorphisms analyzed in the present study there was no difference between the healthy controls and BPH patients.

The Indian population is believed to be the most diverse because of different socio-cultural traditions. The variation of the Indian population from the rest of the world signifies the impact of ethnicity. It is important to note that certain genes may be in linkage disequilibrium with other gene polymorphisms in certain populations and not in others. It is also possible that different ethnic groups have different modifiers of gene function, not necessarily linked to specific polymorphisms. In this case, a complex ethnic-specific pattern of gene function and disease association was observed, including differential effects of the polymorphisms.

The study is the first of its kind in South Indians and has proposed susceptibility markers and genotype profiles that attribute to an increased risk of prostate cancer. It has also suggested certain prognostic markers for response to androgen ablation therapy. In addition to evaluating the risk attributed by the polymorphisms, the present study has also revealed ethnic differences in the distribution of the various genotypes of importance in prostate cancer. The genetic susceptibility markers in each of the pathways as well as the gene-gene interaction within each pathway as well as among the genes of the four pathways have been established.
Topics for Future research

The present study as already stated has established a few susceptibility genes and genotype profiles for prostate cancer in South Indian men. Extension of the present study with more samples and SNP profiling of other genes like vitamin D receptor, Estrogen receptor, N-acetyl transferases, MSH1, etc will enable identification of additional susceptible SNPs in the South Indians. Construction of an SNP profile of susceptibility will enable development of a SNP array to screen for genetically predisposed individuals.

**Functional characterization of the SNPs** will enable an understanding of the exact molecular mechanism of cancer susceptibility and progression. **Gene expression studies** should be performed and the expression profile of latent and metastatic cancer will enable characterization of differential gene expression.

With hormone refractory prostate cancer posing a major threat to the therapeutic management of prostate cancer, it is essential to understand the genetic basis of the hormone resistance. Though the present study has proposed certain markers, which attribute to the relapse of cancer after androgen ablation, it is essential to periodically follow up the newly treated patients, monitor their therapeutic response and identify genetic profiles, which attribute to androgen independence. Establishing genotype profiles for androgen independence will help in modification of therapeutic regimen and enable individualized therapy for patients.