SUMMARY AND CONCLUSION

The following main points are evident from the present study.

- As most of the patients were above 56 years of age, it is evident that prostate cancer is a disease of middle and old age.

- The parameter such as education levels and marital status have been seen not to be associated with an increased risk of prostate cancer development as most of the patients were educated and married.

- Similarly, no association with eating habits, utensil used for cooking and tea or coffee consumption with prostate cancer was observed.

- No statistically significant association of alcohol consumption with increased risk of prostate cancer was observed.

- Association of rise of prostate cancer with smoking habit was not evident. The gene-smoking interaction patterns also resulted in negative association of smoking habit with prostate cancer risk.

- Excepting some cases, no mutations were observed in DNA-binding (exons 2 and 3) and ligand-binding (exons 4-8) domains of AR gene when analysed by PCR-SSCP. On the basis of this, no association was found between AR gene mutations and other gene polymorphisms, stages, grades, as well as other risk factors with prostate cancer risk in this group of Indian population.

- An increased risk associated with the ERα −/− genotype was found. There was 3, 5 and 6-fold higher risk of prostate cancer in individuals carrying CYP17 A1/A2+A2/A2, PR A1/A2 or CYP1B1 Leu/Val+Val/Val genotypes respectively, when combined with ERα +/− + −/− genotype. Although 3 and 4-fold, probability of prostate cancer risk was observed in individuals having ERβ RR or CYP2D6 HEM+PM respectively, when combined with ERα +/− + −/− genotype, but the association was not statistically
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significant. No association of risk with ERα gene in relation to CYP19, SRD5A2 or VDR genes was seen.

> The observations showed that ERβ gene does not play any role in the development of prostate cancer alone and also in relation to PR, CYP19, CYP17, SRD5A2, VDR or CYP2D6 genes. But in the case of CYP1B1 Leu/Leu genotype, a 2-fold higher risk was found in individuals carrying Leu/Leu genotype in relation to ERβ gene.

> There was no difference between prostate cancer patients and control individuals with reference to any of the PR genotypes, therefore, no association of prostate cancer risk was found with this gene when studied alone and also in relation to CYP19, CYP17, SRD5A2, VDR or CYP2D6 genes. Just a 2-fold higher risk associated with CYP1B1 Leu/Leu genotype was apparent in relation to PR gene.

> An increase in risk associated with CYP19 CT genotype was observed. Patients with CYP17 A1/A2+A2/A2 or CYP1B1 Leu/Val+Val/Val genotypes showed a 4-fold higher risk in relation to CYP19 CT+TT genotype and this association was statistically significant. Such association was not observed in the case of SRD5A2 or VDR genes when combined with CYP19 gene.

> The prevalence of the CYP17 A2/A2 genotype was significantly higher among patients. There was a 4-fold higher risk of prostate cancer in individuals carrying CYP17 and CYP1B1 mutant alleles. While, presence of CYP17 and CYP2D6 mutant alleles in individuals did not show statistically significant association with the risk, although there was a 3-fold higher OR. No association of SRD5A2 or VDR genes with risk was seen when combined with CYP17 gene.

> No difference was seen in the prevalence of the SRD5A2 LL genotype between prostate cancer patients and control group, therefore, there was no significant association between this genotype and risk for prostate cancer. A non-significant association was seen in individuals carrying
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CYP1B1 VL+LL and SRD5A2 Leu/Leu genotypes. No association of this gene with the risk was observed in relation to VDR or CYP2D6 genes.

- There was an overall lack of association between the VDR gene and prostate cancer risk when studied alone. But when VDR Tt+tt genotype was combined with CYP1B1 VL+LL, however, a 4-fold higher risk was observed. There was a non-significant association of VDR Tt+tt and CYP2D6 PM genotypes with prostate cancer risk.

- The present results showed that the heterozygosity for the Leu allele (Leu/Val) in CYP1B1 was not associated with prostate cancer risk, while the individuals with the Val/Val genotype had a 4-fold increased risk for prostate cancer. A 2-fold increased risk was observed in individuals carrying CYP1B1 mutant allele and CYP2D6 EM genotype, which resulted in a statistically significant association with risk of prostate cancer.

- The data showed no overall statistically significant association between the CYP2D6 B allele and prostate cancer risk when studied alone.

- When ORs were adjusted for the risk factors, neither cigarette smoking habit nor other variables, such as age and alcohol consumption, were clearly associated with prostate cancer risk in ERβ, SRD5A2 and VDR genes but in the case of ERα gene, the odd ratio for having −/− genotype was 3-fold higher compared to +/+ genotype. In the case of CYP19 gene, individuals carrying CT genotype had a 2-fold higher risk of developing prostate cancer than patients with the CC genotype. The risk was 4-fold higher in individuals with CYP1B1 mutant allele (Val/Val) when ORs were adjusted for the risk factors. Although there was a 2-fold higher risk of developing prostate cancer in individuals carrying PR A1/A2, CYP1B1 Leu/Val or CYP2D6 HEM genotypes, and a 3-fold elevated OR with CYP17 A2/A2 or CYP2D6 PM genotypes, but these associations were not statistically significant.
When stratified according to the stages of disease, no statistically significant association of \( ER\beta, PR, CYP19, CYP17, CYP1B1 \) and \( CYP2D6 \) genes was found with increased risk for prostate cancer. Although a 2-fold elevated OR associated with \( ER\alpha -/-, SRD5A2 \) LL or \( VDR \) tt genotype was observed, but these associations were not statistically significant.

When stratified according to different grades of prostate cancer, no statistically significant association of \( ER\alpha, ER\beta, PR, CYP19, CYP17, SRD5A2 \) and \( CYP1B1 \) genotypes with tumour grade (low grade; <7 vs. high grade; ≥7) was observed. A 2-fold higher OR associated with \( VDR \) tt and \( CYP2D6 \) PM genotypes, but statistically not significant association was found.

Cumulative lifetime exposure to androgens, androgen metabolites and other physiologic factors, as well as environmental exposures, could play an important role in the development of prostate cancer in genetically predisposed men. Future studies that examine associations among several genetic polymorphisms should take into account the risk factors for prostate cancer, such as diet and other environmental exposures, as well as possible biological pathways. However, the initiation and progression of prostate cancer most likely result from a complex series of genetic events and environmental influences, and future studies are needed to identify potential causes for the distinction between latent and symptomatic prostate cancer. It seems more likely that there is a heterogeneous genetic alteration that occurs in prostate cancer, rather than a single “smoking gun.” Although the sex hormone appears to be involved in prostate carcinogenesis, the role of various polymorphisms in genes comprising the steroid biogenesis pathway is still not clear. The small number of subjects in genotype subgroups may make the magnitude of our risk estimates uncertain; therefore, studies with a larger sample size are needed to clarify the complex interaction among these genes and prostate cancer risk.