DISCUSSION

1. **Etiology Studies**

   The dramatic international variation in prostate cancer mortality rates suggests an environmental influence with diet, nutrition, age, familial predisposition and ethnicity as major determinants of risk for this disease.

   Age is an important prognostic factor in prostate cancer due to the fact that younger patients more seldom die from concomitant disease (Gronberg *et al.*, 1994). Tumours at this site occur with negligible frequency in men less than 55 years of age, and the vast majority of the cases (86%) occur over the age of 66 (Feigelson *et al.*, 1998). In the present study, as most of the patients were above 56 years of age with mean of 66.21, it is evident that prostate cancer is a disease of middle and old age.

   Most of the patients in the present study were educated and hence education was not found to be associated with the risk of prostate cancer agreeing thereby with the results of Bosetti *et al.* (2004) who in a case-control study, conducted in Italy on 1,294 prostate cancer patients and 1,451 controls found no association between education levels and risk of prostate cancer. Lund Nilsen *et al.* (2004) however, have reported an elevated risk of prostate cancer among men with high educations as compared to those with least education (OR, 1.56; 95% CI, 1.11-2.19).

   In the present study, 92% of the patients were married agreeing thereby with Lightfoot *et al.* (2004) who have observed no significant relation between marital status and risk for prostate cancer among 760 prostate cancer cases and 1632 age-matched controls. Marriage therefore, does not seem to have impact on the risk of prostate cancer. As against this Lund Nilsen *et al.* (2004) believe that divorced or separated men are at higher risk of prostate cancer as compared to married ones.
Nutrition is also a very important risk factor for prostate cancer. Men who eat more red meat or who consume high-fat dairy products in their diet appear to have a greater chance of developing prostate cancer (Rodriguez et al., 2004). No association of this variable with risk in Indian prostate cancer patients was however found. There was no association between consumption of vegetables and decreased risk of prostate cancer agreeing thereby with Dagnelie et al. (2004) who had found no impact of consumption of meat and vegetables with prostate cancer risk. However, similar are the observations of Givannucci et al. (2004) who had found no impact of consumption of meat and vegetables with prostate cancer risk. Even in a case-control study on the follow-up for cancer incidence among 130,544 men from 7 countries, no significant association between vegetables consumption and prostate cancer risk was observed (Key et al., 2004). An association of preserved meat with a significant increased risk of prostate cancer was observed in China among 130 cases and 274 controls (Jian et al., 2004). Similar observations were made by Sonoda et al. (2004) in a study in Japan on 140 cases and 140 controls.

The present study failed to find any association between tea and coffee consumption with the risk of prostate cancer among Indian patients. In fact Jian et al. (2004) in a case-control study on 130 cases and 274 controls in China, had found green tea to be a protective against prostate cancer as risk declined with increasing frequency, duration and quality of green tea consumption.

In the present study, no association of alcohol consumption with prostate cancer risk was found. This observation is in consistence with that of Dennis (1999) who also had found no such association. Similar were the observations made by others (Dagnelie et al., 2004; Hodge et al., 2004; Schoonen et al., 2004) who had found no clear association of alcohol consumption with prostate cancer risk. All these observations are further supported by a cohort study of 2,479 prostate cancer men conducted by Platz et al. (2004) who found that moderate or greater alcohol consumption was not a strong contributor to prostate cancer risk, except possibly in men who consume a large amount infrequently. Albertsen and Gronbaek, (2002), from a mean follow-up of 12 years, among study population (n=12,989) in Denmark, concluded that neither
amount nor type of alcohol is associated with the risk of prostate cancer. However, Schoonen et al. (2004) are of the view that since alcohol alters the hormonal milieu and it contains chemical substances, it may alter tumour cell growth.

In a case-control study, Honda et al. (1998) reported that cigarette smoking is a risk factor for prostate cancer. In the present series of patients through 51% of cases were smokers, but no association was found with prostate cancer risk. Similarly Lightfoot et al. (2004) have not found any association of cigarette smoking with prostate cancer risk among 760 cases and 1632 controls. Pickles et al. (2004) however, believe that current smokers have an increased risk (OR, 1.4; 95% CI, 1.0-2.0) of prostate cancer relative to non-smokers.

2. Mutational and Polymorphism Studies

Prostate cancer is a heterogeneous lesion and this suggests that the predisposition to prostate cancer may involve multiple genes and variable expression (Visakorpi, 2003). The molecular genetics of progression of prostate cancer is poorly understood, but it is generally believed to be involving an accumulation of genetic changes. Although some tumours have inherited genetic mutations, they acquire genetic alterations during their progression (Elo and Visakorpi, 2001). Dominant oncogenes are usually activated by gene amplification, translocations/or point mutations (Visakorpi, 1999). Recessive tumour-suppressor genes may be inactivated by the loss of an allele and inactivation of the others by a mutation (Visakorpi, 2003).

2.1 AR mutations and prostate cancer

The growth and development of the human prostate gland, together with the maintenance of its physiological integrity, are dependent on the presence of circulating androgens and intact intracellular steroid signaling pathway (Cunha et al., 1987). The cellular effects of androgens, including differentiation, homeostasis, morphogenesis and growth are mediated by androgen receptor (AR). AR is a member of the nuclear receptor family that includes receptors for steroid and thyroid hormones, vitamin D₃ and retinoic acids and numerous
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orphan receptors for which no ligands are known (Ewans, 1988; Mangelsdorf et al., 1995). As many as 85 AR mutations are there in prostate cancer tissues (MIM# 176807) (Gottlieb et al., 2004), almost all being single-base substitutions due to somatic mutations, rather than germline mutations. These mutations are unequally distributed along the length of the AR and their types vary. Only 54 mutations have been reported in exon 1 of the AR in patients suffering from some form of androgen insensitivity syndrome (AIS), despite the fact that it encodes more than half of the AR proteins (Gottlieb et al., 1999). In the C-terminal ligand-binding domain (LBD), there is a striking preponderance of missense mutations, with a significantly greater number of complete androgen insensitivity syndrome (CAIS) than partial AIS (PAIS) cases. It has been observed that AR mutations only appear during the latter stages of prostate cancer and in addition, some studies have indicated that anti-androgen treatments may result in AR mutations (Hyytinen et al., 2002).

Mutations in the X-linked androgen receptor gene cause the androgen insensitivity syndrome by impairing androgen-dependent male sexual differentiation to varying degrees. Complete androgen insensitivity (CAIS) yields an external female phenotype, whereas affected cases of partial androgen insensitivity have various ambiguities in the genitalia (Coffy, 1979).

In the present case-control study by PCR-SSCP analysis, excepting in case numbers 4, 5 and 6 in exon 2, case numbers 7, 8, 9 in exon 3 (Fig. 3) and case number 6 in exon 5 (Fig. 4), no mutations either in DNA-binding (exons 2 and 3) or in hormone-binding (exons 4-8) domains were found and it might be due to the small sample size. The mutations seen in exceptional cases on sequencing were found to be non-sense mutations.

2.2 Relationship between ERα and ERβ genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer

ERα gene has three PvuII, Xbal and B-variant polymorphisms, which are reportedly associated with receptor expression and altered function in some disorders including breast cancer, hypertension and spontaneous abortions. All
three RFLPs are located in the A/B domain, the transactivating factor 1. It is an important site for stimulating transcription from certain estrogen-responsive promoters.

In the present study, an analysis of ERα after digestion with Pvull restriction endonuclease, showed there 3-fold increase in risk associated with the −/− genotype with an OR of 3.34 (95% CI, 1.08-10.30; P=0.034) and the results are statistically significant. The present results are in consistence with the observations of Suzuki et al. (2003) who also have found a significant association of the −/− genotype of the Pvull site in the ERα gene in a study on 101 cases and 114 healthy individuals among Japanese population (OR, 3.44; 95% CI, 1.97-5.99; P=0.0028).

In a case-control study by Modugno et al. (2001), which was performed among Caucasian population of 88 prostate cancer patients and 241 male controls, no significant association was found between −/− and +/− genotypes of ERα gene. In a study conducted in Urban Shanghai in China, there was an association of Pp (+/−) and pp (−/−) genotypes with risk of breast cancer as compared to PP (+/+ genotype (Cai et al., 2003). Nonetheless, the authors suggested a possible role for ERα in hormone-dependent tissues such as prostate and breast. In a population-based case-control study in Sweden, Weiderpass et al. (2000) showed an association of PP (−/−) with a non-significantly decreased risk for endometrial cancer (OR, 0.70; 95% CI, 0.34-1.44) compared with the +/+ genotype.

When heterozygous mutant (+/−) and mutant −/− genotypes of ERα gene were combined as a single genotype and used for studying the impact of this gene with other genes, it was found that PR A1/A2+A2/A2, CYP17 A1/A2+A2/A2 and CYP1B1 Leu/Val+Val/Val genotypes when combined with ERα mutant allele respectively have 5, 3 and 6-folds increased risk of prostate cancer.

The risk is 4-fold higher in patients carrying CYP2D6 HEM+PM genotype in combination with ERα (+/− + −/−) allele. Similarly, when ERβ RR genotype is
combined with \( ER\alpha \) \((+/- + -/-)\) the risk is 3-fold. The risk is 2-fold when the \( ER\beta \) Rr genotype is considering along with \( ER\alpha \) wild-type \((+/+)\).

These results clearly indicate that \( PR, CYP17, CYP1B1 \) and to the lesser extent, \( ER\beta \) and \( CYP2D6 \) genes in combination with \( ER\alpha \) gene play an important role in prostate carcinogenesis as against \( CYP19, SRD5A2 \) and \( VDR \) genes having no such role.

Though the genotype frequency of \( ER\beta \) Rr genotype is higher in prostate cancer patients as compared to controls, but the \( P \) value is not statistically significant. This observation shows that \( ER\beta \) when analyzed alone does not play an important role in prostate cancer risk in the present series of cases. Consistent with our results are the observations of Fukatsu et al. (2004), who have found a non-significant association between \( ER\beta \) gene and prostate cancer risk on 147 Japanese prostate cancer patients and 266 urological controls (OR, 0.73; 95% CI, 0.46-1.16; \( P=0.182 \)).

The impact of \( ER\beta \) gene polymorphism in relation to other genes shows that there is a 2-fold high probability of risk with \( ER\beta \) Rr when combined with \( CYP1B1 \) Leu/Leu genotype and such an association has not been found in the case of other genes.

2.3 **Relationship between PR genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer**

In the present study no impact of \( PR \) genotypes on the risk of prostate cancer has been seen. Compared with the wild type A1/A1 homozygotes, the OR for A1/A2 heterozygotes is 2.32 but it is not significant statistically (95% CI, 0.72-7.47; \( P=0.158 \)) and 1.07 (95% CI, 1.73-6.61; \( P=0.942 \)) for A2/A2 homozygotes. The present results are not in agreement with those of Fukatsu et al. (2004) who have found an association of Alu of \( PR \) gene with prostate cancer risk among 147 Japanese prostate cancer patients and 266 controls (OR, 4.17; 95% CI, 1.26-13.85; \( P=0.02 \)).

A polymorphism in intron 7 of the human progesterone caused by an Alu insertion has been reported to be associated with ovarian carcinoma in a group
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of 67 patients of pooled German/Irish population (Mckenna et al., 1995). Later on, a G to T substitution in exon 4, causing a valine to leucine change in the hinge region of the receptor, and a synonymous C to T substitution in exon 5 was linked to the Alu insertion (Agoulnik et al., 1997). The association of PROGINS with breast cancer was examined in North America (68 patients and 101 hospital controls) and in the south of England (292 patients and 220 healthy volunteers) (Manolitsas et al., 1997; Lancaster et al., 1998). The allele frequency of PROGINS was slightly lower in the North American Caucasian breast cancer patients compared with the hospital controls, but the difference was not significant statistically (Lancaster et al., 1998). No difference between cases and controls was observed in the English study (Manolitsas et al., 1997).

As for combined effects, there was a 2-fold increased risk in PR A1/A2+A2/A2 in relation to CYP1B1 Leu/Leu genotype with an OR of 2.05 (95% CI, 1.03-4.11; P=0.041). Our results are in consistency with those of Fukatsu et al. (2004), who have found that the CYP1B1 polymorphism together with heterozygosity for Alu in the PR is more frequent among prostate cancer patients (1.45%) than controls (0.41%), although it is not significant statistically (OR, 3.99; 95% CI, 0.36-44.8).

The association is non-significant for CYP19, CYP17, SRD5A2, VDR and CYP2D6 genes when combined with PR gene. These results suggest that only CYP1B1 Leu/Leu genotype has some association with prostate cancer risk when combined with PR gene in North Indian prostate cancer patients.

2.4 Relationship between CYP19 genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer

In the present case-control study, an increased risk associated with CYP19 CT genotype has been found and this association is statistically significant (OR, 2.11; 95% CI, 1.02-4.35; P=0.044). Consistent with the present results are observations of Suzuki et al. (2003) who have found an association of CT and TT genotypes of the CYP19 gene (OR, 1.77; 95% CI, 1.02-3.09; P=0.037) with prostate cancer risk among Japanese population. In another study, Modugno et al. (2001) have found that the CYP19 CT genotype is associated
with an increase in risk of borderline significance (age-adjusted OR, 2.50; 95% Cl, 0.99-6.28). These data suggest that \textit{CYP19} gene could be used as an indicator for prostate carcinoma prevention in men in Asia.

The impact of \textit{CYP19} gene polymorphisms in relation to other different genes shows a 4-fold increase in risk of prostate cancer with \textit{CYP17} A1/A2+A2/A2 and \textit{CYP1B1} Leu/Val+Val/Val genotypes when combined with \textit{CYP19} CT+TT genotype and these associations were statistically significant. No association with risk was observed in \textit{CYP19} gene in relation to \textit{VDR} and \textit{CYP2D6} genes.

\textbf{2.5 Relationship between \textit{CYP17} genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer}

The 5' UTR of \textit{CYP17} contains a single T (A1 allele) to C (A2 allele) base substitution that creates a recognition site for MspAI restriction enzyme. The \textit{CYP17} polymorphism is either in linkage disequilibrium with others, as yet unidentified, genetic variations located near this site or has a direct quantitative effect on \textit{CYP17} gene expression. A positive association first reported by Carey \textit{et al.} (1994) between the A2 allele of \textit{CYP17} and hyperandrogenic diseases, polycystic ovarian syndrome and male pattern baldness compared with controls, led to the selection of \textit{CYP17} as a candidate gene for study in relation to hormone-related cancers. Several previous case-control studies have examined the relationship between polymorphism in the \textit{CYP17} promoter region and prostate cancer risk. In a North Carolinian Caucasian population, Lunn \textit{et al.} (1999) in a urology clinic-based case-control study of predominantly white men, found that carriers of the A2 allele (A1/A2 genotype) have an increased risk for prostate cancer (OR, 1.7; 95% CI, 1.0-3.0; \(P=0.05\)). In a larger study which was conducted among United States physician’s Health study cohort of 590 prostate cancer cases and 782 control, Haiman \textit{et al.} (2001) found a borderline significant association between the A2 allele (A1/A2 or A2/A2 genotypes) and prostate cancer risk (OR, 1.2; 95% CI, 0.99-1.5). In parallel, in a population-based case-control study, Gsur \textit{et al.} (2000) have reported an increased risk of A2/A2 allele among Caucasian men (OR, 2.80; 95% CI, 1.02-77.76). Yamada \textit{et al.} (2001)
from Japan have reported an OR of 2.4 (95% CI, 1.04-5.46) in men homozygous for the A2 allele compared with those with the A1/A1 genotype. Kittles et al. (2001) have found a 3-fold higher risk of A2/A2 genotype among 71 prostate cancer cases and 111 healthy individuals (OR, 2.80; 95% CI, 1.00-7.40). Habuchi et al. (2000) however, observed that men with the A1/A1 genotype have an increased risk of prostate cancer (OR, 2.57; 95% CI, 1.39-4.87). Similarly, in a Swedish study, Wadelius et al. (1999) have reported a significant elevation in the risk for the A1/A1 genotype (OR, 1.61; 95% CI, 1.02-2.53).

In the present study it has been observed that the A2 allele occurs more frequently in the prostate cancer group (15%) than in the controls (6.0%). The prevalence of the A2/A2 genotype is significantly higher (P=0.048) among Indian prostate cancer patients. Men with the A2/A2 genotype have a significant increased risk for prostate cancer (OR, 3.4; 95% CI, 1.01-11.41; P=0.048). Consistent with the results of Gsur et al. (2000), in the present study group an altered prostate cancer risk for A1/A2 heterozygotes, has not been observed (OR, 1.45; 95% CI, 0.75-2.82; P=0.268). dos Santos et al. (2002) and Cicek et al. (2004), however, have failed to found an evidence for an association between prostate cancer risk and CYP17 A2/A2 polymorphism. These data clearly indicate that genetic polymorphisms of genes involved in the estrogen metabolism pathway is different among Asian men with men of different ethnic group, which may be one of the reasons for the racial difference in prostate cancer risk.

The present results are in consistently with the observations of Lunn et al. (1999), Gsur et al. (2000), Kittles et al. (2001) and Yamada et al. (2001), but not with those of Haiman et al. (2001) and Cicek et al. (2004).

An association was found for CYP1B1 Leu/Val+Val/Val genotype with a 4-fold increase in risk of having prostate cancer when combined with CYP17 gene. The data have suggested that individuals with this genotype are at a high risk towards prostate cancer, especially when combined with CYP17 gene. No associative risk for prostate cancer has been found with polymorphism in SRD5A2, VDR and CYP2D6 genes when combined with CYP17 gene.
2.6 Relationship between SRD5A2 genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer

The SRD5A2 V89L polymorphism is caused by a G to C transversion that results in the substitution of valine for leucine at codon 89 (denoted the L allele) at exon 1. Following the hypothesis of Makridakis et al. (1997) that the L allele of the SRD5A2 gene should be protective for prostate cancer, it was tried to evaluate the genotype distribution in the present case-control study on North Indian population. No difference in the occurrence of the LL genotype between prostate cancer patients and control group was obtained. Compared with men with W genotype, there was no significant association between LL genotype and risk for prostate cancer (OR, 0.75; 95% CI, 0.33-1.70; P=0.492). There was also no association of VL genotype with prostate cancer risk (OR, 0.52; 95% CI, 0.25-1.07; P=0.078). Similarly, no association between prostate cancer and SRD5A2 polymorphism was found by Latil et al. (2001) in a case-control study of 226 patients with the pathologic diagnosis of sporadic prostate tumour and 156 healthy male controls. In a larger study of 592 prostate cancer cases and 799 controls among Caucasian population, Febbo et al. (1999), also found no significant association between LL genotype and prostate cancer risk (OR, 0.84; 95% CI, 0.57-1.24). Li et al. (2003) also failed to find significant difference in frequencies with respects to SRD5A2 genotypes in patients and controls (P=0.071) or in BPH and male controls (P=0.219). Yamada et al. (2001) from Japan and Hsing et al. (2001) from China reported a lack of association of LL genotype with risk of prostate cancer. In another case-control study among Greece population, Ntais et al. (2003) have excluded the role of V89L polymorphism in conferring the susceptibility of individuals to prostate cancer as they found no difference in the frequency of LL and W genotypes among patients and control groups (OR, 1.03; 95% CI, 0.83-1.28). Nam et al. (2003) have also found no association between the SRD5A2 polymorphism and prostate cancer risk. In a population consisting of 300 prostate cancer cases and 300-age- and race match controls, there was no association between V89L genotypes and prostate cancer risk. The age-and race-adjusted odds ratio associated with the VL and LL genotypes were 1.06 (95% CI, 0.75-1.49) and
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0.99 (95% CI, 0.57-1.73) respectively, (Lamharzi et al., 2003). In another study among the Han nationality population of North China, Liu et al., (2004) have found no significant difference of SRD5A2 genotypes between the prostate cancer patients and the controls (P>0.05).

The present results are in agreement with those of all the studies mentioned above since there is an overall lack of association of SRD5A2 V89L polymorphism with the risk for prostate cancer in North Indian population.

Also the association is weak and non-significant for SRD5A2 when combined with VDR or CYP1B1 genes. These results clearly indicate that the SRD5A2 gene does not play an important role in prostate carcinogenesis since no association has been found when studied separately or in combination with other genes. These observations need to be confirmed on a larger population group.

2.7 Relationship between VDR genotypes alone and in combination with other studied genes in relation to the risk of prostate cancer

The mechanism through which the TaqI polymorphism in the VDR gene may be influencing the risk for prostate cancer is not clear, because the TaqI and the other two VDR polymorphisms do not alter the amino acid sequences of the VDR protein. The TaqI, BsmI, and Apal polymorphisms are in strong linkage disequilibrium with poly(A) length polymorphism in the 3’ UTR (Ingles et al., 1997). Because the 3’ UTR may be involved in the regulation of VDR mRNA stability and degradation of RNA, these polymorphisms may alter its level (Morrison et al., 1994). It is also possible that these polymorphisms are in linkage disequilibrium with other mutations that alter VDR function. Morrison et al. (1994) reported higher serum levels of 1,25 (OH)2 D3 in people who are homozygous for the t allele (the active allele of VDR) relative to those who are heterozygous or homozygous for T allele. Taylor et al. (1996) have reported that men with tt genotype are at decreased risk of developing prostate cancer and a 3-fold increased risk with the T allele. Furthermore, two Japanese groups have reported that the TT genotype is associated with advanced prostate cancer and a higher mortality (Furuya et al., 1999; Hamasaki et al., 2001). However, results
about the role of VDR polymorphisms in prostate cancer susceptibility in different populations are contradictory (Watanabe et al., 1999; Blazer et al., 2000; Bousema et al., 2000; Chokkalingam et al., 2001; Luscombe et al., 2001a; Schatzl et al., 2001).

In the present case-control study of North Indian population, there is an overall lack of association between the VDR Taql polymorphism and prostate cancer risk. No association of either Tt or tt genotypes with prostate cancer risk with ORs of 0.61 (95% CI, 0.31-1.18; P=0.144) and 0.35 (95% CI, 0.10-1.20; P=0.144) respectively, has been observed. In a hospital based case-control study on a subgroup of whites, including 96 cases and 162 controls, Taylor et al. (1996) have observed that men with the homozygous tt genotype are at decreased risk of developing prostate cancer compared with the TT or Tt genotypes (tt vs. TT+Tt: OR, 0.32; 95% CI, 0.15-0.75; P<0.01). In a larger case-control study among physicians' Health study on 372 incidents prostate cancer cases and 591 controls, Ma et al. (1998) have observed no significant association of the investigated two VDR polymorphisms (Taql and Bsml) and prostate cancer risk. Similarly, in a case control study consisting of 222 prostate cancer, 209 benign prostatic hyperplasia (BPH) and 128 male controls among Japanese populations, the Taql polymorphism has not shown any significant association with either prostate cancer or BPH (Habuchi et al., 2000). Blazer et al. (2000) have also reported a lack of association between the Taql genotype and prostate cancer risk among 77 prostate cancer cases and 183 controls (tt vs. TT+Tt: OR, 1.4; 95% CI, 0.7-2.8). A lack of association with VDR Taql polymorphism has also been observed by Hamasaki et al. (2001) among 115 cases, 133 age-matched controls. Similar observations have been made by Figer et al. (2003) among Israeli and Suzuki et al. (2003) among Japanese patients. In a larger study of 1870 prostate cancer cases and 2843 controls on Greece population, comparison of tt and TT genotypes has shown no difference in the frequency of these two genotypes in prostate cancer population (OR, 0.88; 95% CI, 0.70-1.10) (Ntais et al., 2003). The frequency of VDR genotype has not been found to be significantly different between prostate cancer and male controls among Chinese population (Liu et al., 2004). Huang et al. (2004) have
investigated the association of the BsmI, Apal and TaqI polymorphisms of VDR gene with prostate cancer risk in a Taiwanese population. No significant association has been found between the Apal and TaqI polymorphisms and the risk of prostate cancer. Similar observations have been made by other authors (Nam et al., 2003; Tayeb et al., 2003; Bodiwala et al., 2004; Cheteri et al., 2004).

No statistically significant association of the TaqI polymorphism with prostate cancer has been found in a study of 190 prostate cancer and 190 age-matched men with BPH (OR, 1.76; 95% CI, 0.90-3.45) (Gsür et al., 2002). There was no suggestion of an overall effect of TaqI polymorphism with prostate cancer susceptibility in subjects of European descent (OR, 0.97; 95% CI, 0.87-1.08), Asian descent (OR, 0.88; 95% CI, 0.66-1.17), or African descent (OR, 0.94; 95% CI, 0.41-2.17) (Ntais et al., 2003). In a case-control study of 368 prostate cancer patients and 243 BPH, no association has been observed for TaqI polymorphism and risk of prostate cancer (Bodiwala et al., 2004).

In the present case-control study, the analysis of VDR gene polymorphisms in relation to CYP1B1 Leu/Leu genotype has shown a 4-fold higher probability of risk when these two genes are combined together (OR, 3.94; 95% CI, 1.30-11.91; P=0.015). Such an association with risk has not been found in case of VDR gene in relation to CYP2D6 gene.

### 2.8 Relationship between CYP1B1 genotypes alone and in combination with CYP2D6 gene in relation to the risk of prostate cancer

Several studies have been devoted to the investigation of a potential relationship between SNPs present in the human CYP1B1 gene and incidence of various forms of cancer. Most polymorphisms result in the formation of a truncated or non-functional protein.

In the present study, heterozygosity for the Leu allele (Leu/Val) has not been found to be associated with prostate cancer risk (OR, 1.88; 95% CI, 0.92-1.84; P=0.081). The individuals with the Val/Val genotype, however, have a 4-fold (OR, 3.84; 95% CI, 1.03-14.31; P=0.045) increased risk. These results are in agreement with those of Tang et al. (2000) who have found an increased risk for prostate cancer among Caucasian population in subjects homozygous for the
Leu432Val form (OR, 3.3; 95% CI, 1.9-9.0; \(P=0.03\)). In another case-control study on 147 Japanese prostate cancer patients and 266 urological controls, Fukatsu et al. (2004) have found a significant association between CYP1B1 Leu432Val polymorphism and prostate cancer risk (OR, 4.80; 95% CI, 1.21-19.05; \(P=0.026\)).

In gene-gene interaction studies, patients carrying the CYP2D6 EM genotype have a 2-fold higher risk for prostate cancer when combined with CYP1B1 Leu/Val+Val/Val genotype. Although a 3-fold higher risk has been observed with CYP1B1 Leu/Val+Val/Val genotype when combined with CYP2D6 HEM+PM genotype, it is not statistically significant.

### 2.9 Relationship between CYP2D6 genotypes alone in relation to the risk of prostate cancer

In a case-control study, Ladero et al. (1991) have found an increased risk for cancer associated with the CYP2D6 PM phenotype in women with breast cancer, a cancer with hormonal dependence. A 3-fold higher probability risk towards prostate cancer in PM genotype with an OR of 2.59 (95% CI, 0.51-12.94; \(P=0.246\)) has been observed in the present study, but this association is not statistically significant. These data show no overall statistically significant association between the B allele and prostate cancer risk.

The present results are in agreement with the study on 571 men with prostate cancer and 767 controls in Caucasian conducted population by Febbo et al. (1998) who have found a lack of significant association (OR, 1.4, 95% CI, 0.9-2.2) between the B allele of CYP2D6 gene within the Physician Health Study. Non-significant results have also been obtained by Agundez et al. (1998) in a case-control study in Spain population consisted of 94 prostate cancer patients and 160 male controls with an OR of 1.4 (95% CI, 0.4-4.6) for the poor metabolizer phenotype. In a case-control study of 147 Japanese prostate cancer patients and 266 urological controls, no association of CYP2D6 gene with prostate cancer risk has been found (OR, 5.52; 95% CI, 0.57-53.84; \(P=0.141\)) (Fukatsu et al., 2004).