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Commentary

Allelic variability in *PSA* & *AR* genes: A novel biomarker on the horizon for carcinoma prostate

Prostate specific antigen (PSA) is an androgen regulated serine protease produced by secretory epithelial cells lining of normal prostatic glands as well as in the majority of prostatic cancer[1,2]. PSA expression has been the most extensively used marker for prostate cancer screening and gauging the therapeutic response following an intervention[1,2]. The serum PSA concentration greater than 4 ng/ml is generally considered as an indicator of a potential prostatic abnormality which warrants a further screening by means of prostate needle biopsy[3]. However, PSA testing has been plagued by numerous controversies and a low sensitivity and specificity for detecting prostate cancer due to numerous factors such as presence of non-cancerous prostatic diseases (*i.e.* prostatitis or benign prostatic hyperplasia) which are very common in India and its variation among different ages and races[4]. To negate the effect of age and race to serum PSA levels there are age- and race-specific cut-off values for serum PSA testing[5,6]. However, there still remains substantial controversy regarding the use of such cut-offs as these are weighed down by further decreased sensitivity for detection of prostate cancer[7].

The PSA gene contains a 6-kb promoter in the 5′ region that contributes to tissue and hormone specificity of PSA expression[8-10]. This promoter contains androgen-responsive elements (AREs) that regulate promoter activity by binding to androgen receptors. ARE I and II are located in the proximal region of the PSA promoter centered at -170 base pairs (bp) and -394 bp, respectively while ARE III is located in the 5′ upstream enhancer region, centered at -4200 bp with respect to the transcription start site[8-11]. ARE I and ARE III are both found to have high affinities for the androgen receptor, whereas ARE II has a low affinity for the androgen receptor[11-14]. Further research into these promoter regions has demonstrated the presence of additional high, medium, and low-affinity AREs within the 5′ upstream enhancer region of the PSA promoter located between -3870 bp and -4366 bp with respect to the transcription start site[14]. Chavan *et al*[15] in their study in this issue have calculated the influence of genetic variants exhibited by *PSA* and androgen receptor (*AR*) genes towards the variable expression of PSA in prostate cancer. *PSA* genotype analysis in promoter region and *AR* gene microsatellite Cytosine / Adenine / Guanine (CAG) repeat analysis in exon 1 region was studied. They found SNPs 158G/A in the proximal promoter region and -3845G/A in enhancer region to be significantly (P<0.001) associated with serum PSA levels[15]. The carriers of homozygous GG genotype showed higher expression of PSA whereas homozygous AA genotype carriers demonstrated lower PSA levels. The authors also found that homozygous GG genotype along with AR long CAG repeats and homozygous AA genotype along with AR short CAG repeats at position -3845 and -158 showed strong interaction and thus synergistically influenced serum PSA levels. Xue *et al*[16] in their study of 420 healthy men from a multiethnic cohort found that men with PSA AA genotype and short *AR* CAG alleles have higher PSA levels. Cramer *et al*[17] found -4643 /A SNP (G allele) is associated with higher mean PSA levels. These studies have further emphasised the enigma of the cut-off level for PSA[16-19]. The role of PSA as a screening marker for prostate cancer has been severely questioned following the Prostate, lung, colorectal and ovarian (PLCO) cancer screening trial[19]. To incorporate SNP in the promoter region of *PSA* gene into the genetic model for prostate cancer may help in improving the sensitivity and specificity of PSA as a screening tool but these studies need to be taken on a larger scale preferably on a prospective multicentric and multiethnic group to validate these findings.

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