

5451 Polymorphisms in the human 5 α -reductase gene and breast cancer. Scorilas, A., Bharaj, B., Glai, M., Diamandis, E.P. *Department of Pathology and Laboratory Medicine, Mount Sinai Hospital and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, M5G 1X5, Canada [A.S., B.B., E.P.D.]. Department of Gynecologic Oncology, Institute of Obstetrics and Gynecology, University of Turin, Turin, 10126, Italy [MG].*

There is an increasing amount of evidence that androgens play a significant role in the development and progression of breast cancer. The SRD5A2 (5- α -reductase) gene harbors two frequent polymorphic sites, one in the coding region, at codon 89 of exon 1, where valine is substituted by leucine (V89L) and the other in the 3' untranslated region where a variable number of dinucleotide TA repeat lengths exists. Both polymorphisms are known to alter the activity of this enzyme which is expressed in androgen dependent tissues and it catalyses the reduction of testosterone to its more bioactive form dehydrotestosterone which transactivates a number of genes. The aim of this study was to evaluate the role of these polymorphisms in breast cancer prognosis. We examined 144 sporadic breast tumors from Italian patients as well as the whole blood of 70 women without cancer for the V89L and TA polymorphisms by sequence and fragment analysis, respectively. Tumor extract prostate-specific antigen concentration as well as a number of well-established clinical and pathological parameters were evaluated. The results showed that TA(0) repeats were found in tumors with VV, LL and VL genotypes. TA(9) repeats were only found in VV homozygotes and were totally absent from either LL homozygotes or VL heterozygotes. PSA expression was significantly elevated in tumors with VV genotype. We found that the LL genotype was also associated with earlier onset and more aggressive forms of breast cancer. The presence of LL alleles in breast tumors was associated with earlier onset and shorter disease-free (RR = 2.66; P = 0.013) and overall survival (RR = 3.06; P = 0.014) rates. Patients with long TA repeats and VV genotype appeared to have more favorable prognosis. We are currently pursuing the significance of the above polymorphisms in breast cancer susceptibility.