

#5116 THE GENOTYPES OF THE 5 α -REDUCTASE GENE ARE RELATED WITH PSA EXPRESSION AND RISK IN SPORADIC BREAST CANCER. Andreas Scorieas, B. Bharaj, B. Hoffman, M. Giai, and E. P Diamandis, *Mount Sinai Hosp, Toronto, ON, Canada, Univ of Toronto, Toronto, ON, Canada, and Univ of Turin, Turin, Italy*

5-alpha-reductase (SRD5A2), an enzyme that is expressed in androgen dependent tissues, catalyzes the reduction of testosterone (TT) to its more bioactive form, dihydrotestosterone (DHT), which in turn transactivates a number of genes. The SRD5A2 gene harbours 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 (3' UTR), where a variable number of dinucleotide TA repeat lengths exists. Both polymorphisms are known to alter the activity of this enzyme. We examined 151 sporadic breast tumors from Italian patients for the V89L and TA polymorphisms by sequence and fragment analysis, respectively. Total prostatic specific antigen (PSA) concentration in all samples was measured with an ultrasensitive time-resolved immunofluorometric assay, which utilizes two monoclonal antibodies specific for PSA and has a detection limit of 0.001 ng/mL. The results showed that PSA expression was significantly elevated in tumors with VV genotype ($p=0.03$). LL genotype was found more frequently in younger patients (below 45 years) as well as in grade III patients ($P=0.008$ and $P=0.037$ respectively). The presence of LL alleles in breast tumors was associated with shorter disease-free ($p=0.01$) and overall survival ($p=0.01$) rates. A statistically significant association between high PSA concentrations and both TA(0)/TA(9) and TA(9) allelotypes was observed ($P=0.004$). These allelotypes were found rarely in patients at stage III or IV disease. Patients with TA(0)/TA(9) or TA(9) repeats, when compared to those with homozygous TA(0) allele, showed a significant reduction in the risk for relapse ($p=0.04$). Our results suggest that the genotype of codon 89 and the TA repeat length of the 5 α -reductase gene are associated with sporadic breast cancer aggressiveness and age of onset, likely due to altered androgen metabolism.