Functional Genetic Polymorphisms in the CYP19 Gene Decrease the Risk of Prostate Cancer and Alter the Response to Androgen Deprivation Therapy

Introduction and Objective: Genetic polymorphisms in the CYP19 gene (*CYP19*), which encodes aromatase involved in estrogen biosynthesis, are reported to be associated with a risk of prostate cancer and prognosis of prostate cancer patients. In this study, we investigated whether the genetic polymorphisms in *CYP19* affect the risk of prostate cancer, serum hormone levels (testosterone, estorone [E1], and estradiol [E2]), gene expression, response to hormonal therapy, and prognosis of prostate cancer patients.
Materials and Methods: We obtained the DNA samples isolated from the blood of 330 prostate cancer patients and 354 normal individuals. Three single nucleotide polymorphisms (SNPs) of *CYP19*, rs10459592, and rs4775936 in the promoter region of exon 2 and rs2470152 in intron 1 were genotyped, and the data were used for the case-control study, circulating hormone level analysis, and survival analysis. Reporter gene assays were performed to assess the promoter activity of *CYP19*. Reporter gene constructs including the two SNPs (rs10459592, rs4775936) were cloned into the pGL4 luciferase reporter vector. PC3 cells were transfected with the constructs. All reporter assays were performed four times or more.
Results: In the case-control study, each variant allele of the three SNPs significantly decreased the risk of prostate cancer. We examined the influence of each SNP on the serum hormonal level of TS, E1, and E2 in healthy men. The E1 to androstenedione ratio was significantly higher in men with a variant allele of each SNP. Haplotype analysis between rs10459592 and rs4775936 showed that the *AG* haplotype increased the risk of prostate cancer in a gene-dosage manner while the *CA* haplotype decreased the risk in a similar manner. A reporter gene assay in PC3 prostate cancer cell line revealed that the promoter activity of the *CA* haplotype was significantly lower than that of the *AG* haplotype (p=0.034). Patients with each variant allele had a significantly higher PSA nadir level (p=0.019 [rs10459592], p=0.016 [rs4775936]) and significantly shorter cancer-specific survival.
Conclusions: Genetic polymorphisms in *CYP19* may influence the serum hormone levels by modifying the promoter activity and affect the risk of prostate cancer, response to hormonal therapy, and survival.