HSD3B1 (1245A>C) germline variant and prostate cancer progression in low- and favorable intermediate-risk patients

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Background: Prostate cancer (PCa) progression depends largely on androgen receptor signaling. The common missense variant rs1047303 in *HSD3B1* stimulates production of bioactive androgens, with the 1245C allele associated with resistance to androgen deprivation therapy and poor clinical outcomes. However, it is unknown whether *HSD3B1* 1245C is associated with progression in patients diagnosed with low- and intermediate-risk PCa, particularly those who would be eligible for active surveillance rather than receiving immediate definitive treatment.

Methods: Patients were from the Canary Prostate Active Surveillance Study (PASS; N=1,220), which included clinically localized PCa patients monitored on an active surveillance protocol and enrolled between 2008-2017, and the Health Interview Study of Men and Prostate Cancer Research Study (HIM/PROS; N=780), which included patients with low- or favorable intermediate-risk PCa who were eligible for active surveillance and enrolled between 1993-1996 and 2002-2005. Associations between *HSD3B1* 1245C and PCa outcomes (upgrading and extreme upgrading in PASS; biochemical recurrence, metastasis, and PCa-specific death in HIM/PROS) were evaluated using competing risk and Cox proportional hazards models.

Results: PASS patients had a median of 6.0 years (IQR: 4.1-8.3, max 19.0 years) of follow-up, while HIM/PROS patients had a median of 16.6 years (IQR: 14.6-22.1, max 26.8 years) of follow-up. In PASS, the 10-year cumulative incidence of extreme upgrading among patients monitored on active surveillance with the CC genotype was 26%, compared to 17% for those with AC and 14% for those with AA genotypes (P=0.035). Compared to AA, the CC genotype was associated with 2.06-fold higher hazard of extreme upgrading within 10 years of diagnosis (95% CI=1.25-3.39, P=0.005), whereas AC had a null association (HR=1.22, 95% CI=0.85-1.75, P=0.27). In HIM/PROS, although *HSD3B1* 1245C was not significantly associated with adverse outcomes, patients with the CC genotype had slightly higher cumulative incidences of PCa death, metastasis, and early biochemical recurrence.

Conclusions: Our findings demonstrate the relevance of *HSD3B1* in low- to intermediate-risk PCa patients, with 1245C associated with increased 10-year risk of extreme upgrading in patients monitored on active surveillance. This suggests the potential for *HSD3B1* 1245C to inform PCa management at early and treatable disease stages.

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