

TITLE: DIABETES AND HER2 INTERACT TO MODIFY PROSTATE CANCER OUTCOMES

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BACKGROUND: Prostate cancer (PC) disproportionately burdens Black men and is frequently complicated by metabolic comorbidities. Diabetes mellitus (DM) is associated with reduced PC incidence yet worse outcomes once PC is established. HER2/*ERBB2*, mechanistically linked to insulin signaling, represents a proposed bridge between metabolic disease and aggressive PC biology. We evaluated whether DM is associated with recurrence and survival, whether HER2 mediates or independently influences these risks, and whether DM and HER2 interact to modify outcomes in a racially diverse cohort.

METHODS: We conducted a retrospective cohort study of 517 men with Stage I–III PC who underwent radical prostatectomy (2009–2020) using data from the Department of Defense Prostate Cancer Biorepository Network and The University of Alabama in Birmingham Tissue Biorepository. HER2 was assessed by immunohistochemistry on tissue microarrays, and West African genetic ancestry was estimated from 105 ancestry-informative markers. Logistic regression evaluated clinical recurrence; Cox proportional hazards models assessed time to recurrence (TTR) and overall survival (OS). Firth penalized regression examined DM×HER2 interactions.

RESULTS: DM (8.1%) was more prevalent among older Black men with higher West African genetic ancestry and BMI (all $p < 0.05$). DM was not associated with recurrence, TTR, or OS, and HER2 did not mediate any DM-outcome relationship. HER2-positivity paradoxically associated with reduced recurrence risk (OR=0.49, $p=0.004$) while independently predicting nearly 5-fold higher mortality (HR=4.71, $p=0.031$) and shorter TTR (HR=1.48, $p=0.2$). Kaplan-Meier analyses confirmed significantly different TTR distributions by HER2 status and combined HER2/DM status (both log-rank $p < 0.05$). DM was protective against recurrence in HER2-negative patients (TTR HR=0.10, $p=0.022$), but this effect was abolished in HER2-positive disease (interaction HR=9.79, $p=0.053$).

CONCLUSIONS: DM was not independently associated with PC outcomes in this surgically treated cohort. HER2-positive status independently predicted mortality, potentially reflecting PSA-independent lethal progression. The DM×HER2 interaction warrants validation in larger cohorts. These findings support HER2 as a clinically meaningful prognostic biomarker and therapeutic target in PC.

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