AKT1/ESR1 and AR/PTEN Alterations Define Cancer-Specific Bone Metastasis in Breast and Prostate Cancer

Cindy Xindi Wang, Paul Guirguis, Mark Youssef, Mina Botros, Susan Marie McDowell

INTRODUCTION:

Bone metastases (BM) are a major cause of morbidity in patients with advanced breast cancer (BC) and prostate cancer (PC). Identifying genetic alterations associated with BM could improve early detection and targeted treatment strategies. The objective of this study was to analyze genomic differences between patients with and without BM in BC and PC, with the goal of identifying cancer-specific genetic drivers of bone metastasis.

METHODS:

We conducted a retrospective genomic analysis using data from cBioPortal, sourced from a large-scale metastatic cancer study (Nguyen et al., Cell 2022). The dataset included 25,000 patients with metastatic disease, of which 4,006 had BM and 6,137 had no bone metastasis (NBM). Subgroup analysis focused on breast cancer (BC-BM, n=769) and prostate cancer (PC-BM, n=658) patients with BM. Comparative genomic analysis was performed between: (1) BM vs. NBM groups, (2) BM vs. NBM within each cancer type, and (3) BC-BM vs. PC-BM to assess cancer specificity. Statistical significance was set at $P < 0.05$. Additionally, the impact of identified genes on survival was evaluated using multi-study cohorts for BC (n=11,657) and PC (n=10,042).

RESULTS:

Fifty-nine genetic alterations were significantly enriched in the BM group compared to the NBM group. Further stratification revealed eight BM-associated alterations in PC and three in BC. After excluding overlapping genes between BC-BM and PC-BM, two cancer-specific genes per group remained: AKT1 and ESR1 in BC-BM, and AR and PTEN in PC-BM. Survival analysis demonstrated significant associations between these genes and patient outcomes (see Table 1).

DISCUSSION AND CONCLUSION:

This study identified distinct, cancer-specific genetic alterations in BC and PC that are enriched in bone metastases and correlate with survival outcomes. The findings suggest that AKT1 and ESR1 may play key roles in BC bone metastasis, while AR and PTEN alterations are prominent in PC bone metastasis. Further investigation is needed to validate these biomarkers and assess their potential clinical utility in early detection, risk stratification, and targeted therapy for bone metastases.