

Amine and lipid metabolites are enriched in advanced prostate cancer

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Background: Obesity is an established risk factor for advanced prostate cancer. We performed whole body metabolomics profiling to identify altered metabolism associated with advanced disease and the extent to which obesity modifies this association.

Methods: Our study was nested in the US Health Professionals Follow-up Study during the study period 1993 to 2014. We selected 212 advanced prostate cancer (\geq stage T3b or lethal during follow-up) patients and 212 matched controls. Metabolomics profiling was performed at the Broad Institute on pre-diagnostic bloods measured a median 6 years before diagnosis. The advanced profiling platform used liquid chromatography-tandem mass spectrometry for 295 known metabolites. We estimated odds ratios and 95% confidence intervals using multivariable conditional logistic regression and performed pathway analysis adapted from gene set enrichment analysis (GSEA) with an $FDR < 0.10$.

Results: We identified 29 circulating metabolites in prediagnostic bloods that were significantly associated with advanced prostate cancer risk: carnitines and phospholipids, 11 diacylglycerols (DAG) and 12 triacylglycerols (TAG). Using pathway analyses, we found metabolites in DAG and TAG pathways were highly significantly ($FDR < 10^{-8}$) enriched in advanced prostate cancer. 166 of the 295 metabolites were significantly ($p < 0.001$) associated with obesity. When we stratified by a man's obesity status, we observed unique metabolomics profiles associated with advanced prostate cancer. Circulating amines (including carnitines) were associated with advanced prostate cancer in overweight men while lipid metabolites (including DAGs and TAGs) were enriched in advanced prostate cancer among the healthy weight men.

Conclusions: Altered levels of TAG and DAG metabolites in prediagnostic bloods are strongly associated with an increased risk of advanced prostate cancer, independent of obesity. The finding that circulating amines and carnitines were specifically associated with advanced prostate cancer in overweight patients is in line with experimental data showing dysregulation fatty acid metabolism in lean versus overweight mice.

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