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Copper Isotope Fractionation and Copper-to-Zinc Ratios as Diagnostic Markers of Prostate Malignancy

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Prostate cancer is the third most common and second most deadly malignancy diagnosed in the United States. Prostate-specific antigen testing was previously used for its routine detection, but patterns of overtreatment led to recommendations against this practice; therefore, finding alternative diagnostic biomarkers remains necessary. Copper isotopes have arisen as potential biomarkers of cancer in recent years. Studies have shown a significant decrease in the $^{65}Cu/^{63}Cu$ ratio ($\delta^{65}Cu$) of blood serum in breast, colorectal, ovarian, and thyroid cancer patients [1]. Copper-to-zinc ratios have also been found to deviate from healthy controls in various malignancies [1]. Separately, historical reports found elevations in serum copper levels of prostate cancer patients and extensive copper uptake into the primary tumor mass [2]. This prior research supports the hypothesis that $\delta^{65}Cu$ measurements can potentially serve as prostate cancer diagnostic markers.

In this study, we measure the serum concentrations of copper and zinc as well as copper isotopic fractionation in 101 patients with various stages of prostate malignancy and 21 healthy controls. The results show that patients with early-stage malignancies without prostate resections have serum significantly enriched in ^{65}Cu compared to healthy controls ($p = 0.00047$) and to patients with metastatic malignancy who had prostate resections ($p = 0.00001$), an enrichment opposite to what has been previously observed in other malignancies. Patients with metastatic cancer and prostate resection notably do not differ significantly from healthy controls. Cu/Zn ratios also vary more widely in cancer patients compared to healthy controls. The observed trends may be explained by metabolic changes occurring in certain prostate cancer phenotypes in which the cells undergo mitochondrial enrichment [3] (with mitochondria favoring ^{63}Cu), thereby sequestering Cu with low $\delta^{65}Cu$ in the mass. These observations support copper isotopes' use for the early detection of prostate malignancy.

[1] Télouk et al. (2015), *Metallomics* 7, 299-308.

[2] Denoyer et al. (2016), *Oncotarget* 7, 37064–37080.

[3] Grupp et al. (2013), *Molecular Cancer* 12, 145.