KIDNEY CANCER

Improving understanding of the obesity paradox in ccRCC

> Upregulation of TGFβ, hypoxia, epithelial-to-mesenchymal transition and angiogenesis pathways was seen in tumours from obese patients compared with those from normal-BMI patients

Insight into the mechanisms underlying the obesity paradox in clear cell renal cell carcinoma (ccRCC) has been gained from the results of a new study published in *Lancet Oncology*.

The obesity paradox is the observation that obesity as defined by the WHO (a body mass index (BMI) of ≥30 kg/m^2) is a risk factor for developing ccRCC, but obese patients with localized or metastatic ccRCC have increased survival compared with those with a normal BMI (18.5–24.9 kg/m^2). However, the biological mechanisms underlying this observation are not well understood.

To address this lack of understanding, Sanchez, Furberg et al. undertook a cohort study to investigate transcriptomic differences between primary tumours and peritumoural adipose tissue in obese patients and those within the normal BMI range. The investigators assessed patient data including overall survival and gene expression differences from the COMPARZ trial and The Cancer Genome Atlas (TCGA) and overall survival in an observational immunotherapy cohort from Memorial Sloan Kettering Cancer Center (MSK). Patients in each cohort who were in the overweight category according to their BMI value were excluded.

To show that the obesity paradox was present in these cohorts, survival was analysed. In the COMPARZ trial, 57 of 128 (45%) obese patients and 76 of 128 (59%) normal-BMI patients died. After adjusting for International Metastatic RCC Database Consortium (IMDC) risk score, median overall survival was 35.7 months for obese patients versus 19.1 months for patients with normal BMI. In the TCGA cohort, 19 of 55 (35%) of obese patients died compared with 28 of 38 (76%) of normal-BMI patients. Median overall survival was not reached in obese patients versus 25.3 months in those with normal BMI after adjusting for stage and grade. In the MSK cohort, 25 of 66 (38%) obese patients died compared with 36 of 63 (57%) patients with normal BMI. Overall survival was 49.9 months for obese patients versus 15.6 months for normal-BMI patients; however, this inverse association between weight and survival did not remain statistically significant after adjustment for IMDC risk score.

After confirming that obese patients survive longer than patients with a normal BMI, the investigators analysed differences in the transcriptome between tumours from obese and normal-BMI patients in the COMPARZ trial. Upregulation of TGFβ, hypoxia, epithelial-to-mesenchymal transition and angiogenesis pathways was seen in tumours from obese patients compared with those from normal-BMI patients. Metabolic pathways, such as adipogenesis, glycolysis and fatty acid metabolism, were also enriched in tumours from obese patients. Gene-set enrichment analysis showed angiogenic differences between tumours from obese and normal-BMI patients, with higher angiogenesis scores in tumours from obese patients. However, local inflammation did not seem to be increased.

Immune deconvolution to characterize differences in tumour immune microenvironment showed total immune infiltration, macrophage, neutrophil, overall myeloid immune cell and T cell infiltration scores were not significantly different. Furthermore, no differences in tumour total mutational burden were seen. Thus, differences in the immunological milieu of the peritumoural fat between tumours from patients with normal BMI and obese patients were examined. Increased expression of canonical inflammatory signatures and immune infiltration was seen in peritumoural fat from obese patients.

"Contrary to our expectations, we did not find a significant difference in tumoural immune cell infiltration pathways between the two groups. However, when we interrogated gene expression differences in the peritumoural fat by BMI, we found that obese patients exhibited increased expression of inflammatory pathways compared with normal-BMI patients," co-first authors Alejandro Sanchez and Helena Furberg tell *Nature Reviews Urology*. "These results led us to hypothesize that important crosstalk might occur between the adipose tissue surrounding the kidney and the tumour," Sanchez continued. "Our findings provide new insights into the mechanistic underpinnings of the obesity paradox and help explain why patients with ccRCC classified as obese by BMI have better outcomes than patients who are normal weight when treated with targeted therapies and immunotherapies," Furberg added. "Importantly, more research is needed before we tailor a patient's treatment programme based on their body size."

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