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The impact of suspected promoters on the clonal architecture of normal tissues from RCC patients

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Cancer is thought to result from the gradual accumulation of genetic mutations in a cell. Environmental and lifestyle exposures to mutagenic agents and endogenous processes may cause mutations in normal cells. Collections of these cells (clones) harbouring driver mutations can exist in different tissues without ever transforming into cancer. However, recent evidence suggest that non-mutagenic promoting stimuli can drive phenotypically normal clones toward malignant transformation.

In the case of renal cell cancer (RCC), high body-mass index (BMI), tobacco smoke and hypertension have been identified as factors associated with an increased risk to develop cancer, however, no evidence of a mutagenic effect of these factors has been found. PROMINENT will try to determine how specific risk factors and exposures influence the clonal architecture of normal tissues.

The International Agency for Research on Cancer (IARC) are unique for their large collection of normal human tissues from cancer patients. This collection includes nearly 1000 renal tissues from 11 countries, ranging from low to high RCC incidence. Accompanying these samples are detailed information on the individuals' lifestyles and exposures, including information on suspected promoters associated with higher RCC risk. IARC will select normal tissue samples from 100 RCC cases to be characterised using different genomic and spatial-omics methodologies. The Institute for Research in Biomedicine (IRB) will perform duplex sequencing utilising a panel of 9 known RCC driver genes. This analysis should accurately identify mutations in normal tissues and reveal their clonal architecture.

Preliminary results have revealed clones possessing mutations in the panel of 9 driver genes analysed. The sequencing of more cases will provide power to explore if different risk profiles based on the exposure to suspected promoters could have an impact on the clonal structure of normal renal tissues. Additionally, geographical trends could emerge to link clonal architecture to higher-risk regions and possible region-specific exposures. This could further elucidate the non-mutagenic factors promoting RCC onset in high incidence countries.

Through understanding the link between exogenous factors and RCC risk, the promoting stimulus causing malignant transformation could be identified, leading to tools to for the prevention of this cancer.

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