First seeds of kidney cancer sown in adolescence

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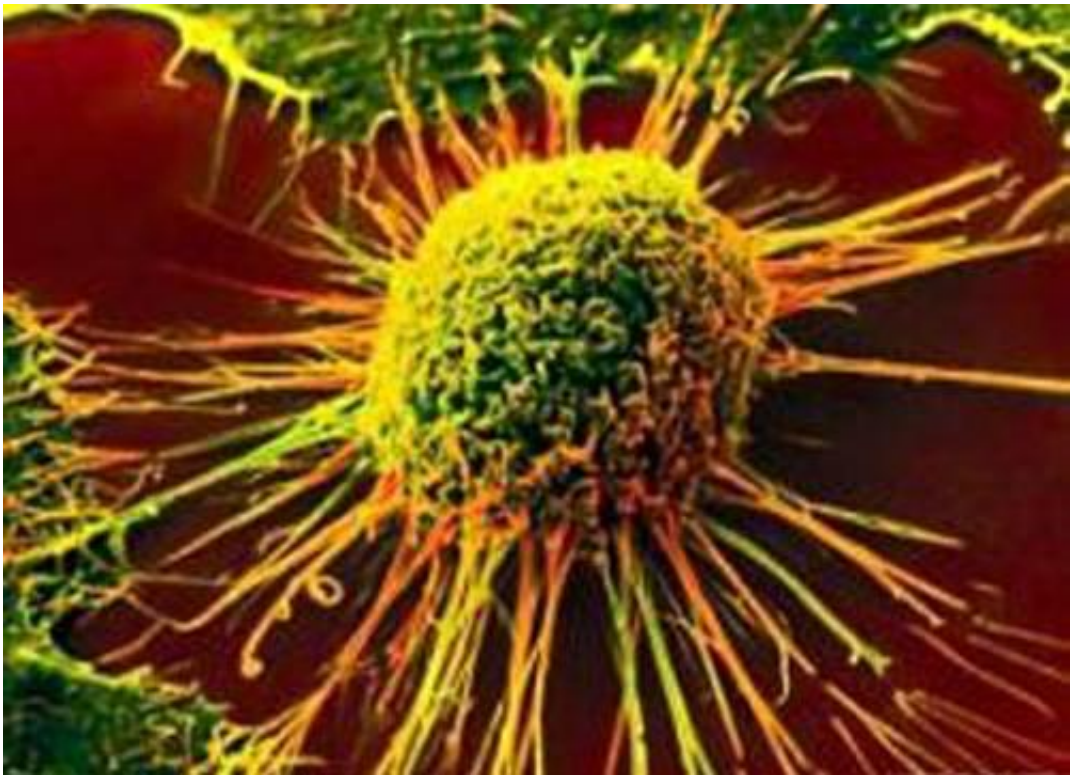

The earliest critical genetic changes that can lead to kidney cancer have been mapped by scientists. The first key genetic change occurs in childhood or adolescence, and the resulting cells follow a consistent path to progress into kidney cancer four or five decades later, scientists from the Wellcome Sanger Institute, Francis Crick Institute and their

collaborators have found.

The results, reported today (12 April) in *Cell*, suggest that whilst most of us carry these 'kick-starter' cells, they will not develop into cancer unless triggered by further mutations. The insights from this study present an opportunity to develop approaches for early detection and early intervention in kidney cancer, particularly in high-risk groups such as those with an inherited risk of the disease.

Kidney cancer was the seventh most common cancer in adults in the UK in 2014, with 12,500 new cases. Treatment options for the cancer include surgery, chemotherapy and radiotherapy.

To understand more about what kick starts kidney cancer, scientists used genomic archaeology techniques to dig into the genomes of kidney tumours and reconstruct the first genetic changes that take place.

Researchers from the Wellcome Sanger Institute, Francis Crick Institute and their collaborators sequenced and analysed the whole genomes of 95 kidney cancer tumours from 33 patients. The team discovered the first significant genetic changes, or driver mutations, in kidney cancer take place very early in life, on average in early teenage years.

The scientists found there are initially only a few hundred cells with these genetic changes, and it is likely that most of us have some of these rogue cells in our kidneys. However, kidney cancer develops in one to two per cent of the population. The cells remain dormant for four or five decades and do not progress into kidney cancer unless triggered by further mutations. Risk factors for these cells progressing to full-blown cancer include smoking, obesity and an inherited risk of kidney cancer.

Dr Peter Campbell, corresponding author from the Wellcome Sanger Institute, said: "We can now say what the initiating genetic changes are

in kidney cancer, and when they happen. What is remarkable is that the hallmark genomic event that characterises kidney cancer takes place on average 40 to 50 years before the cancer is diagnosed. These first seeds are sown in childhood or adolescence - knowing the sequence of events and their timings opens opportunities for early intervention."

Researchers discovered that the first mutation is the loss of chromosome 3p in more than 90 per cent of kidney cancer patients studied.

Dr Thomas Mitchell, joint first author from the Wellcome Sanger Institute and Addenbrooke's Hospitals NHS Foundation Trust, University of Cambridge, said: "We uncovered that the genetic change initiating kidney cancer in most people is the deletion of chromosome 3p, which takes with it several tumour suppressor genes. We also found around 35-40 per cent of patients simultaneously gain chromosome 5q in a process called chromothripsis - the shattering and rearrangement of chromosomes that causes several mutations at once."

Professor Charles Swanton, joint corresponding author from the Francis Crick Institute and Cancer Research UK's chief clinician, said: "Understanding how cancers develop and evolve over time is likely to be critical in helping us piece together the information that will point the way to new treatment approaches and predicting outcomes. We hope that in the future this work will help tailor surgical and medical intervention to the right patients at the right time."

More information: Thomas J. Mitchell et al, Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal, *Cell* (2018). DOI: 10.1016/j.cell.2018.02.020

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