PERSPECTIVE


Beyond the genome

We need to combine epidemiology and exposures research to fulfil the potential of precision medicine, say **John Leppert** *and* **Chirag Patel**.

People diagnosed with kidney cancer often ask 'Why?' The diagnosis prompts patients to examine their family history, or consider whether they have a history of exposure to a possible carcinogen. Many people ask whether their diet, health behaviours (such as smoking, drinking alcohol or lack of exercise) or other issues (such as hypertension or chronic kidney disease) could have caused their disease. They wonder what behavioural changes they should make to maximize their chance of responding to treatment or to decrease their odds of recurrence after surgery. Unfortunately, we have few answers to any of these questions. That state of ignorance must change.

Granted, our understanding of the biology of kidney cancer has advanced at a remarkable pace over the past 20 years. Molecular classification has reshaped our understanding of the disease, which is now considered to be a group of cancers that arise from the kidney, each with a distinct biology and prognosis. The discovery of mutations in the *VHL* gene has helped to identify the importance of angiogenesis in the most common subtype of kidney cancer[1]. Efforts such as The Cancer Genome Atlas have catalogued additional molecular and genetic events that are thought to be related to oncogenesis, and have identified disease-specific alterations and potential new therapeutic targets[2]. Commendable as these efforts are, we think that they are fundamentally flawed because they overestimate the importance of the role of genetic variation in kidney cancer. This mindset has encouraged the misperception that precision-medicine efforts alone can deliver truly patient-centred care and an attendant improvement in public health.

The most fundamental questions begin with 'why'. Not only patients' poignant query: "Why me?" But also broader issues, such as: why is kidney cancer one of the few cancers with a steadily increasing incidence? The increased use of abdominal imaging can only partly explain this phenomenon: the rise in incidence pre-dates the widespread use of sensitive abdominal imaging studies[3]. To address the 'why' questions, the knowledge gap must be filled by epidemiological and risk-factor research.

Efforts to investigate the epidemiology of kidney cancer have established several potential patient-level and environmental risk factors[4]. Smoking and obesity are known, but modest, factors. Exposure to substances such as asbestos and solvents have also been tentatively associated with the disease, but don't affect clinical decisions. However, conventional epidemiology studies examine a single exposure at a time, and in cases where strong observational evidence has implicated an exposure, few attempts have been made to validate the link. Furthermore, these studies often lack detailed clinical, oncological and therapeutic data, making it hard to associate an exposure with the onset of cancer. These challenges have resulted in a highly fragmented body of literature that is subject to reporting bias and is unlikely to be reproducible, and that, therefore, has had little impact on clinical decisions.

We can do better. To untangle complex cancers, we must analyse and embrace the complexity of environmental and patient-level factors. Epidemiology, when partnered with bioinformatics, genetics and epigenetic exploration, is poised to dramatically accelerate our understanding of the aetiology of kidney cancer. Analysing exposure and outcome data from existing data sets is an ideal way to target specific exposures that warrant further investigation. For example, electronic health records can now provide comprehensive information about a person's medical history. Cohorts such as the US Women's Health Initiative have stored biospecimens to allow investigators to connect molecular changes with cancer outcomes. These data sets, as well as those in cancer registries, provide a cost-effective way to assess kidney-cancer risk so that genetic and environmental influences are taken into account. Furthermore, merging these already valuable data sets is an opportunity to increase the discovery yield — and replication — of patient-level risk factors in kidney cancer.

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Historically, population-level environmental exposure data has been difficult to collect and to link with cancer incidence, so extending and expanding ongoing cohort studies to provide both genomic and exposure data is crucial. For example, linking the US National Health and Nutrition Examination Survey (NHANES), which contains an unprecedented number of patient-level risk factors and biomarkers of environmental exposure, to national cancer registries would allow us to discover associations between environmental exposures, cancer incidence and clinical outcomes. Population-level exposure data would allow us to develop better predictive models that use more of the relevant variables than just genetic information.

To modernize kidney-cancer epidemiology so that it is geared towards a precision-medicine approach will require a multidisciplinary approach to integrate these diverse data sets. The potential gains from this work cannot be overstated. These data and collaborations are paramount to understanding the importance of newly discovered gene alterations and gene–environment interactions. They will also provide clues as to which populations of patients are most likely to respond to new therapies, and offer insight into the mechanisms of resistance. And, most importantly, they could help to answer "Why?" Understanding the aetiology of kidney cancer may answer the greatest question of all — how do we prevent or significantly reduce its incidence at a population level? ■

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