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International cancer seminars: a focus on kidney cancer

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Recent years have seen important advances in our understanding of the etiology, biology and genetics of kidney cancer. To summarize important achievements and identify prominent research questions that remain, a workshop was organized by IARC and the US NCI. A series of 'difficult questions' were formulated, which should be given future priority in the areas of population, genomic and clinical research.

Key words: kidney cancer, genomics, epidemiology, clinical research

introduction

Recent years have seen important advances in our understanding of the etiology, biology and genetics of kidney cancer, some of which have been accompanied by impressive clinical advances. While these have occurred at a time when the incidence of kidney cancer among adults continues to increase in North America and most parts of Europe, elsewhere globally, rates remain stable. In order to summarize important achievements and identify prominent research questions that remain for kidney cancer, a workshop was organized by the International Agency for Research on Cancer (IARC) and the US National Cancer Institute (NCI) in the Spring of 2015. Based on a review of major themes in population, genomic and clinical research, a series of 'difficult questions' were formulated, which should be given future priority within each of these areas.

overview

Worldwide, it is estimated that there are over 300 000 new cases of kidney cancer per year. Rates are generally lower in most parts of Asia and Latin America when compared with Europe and North America [1]. In the United States, kidney cancer incidence varies across distinct populations, with rates highest among African Americans and lowest among Asian Americans. In Europe, a particularly notable feature is the strikingly high rate observed in the Czech Republic, with elevated rates observed in surrounding regions including Slovakia, the Baltic countries, eastern Germany and Northern Italy [2], yet there is no evident explanation to account for this geographic pattern.

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There is also a consistent male to female excess of kidney cancer observed in both low- and high-incidence regions that is similarly not explained. Understanding these basic epidemiologic patterns of kidney cancer across the world could lead to insights into the biological mechanisms that contribute to this malignancy. Genetics and differences in detection of asymptomatic cases from diagnostic imaging could partially explain these geographic and ethnic discrepancies, although it is also likely that exposures and lifestyle choices contribute. The main established risk factors of kidney cancer are elevated body mass index (BMI), hypertension and tobacco use [3], which have moderate estimated effects.

Kidney cancer includes a spectrum of pathologies that can vary substantively, both with respect to rare inherited and sporadic forms, although clear cell renal cell carcinoma (ccRCC) is the most common. Family and population-based studies have successfully identified key components of the underlying genetic architecture of susceptibility to kidney cancer. Family studies have uncovered a series of rare but highly penetrant mutations, such as in the *VHL* gene, which not only have proven to be useful for screening and counseling in families laden with kidney cancer across generations but also for highlighting the importance of the VHL pathway in sporadic ccRCC [4]. Other rare syndromes have revealed important insights into additional key genes for different kidney cancer subtypes and together have emerged as a panel for testing in kidney cancer family screening [5]. Using genome-wide association studies, it has been possible to detect a fraction of the common variants conferring susceptibility to kidney cancer; these possess smaller estimated effects and tend to fall in regulatory regions that have an impact on redundant, key pathways related to kidney cancer development [6–9]. Building on the knowledge of rare mutations and common variants, it is now possible to begin to build a polygenic risk model that will predict the familial risk for family members of a newly diagnosed case.

The application of new genomic technologies to investigate the spectrum of somatic alterations in kidney cancer has led to new insights into a series of events, which could lead to new therapeutics and possibly earlier detection of kidney cancer. Large-scale sequence analyses of sets of adult and pediatric kidney cancers have provided a view of the landscape of the more common types of events across the genome [10–22]. Adult kidney cancers harbor large numbers of somatic mutations of all classes, from point mutations to structural alterations, whereas in pediatric kidney cancers (e.g. Wilms tumor and at least half a dozen rarer types), there are fewer somatic events and in fact, few instances in which a driver mutation has been identified. The loss of the 3p chromosomal arm, which harbors the *VHL* gene, is commonly observed in ccRCC, underscoring the importance of the VHL network and its effect on key metabolic pathways in kidney carcinogenesis. VHL alteration also is the likely reason that VEGF pathway-directed anti-angiogenic strategies have shown some success. New drivers of kidney cancer have been identified, partly on the basis of the frequency of mutations in key genes, and partly on the basis of corroborative laboratory work [23].

Characterization of rarer types of kidney cancer has led to new insights, in some instances providing opportunities to understand how germline mutations inform an understanding of the somatic alterations. Similarly, initial studies have revealed the importance of the dynamic genome, known as the epigenome in both adult and in particular, pediatric subtypes of kidney cancer [24]. In this regard, the microenvironment has emerged as a critical focus for ongoing research in order to understand how and in what way the ongoing interaction between host factors and developing tumors either accelerates or inhibits tumor formation.

An important characteristic of kidney carcinogenesis is the role of alterations in metabolic pathways, beginning with the VHL network [25]. Germline genetic susceptibility (e.g. both common variants and highly penetrant familial mutations) has pointed toward *VHL* and associated genes, such as *EPAS1*. Metabolic disruption can directly contribute to kidney cancer development, both in genomic studies and in laboratory investigations of models, tissue culture and tumor tissue studies. In parallel with these seminal discoveries has been a strong interest in characterizing the role of an elevated BMI, perhaps through a range of metabolic syndromes or disruptions.

The discovery of stable and reproducible biomarkers for risk or earlier diagnosis of kidney cancer using germline genetics or serum/urinary biomarkers remains a daunting challenge. Many small studies have provided preliminary observations but in larger datasets, the utility of candidate or pathway analyses remains elusive. Such molecular epidemiologic studies could provide insight into mechanisms of kidney cancer development and improve prediction models. Our capacity to achieve these goals will be based on increasing the scope of our understanding of mutations and biomarkers applied to substantively larger investigations, preferably using prospectively collected biospecimens in order to identify markers of risk.

Therapeutic approaches to kidney cancer have blossomed in the last decade, fueled by new targeted therapies (e.g. designer drugs that attack specific proteins or pathways critical for angiogenesis and immune regulation). There are more than half a dozen new-targeted agents in use for metastatic cases, many showing impressive initial responses, but resistance is invariably observed which limits the ability to impact long-term survival [26]. Proteomic and circulating biomarker studies have provided promising leads for understanding determinants of tumor progression and metastases, a major problem in kidney cancer. Immunotherapy for kidney cancer has progressed from cytokine-based therapies to PD-1 and PDL-1 blockade. Many exciting reports have detailed successful applications of immunotherapy, with a recent phase 3 trial showing longer survival in patients receiving this new treatment [27]. More studies will be needed to advance this exciting component of precision medicine, particularly as it relates to selection of patients with a high probability of response to therapy.

future directions

The exciting trends in molecular characterization and targeted therapy of kidney cancer should be matched with a new

commitment to understanding the etiology and pathogenesis of this malignancy. How and why there are major differences by sex, race, geography and exposure histories underscores the complexity of kidney cancer etiology. Global assessment of incidence but also outcomes of therapeutic approaches could reveal important observations that, in turn could inform both the underlying biology and identify new targets for early detection or therapy. The shift toward molecular characterization of adult and pediatric cancers has uncovered a series of important questions related to the key pathways underlying the spectrum of kidney cancer. Heterogeneity in somatic changes has emerged as a significant challenge in kidney cancer, revealing that distinct molecular phenotypes within an individual's tumour may have to be targeted in parallel, unless there is a common somatic mutation that can be targeted upstream [28]. Moreover, the analysis of somatic signatures could reveal important clues to environmental and lifestyle factors that contribute to kidney cancer [16, 29].

Over the past two decades, the detection of germline susceptibility alleles, both common and rare, has accelerated our understanding of the underlying genetic architecture of how kidney cancer develops. The new tools of genome-wide association and next-generation sequencing studies should continue to be applied to progressively larger and better-annotated datasets to further add to the comprehensive catalog of susceptibility alleles. The utility of sequencing subsets of newly diagnosed cases of kidney cancers has already emerged as a compelling argument and merits further investigation, particularly in families or outliers (such as younger cases of ccRCC or the spectrum of rare subtypes). Similar commitment to the genetics of pediatric forms of kidney cancer could be useful for future screening approaches, especially in high-risk settings. It will be important to conduct these studies in populations with different genetic histories and exposures. The ability to examine gene–environment interactions either directly or through the approach of Mendelian randomization should be a high priority for discovery of new relationships, some of which could be harnessed for detection or prevention [30].

Further characterization of the genomic landscape of kidney cancers, including larger numbers of rarer cancers, should provide an important foundation for identifying the catalog of driver events. While The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) have provided an impetus to conduct large-scale characterization projects, the international community should develop a shared data resource to combine academic, clinical and research resources to rapidly accelerate the bioinformatics analyses of the spectrum of kidney cancer. So far, the number of samples studied has led to the identification of genes that are commonly mutated. As kidney cancer has emerged as one of the pivotal examples of tumor heterogeneity, together with its spectrum of rare and common subtypes, many more tumor/normal pairs will require characterization in order to capture key events, both for targets and for prognostic factors [31]. The next generation of genomic characterization efforts should be conducted in studies that have collected both epidemiologic risk factors, including pre-diagnostic biomarkers when possible, and extensive annotation of the clinical parameters including long-term outcome. The investigation of somatic alterations with clinical outcomes should be a high priority, including detailed analyses of tumor heterogeneity, which might require regional sampling guided by imaging. The challenge of heterogeneity has important implications for therapeutic decisions, and perhaps in the future, therapeutic monitoring, especially if circulating tumor DNA or tumor cells can be adapted as an efficient and widespread technique. Current approaches to develop models for the evolution of kidney cancer represent an important parallel approach, one that should be iteratively coordinated with clinical characterization of the cancer genome and its epigenomic changes [28]. Serial and regional biopsies in well-characterized biorepositories should be available and include detailed follow-up on outcomes, therapeutic interventions and new imaging techniques. A critical question of the future will be how and in what way imaging-based techniques can be harmonized with genomic technologies to identify targets, but equally new target identification will need to be combined with the parallel development of predictive genomic and proteomic biomarkers to enable patient stratification.

The rapid acceleration of immune-based therapies should remain a major focus of kidney cancer research, providing new insights into how and in what way the immune system could better conduct surveillance against emerging cancers and to treat kidney cancer. The collective assessment of the different strategies could shed light on prognostic factors, such as the HLA haplotypes and circulating biomarkers. Eventually, the use of immunotherapy may be a central component in the armamentarium of precision medicine tools. Determinants of immune-based therapeutic success should provide new insights into stratification of individual patients, perhaps based on emerging immune profiles of both measured biomarkers and genetic predisposition.

In conclusion, the tools of genomic characterization and targeted therapy have begun to accelerate the investigation of the basic biology of kidney cancer, thus providing novel approaches toward improving early detection, intervention and monitoring this malignancy. The development of a more refined molecular taxonomy of the spectrum of kidney cancer will advance most efficiently if the community continues to develop more robust approaches to data sharing. Interoperability between data resources should remain a central goal both for resources generated by '-omic' technologies and more precise phenotyping, based on sound epidemiologic and clinical practice. By integrating datasets, the opportunity to determine shared and unique features should benefit the diagnosis, treatment and monitoring of rare and common kidney cancers alike. In the distant future, it may emerge that precision prevention strategies are possible, but they will be based on further research in all corners of the globe.

Difficult questions that should be prioritized

1 What factors explain the geographical, racial/ethnic and sex differences in the incidence of kidney cancer?
2 What underlying biologic pathways drive the association with kidney cancer risk for obesity and hypertension?
3 Can a greater understanding of germline variation of kidney cancer inform us about the unknown lifestyle and environmental causes?
4 Can a better understanding of the somatic signatures (both genomic and proteomic) of kidney cancer and its subtypes provide clues to etiologic risk factors and prognosis?
5 How is response to targeted therapy and immunotherapy influenced by epigenetic variation?
6 With more than a half a dozen approved drugs targeting the VHL/HIF pathway in clear cell renal cell carcinomas, what are the next steps toward improving therapy and survival in both early and advanced cases?
7 What are the barriers for rapid data sharing of sequencing of kidney cancers, which could accelerate identification and characterization of drivers of oncogenesis?
8 How do we select kidney cancer patients for constitutional genetic testing, beyond those fitting a 'classic' kidney cancer susceptibility syndrome?
9 Why do more than half of pediatric Wilms tumors lack identifiable driver mutations and what does this suggest about epigenetic regulation?
10 What new data are critical to develop more accurate models for understanding genomic and epigenetic changes across the spectrum of renal cancers?
11 Are current pathological subtype classifications still clinically relevant?
12 What factors can reliably predict durable response to immunotherapy?

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disclosure

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