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Lessons Learned from the Global Epidemiology of Kidney Cancer: A Refresher in Epidemiology 101

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In first world countries, clinicians treating kidney cancer, much like prostate cancer, have had to address the potential for overdiagnosis and overtreatment of incidentally detected small renal masses. This has led to an effort advocating for active surveillance of small renal masses, particularly among the elderly and those with medical comorbidities [1]. However, even in economically advantaged countries, nearly one in five patients diagnosed with kidney cancer will present with de novo metastatic disease [2], contributing to 14 970 kidney and renal pelvic cancer–specific mortalities in the USA in 2018 [3].

In this issue of *European Urology*, Capitanio and colleagues [4] provide a global perspective on the epidemiology of renal cell carcinoma, with a specific focus on risk factors for nonhereditary, sporadic disease. Not surprisingly, kidney cancer incidence and mortality rates differ significantly across individual countries and regions of the world, ranging from an age-standardized rate (ASR) incidence per 100 000 people exceeding 12.0 in the Czech Republic, Lithuania, Slovakia, and USA to an ASR of 0–0.6 per 100 000 people in many African and Asian countries [4]. In addition, the authors highlight several risk factors for kidney cancer, including obesity/physical activity, fruit and vegetable intake, smoking, alcohol intake, and medical comorbidities such as hypertension, urinary stones, diabetes, and chronic kidney disease. This article offers several important lessons in our understanding of both kidney cancer and epidemiology.

The authors present a descriptive, narrative summary of geographic differences in the incidence and mortality of kidney cancer and summarize common risk factors. In doing so, they cite a number of published systematic reviews and meta-analyses regarding kidney cancer risk factors. However, these results are presented without critical appraisal despite the availability of relevant tools [5]. AMSTAR 2 highlights several critical domains for evaluating the validity of a review, including: protocol registration before review, the adequacy of the literature search, the justification for study exclusion, the risk of bias from study inclusion, the appropriateness of meta-analytical methods, consideration of the risk of bias during interpretation, and assessing the likelihood of publication bias [5]. Such an approach would help to guide readers in understanding the strengths and limitations of the available data regarding identified risk factors associated with kidney cancer.

Assessment of methodologic rigor is critical in understanding the available evidence regarding risk factors for nonhereditary kidney cancer. Among the data cited by Capitanio et al, eating cruciferous vegetables was associated with lower odds of kidney cancer among case-control studies, but no difference was found among cohort studies (Section 3.2.1.3) [6]. While both these study designs are retrospective, case-control studies rely on a patient's recall of exposure to a defined risk factor (vegetable consumption). Thus, there is a significant risk of recall bias, often requiring participants to self-report their exposure to a risk factor many years later. By contrast, cohort studies start with exposed and unexposed groups (levels of vegetable consumption) and assess the proportion of participants who develop the event (kidney cancer). These studies are less prone to recall bias and can more directly establish

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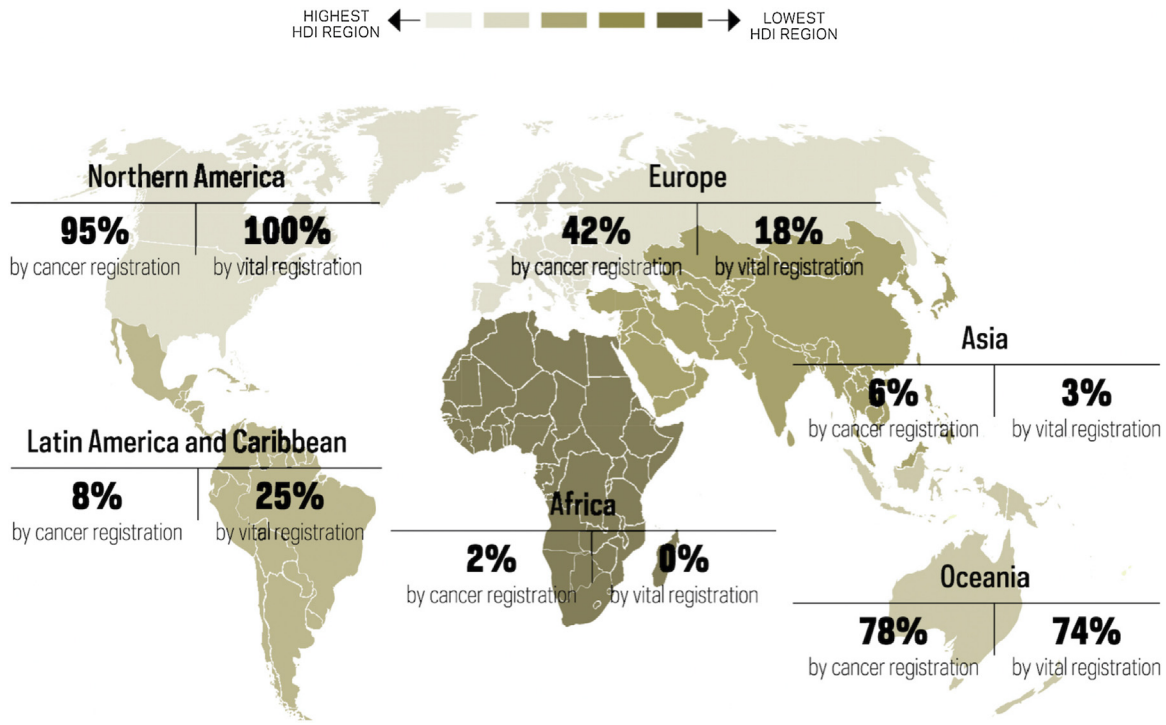

Fig. 1 – Proportion (%) of the regional population covered by high-quality cancer registration and high-quality complete vital registration of death. Reproduced with permission from The American Cancer Society, The Cancer Atlas [8]. Copyright © 2014 The American Cancer Society, Inc. All rights reserved. HDI = Human Development Index.

risk. Thus, on the basis of the evidence provided in this review, vegetable intake is unlikely to be a risk factor for developing kidney cancer. Similar issues plague the data supporting many of the other risk factors discussed in the manuscript.

Global kidney cancer epidemiology is a lesson in diagnostic access bias, variability in people's ability to access diagnostic testing that establishes the presence of a given disease. Given that, even within the USA, the frequency of nephrectomy is strongly related to the population-level utilization of abdominal computed tomography [7], it is likely that the geographic variation in kidney cancer diagnosis identified across both global regions and individual countries reflects differences in health care access rather than true differences in underlying biology, with the true incidence and mortality probably grossly under-represented in developing countries. Furthermore, a closer assessment of the incidence and mortality data presented in this article (Tables 1–5 [4]) demonstrates that nations with high incidence ASR per 100 000 people almost universally encompass developed countries with high-quality availability of incidence and mortality data. Conversely, countries with low incidence ASR per 100 000 people have poor-quality availability of incidence and mortality data. In addition to diagnostic access bias, the lack of well-organized cancer registries and vital registration of death (Fig. 1) precludes reliable epidemiologic data. For example, in Africa, 2% and 0% of the population is covered in a cancer registry and by vital registration of death, respectively [8]. Similarly, in Asia, 6% of the population is recorded in a cancer registry and only 3% by vital registration of death [8].

Finally, the applicability and appropriateness (or lack thereof) of widespread kidney cancer screening is a lesson in cost-effectiveness and resource utilization. Screening for kidney has not been widely adopted, most notably because of the high number needed to screen in order to detect a single renal mass. Using ultrasonography in a screening study among 9959 volunteers from Germany, only 13 participants (0.1%) were found to have a renal mass, of whom nine had renal cell carcinoma [9]. However, Capitanio et al. [4] suggest that perhaps targeted screening in at-risk populations is warranted, even though, for the most part, these subgroups remain poorly delineated. Thus, improving global care for kidney cancer patients needs to start with improving cancer registries and vital registration of death in an effort to delineate the true incidence and mortality rates of this disease, which may subsequently assist in identifying who might benefit from targeted screening. Within any screening program, treatment of identified cancers must be reliably and safely offered. This is not inherently the case in many developing nations. In 2015, the Lancet Commissions published *Global Surgery 2030*, an initiative to increase life-saving surgical care to low- and middle-income countries [10]. Although radical/partial nephrectomy for kidney cancer was not listed among the essential surgical procedures, lessons learned for instituting an infrastructure to improve surgical access for kidney cancer patients in such countries may prove valuable for this patient population.

Conflicts of interest: The authors have nothing to disclose.

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