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REVIEW ARTICLE

Epidemiology and Risk Factors for Kidney Cancer

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A B S T R A C T

The purpose of this narrative review is to summarize evidence of the epidemiology of and risk factors for kidney cancer with a focus on renal cell carcinoma in adults. The etiology of kidney cancer is largely unknown and the main epidemiologic determinants are large geographic and temporal variations in incidence rates. Established risk factors include tobacco smoking, body size, and history of hypertension and chronic kidney disease. Other suspected risk factors require additional investigation, as do the underlying biologic mechanisms that are responsible for disease occurrence. Opportunities to prevent kidney cancer include targeting modifiable risk factors—for example, smoking abstinence/cessation and body weight control—as well as interventions along the diagnostic pathway to improve early diagnosis. Molecular epidemiology, including, but not limited to, metabolomics and tumor genomics, are new areas of research that promise to play important roles in identifying some of the underlying causes of kidney cancer.

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INTRODUCTION

Kidney cancer develops from the renal parenchyma. Clear cell renal cell carcinomas represent approximately 70% of kidney cancer cases in adults.[1] Much of the epidemiologic knowledge pertains to kidney cancer as a whole, with a paucity of data on histologic subtypes. Tumors that arise from the renal pelvis and kidney cancer in children—Wilms tumors—are far less common than renal cell carcinomas and have different epidemiologic features that are beyond the scope of this review.

The main epidemiologic characteristics of kidney cancer are the large geographic and temporal variations in incidence rates. The list of established risk factors is limited to tobacco smoking, body size, and history of hypertension and chronic kidney diseases.

INCIDENCE AND SOCIODEMOGRAPHICS

Kidney cancer is the 13th most common cancer worldwide, accounting for 2.4% of all cancers, with more than 330,000 new cases diagnosed yearly.[2] It ranks higher in Europe, North America, Australia/New Zealand, and Japan, where it is on average the 7th most common cancer. For the purpose of comparability across countries and over time, descriptive epidemiology databases often group renal cell carcinomas together with other upper urinary tract cancers.[2,3]

Age and Sex

Incidence rates of kidney cancer increase steadily with age, with a peak of incidence at approximately age 75 years.[4,5] Worldwide, approximately one half of all cases are diagnosed before age 65 years.[2]

The incidence of kidney cancer is two-fold higher in men compared with women.[6] This pattern has been reported repeatedly over time, across countries, and by age groups, and has so far remained unexplained. The stability of the sex ratio indicates that biologic differences between men and women, rather than lifestyle differences, such as tobacco smoking, are likely to account for much of the incidence disparities.

Geography and Ethnicity

There are large variations in incidence rates around the world, with the highest incidence rates at the country level found in the Czech Republic (age-standardized rate, 21.9/100,000 in males) and Lithuania (age-standardized rate, 18.7/100,000 in males). Incidence rates are less than 2/100,000 in low-risk countries, such as China, Thailand, and African countries[4] (Fig 1). In the United States, incidence rates are higher in black men (age-standardized rate, 15.6/100,000) than in white men (age-standardized

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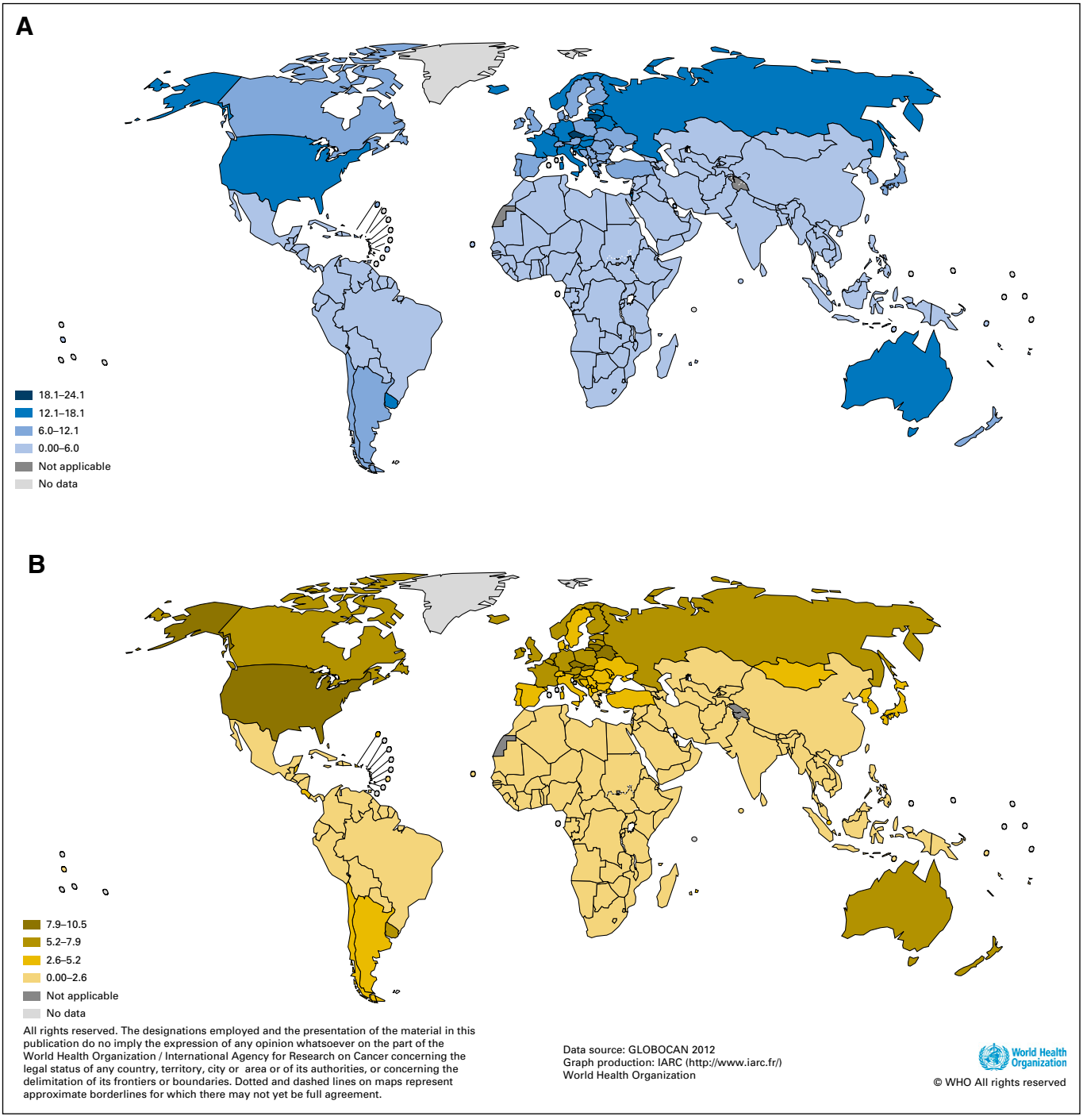

Fig 1. International variations in national estimates of kidney cancer age-standardized incidence rates per 100,000 for (A) men and (B) women. For men and women separately, countries were divided into four groups of fixed incidence rate intervals. Reproduced with permission from International Agency for Research on Cancer.[2]

rate, 14.0/100,000). Hispanics and non-Hispanics show similar rates. American Indians in the United States have intermediate rates (age-standardized rate, 10.9/100,000 in males), whereas Asians in the United States have low incidence rates (age-standardized rate, 6.4/100,000 in males). In Europe, large intracountry regional variations have been described in some countries, notably in Germany (higher incidence rates in the eastern regions of the country) and Italy (higher incidence rates in the north).[7]

Temporal Trends

Incidence rates of kidney cancer have been increasing worldwide since the 1970s (Fig 2).[3] In the United States, rates were 8.0/100,000 in males in 1975 and have increased steadily to reach 13.4/100,000 in 2012. The average annual percentage increase is approximately 2% to 3% in most countries.[5] Only Austria and Poland have reported significantly decreasing rates since the early 2000s. Birth cohort and calendar period effects both contribute to the increasing rates, which indicates that changes in lifestyle and

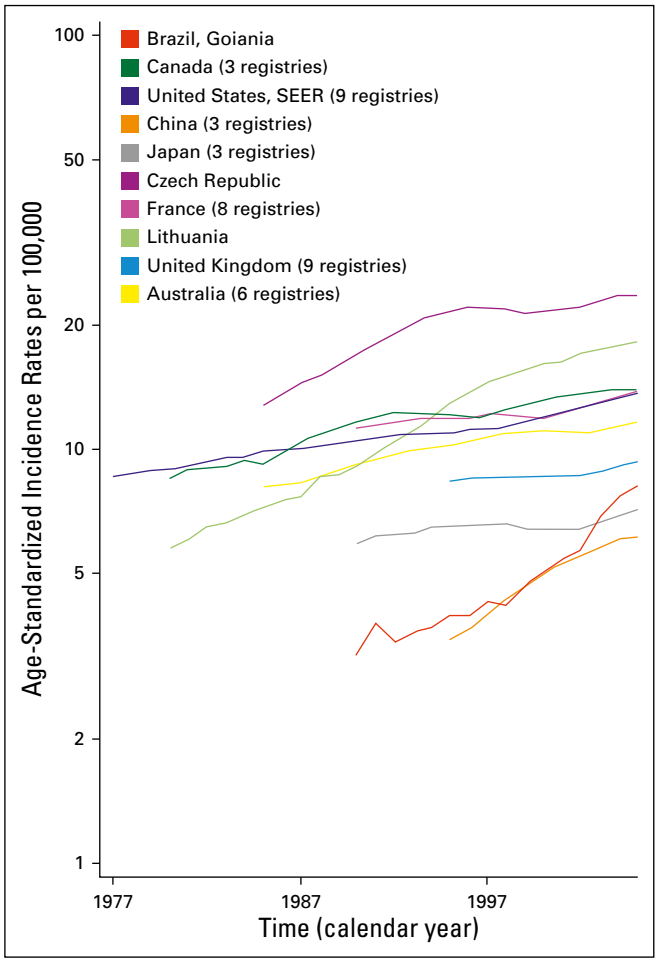

Fig 2. Temporal trends in age-standardized kidney cancer incidence rates for 10 selected registries/groups of registries (males, 1977 to 2005). Rates have been smoothed using a 5-year average. Reproduced with permission from International Agency for Research on Cancer.[3]

exposures to risk factors, as well as changes in tumor detection and diagnostic practices over time, are responsible for the observed temporal trends.[8] In the United States, the proportion of localized kidney cancer cases increased from 45% in the 1970s to 54% in the 1990s, although trends toward increased incidence have been observed at all stages.[9]

MORTALITY PATTERNS

International variations in mortality follow the incidence pattern, with the highest rates observed in the Czech Republic (9.1/100,000 in males) and the Baltic countries.[2] Mortality rates have been stable globally since the 1990s.[5] In recent years, a decrease in mortality has been observed in most countries, with the notable exception of Brazil, Croatia, Greece, Ireland, Portugal, and Slovenia, where rates have continued to increase. In general, mortality seems to be decreasing faster in women than in men. In the United States, the decline in mortality is more pronounced for black patients, and mortality rates among black patients have remained lower than those of white patients since the 1970s[4,10,11] (Fig 3). Ethnic differences in the biology and aggressiveness of kidney cancer could explain this variation, although other factors, such as competing mortality, could also play a role.[12]

LIFESTYLE RISK FACTORS

Tobacco Smoking

Tobacco smoking has been classified as carcinogenic for the kidney by the International Agency for Research on Cancer and the United States Department of Health and Human Services.[13,14] The effect size on kidney cancer risk is modest, with an approximate 30% increased risk in current smokers and a 15% increased risk in former smokers compared with never smokers.[15] Epidemiologic evidence for a causal role for tobacco smoking includes a dose-response relationship between risk and the quantity of tobacco smoked per day, as well as decreased risk with increasing years of smoking cessation.[16] In developed countries, it is estimated that 6% of kidney cancer deaths are a result of tobacco smoking.[17]

Excess Body Weight

The association between excess body weight and risk of kidney cancer has been extensively reported in large, prospective cohorts.[18,19] Excess body weight has been overwhelmingly assessed via an elevation of body mass index (BMI; in kilograms per square meter). Compared with the reference BMI category ($18.5 \leq 25$ kg/m^2), overweight (BMI, $25 \leq 30$ kg/m^2) and obese (BMI, ≥ 30 kg/m^2) individuals have an estimated 28% and 77% increased risk, respectively.[18] The association was demonstrated to be linear in several studies, with a 4% increase in risk for each 1-kg/m^2 increment in BMI[18] or a 25% increase in risk for each 5-kg/m^2 increment.[19] A prospective cohort study of male teenagers with BMI measured at age 16 to 19 years reported that excess body weight earlier in life is associated with an excess risk of kidney cancer later in life.[20] High BMI is estimated to be responsible for 26% of incident kidney cancer cases worldwide.[21]

Body fatness has also been assessed using waist circumference and waist-to-hip ratio. Results have been consistent across studies, demonstrating a significant increase in risk with increasing waist circumference and waist-to-hip ratio.[22] Weight cycling during adulthood has not been shown to significantly modify kidney cancer risk after accounting for baseline BMI.[23] There are also no data available on the benefit of weight loss and/or long-term stabilization of lower BMI in association with the risk of kidney cancer.

Mechanisms involved have not yet been demonstrated, and research is ongoing on the role of inflammatory status, sex and growth hormone levels, metabolic state (insulin resistance and insulin-like growth factor-1 levels), and adipokine levels.[24,25] It will be important to understand the mechanisms in play, particularly in the context of the obesity paradox phenomenon, whereby overweight and obese patients were shown in multiple series to have a prognostic advantage compared with patients with normal BMI.[26] *FASN* gene expression has been implicated as a possible underlying biologic pathway that may influence the obesity paradox phenomenon,[27] but replication of this finding is still needed.

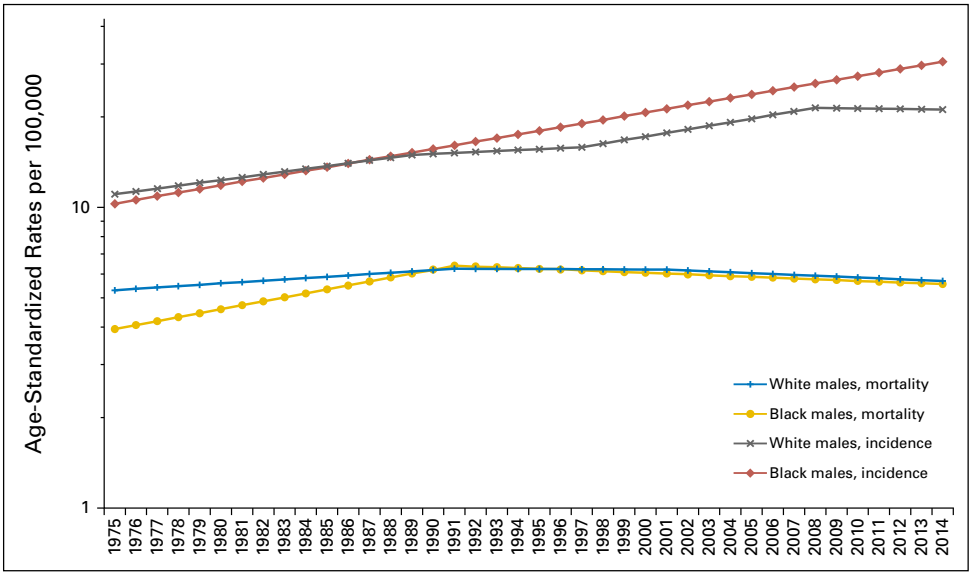

Fig 3. Temporal trends in age-standardized (2000 US population) incidence and mortality rates of kidney cancer by race in men in the United States, 1975 to 2014. Modeled rates derived from SEER data originally published by the National Cancer Institute.[11]

Alcohol Consumption

Several meta-analyses and large prospective cohort studies were conducted on the association between alcohol consumption and risk of kidney cancer.[28-32] All studies reported reduced risk in drinkers compared with nondrinkers or light drinkers. Drinkers typically have a 20% reduction in risk compared with nondrinkers and light drinkers.[32] As there is no association between nonalcoholic beverage intake, nor total fluid intake and kidney cancer risk,[33-36] and because the effect of alcohol consumption does not differ by type of alcoholic beverage,[32] ethanol exposure likely has a mechanistic role. Hyperinsulinemia and insulin resistance in general have been associated with kidney cancer risk.[37] Alcohol consumption has been shown to increase insulin sensitivity and could be associated with a reduction of kidney cancer risk via this indirect route.[32,38,39]

Physical Activity

Physical activity has been associated with a modest reduction in risk in a large meta-analysis of prospective cohorts.[40] When considering all types of physical activities together, the highest activity category had a 13% decreased risk compared with the lowest category. Similarly, a large pooled analysis of cohort studies reported a reduced risk associated with higher levels of leisure-time physical activity.[41] Sedentary behavior as measured by time spent sitting does not seem to increase the risk of kidney cancer.[42] How physical activity might influence the risk of kidney cancer is unclear, and physical activity as a risk factor that is independent of excess body weight and hypertension has not been demonstrated. In its 2015 report, the World Cancer Research Fund and American Institute for Cancer Research concluded that there was limited to no evidence of a link between physical activity and kidney cancer risk.[22]

Diet

Conclusive epidemiologic evidence on diet and kidney cancer risk is lacking in the literature.[22] Results on fruit and vegetable intake from prospective cohorts demonstrated mostly null or nonsignificant associations, or a modest reduction in risk in the highest fruit and vegetable intake categories. Data on nutrient-specific associations are lacking. Furthermore, studies that investigated the intake of fat and protein in association with the risk of kidney cancer mostly reported null associations.

MEDICAL HISTORY

Hypertension

Hypertension predisposes to kidney cancer.[43,44] In the United States, a history of hypertension has been estimated to double the risk of kidney cancer in white patients and triple the risk in black patients.[45] Prospective cohort studies consistently report dose-response associations between blood pressure at baseline and kidney cancer risk,[46-49] even when restricting the risk analysis to more than 5 years after blood pressure measurement when reverse causation is less likely.[50]

Antihypertensive medication has also been associated with an increased risk of kidney cancer, but it is difficult to disentangle the effect of the condition from the effect of treatment.[51] In a study with repeated measures of blood pressure over time, a decreased risk was observed with the reduction of blood pressure.[50] This indicates that the hypertensive condition, rather than the treatment, is more likely to be the risk factor. Furthermore, controlling the condition through the use of hypertensive medication may be an effective therapeutic intervention in the prevention of kidney cancer. Hypertension also seems to be biologically independent from obesity in increasing the risk of kidney cancer, with a cumulative effect among individuals who present with both conditions.[46,50] Although underlying mechanisms are not yet well described, renal injury, hypoxia, or inflammation caused by hypertension may play a role.[52,53]

Chronic Kidney Disease and Kidney Stones

Chronic kidney disease increases the risk of kidney cancer two-fold to three-fold.[54-57] Evidence suggests that the increase in

risk is more pronounced in black than in white Americans, which might contribute to the higher incidence rates in black patients considering that chronic kidney disease is also more prevalent in black patients.[57-59]

An association between a history of kidney stones and a subsequent risk of kidney cancer was reported in several case-control studies, but prospective cohort studies have been inconclusive, which indicates that surveillance and reporting biases may have artificially increased risk estimates in case-control studies.[60-62]

Diabetes Mellitus

The association between diabetes mellitus and kidney cancer risk has been assessed in several prospective cohort studies, with some suggestive evidence of an independent biologic effect from diabetes comorbidities, such as obesity and hypertension.[63-65] A history of diabetes would be associated with a 40% excess risk of kidney cancer.[63]

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Trichloroethylene

Trichloroethylene is mostly known for its use as a metal cleaner and degreaser.[66] The International Agency for Research on Cancer classified the occupational exposure to trichloroethylene as carcinogenic to humans, relying on a body of sufficient evidence that this chemical causes kidney cancer.[66] The latest meta-analysis on the topic estimated that occupational exposure to trichloroethylene confers a 30% to 40% excess risk of kidney cancer.[67] Levels lower than those found in an occupational setting have not been reported to be associated with kidney cancer.

Aristolochic Acid

Chronic and acute exposures to aristolochic acid have historically been linked to Balkan endemic nephropathy and carcinomas of the upper urinary tract.[68] Exposure comes from the ingestion of *Aristolochia* plants, either unintentionally through contamination of food (chronic exposure) or intentionally as herbal traditional remedies (acute exposure). It was more recently hypothesized that this renal toxicant could also increase the risk of renal cell carcinoma, as typical mutational signatures and specific DNA adducts were found in patients who were diagnosed in Romania.[69,70]

Others

Other environmental exposures, such as outdoor air pollution, pesticides, arsenic in drinking water, and lead, were examined in several studies, which demonstrated suggestive but not conclusive evidence of an association with kidney—renal parenchyma—cancer risk.[71-74]

GENETIC RISK FACTORS

The majority of kidney cancer cases are sporadic, with only 3% to 5% occurring within a familial context.[75] Von Hippel-Lindau syndrome is the most common genetic syndrome associated with an increase of kidney cancer risk and accounts for approximately 1% of renal cell carcinomas.[76] Common genetic variants associated with kidney cancer risk were discovered through genome-wide association studies, and 13 loci have so far been implicated.[77]

OTHER RISK FACTORS

Height has been consistently associated with kidney cancer risk—independently of weight—with an approximate 30% increased risk for every 10-cm increase in height.[78,79] Mechanisms involved are not clear but could involve growth hormones levels, genetic background, and childhood exposures.

Several studies have investigated the link between reproductive factors in women and kidney cancer risk. In a large meta-analysis, a significant increased risk was reported in women who underwent hysterectomy, but surveillance bias cannot be ruled out in this observation.[80] The roles of other reproductive related–factors, such as parity and age at menarche/menopause, have remained inconclusive.[44]

Association between vitamin D levels and kidney cancer risk cancer has been systematically reviewed by the World Cancer Research Fund and American Institute for Cancer Research.[81] Whereas the existing evidence does not rule out a possible protective effect of adequate vitamin D levels against kidney cancer development, results were inconsistent across studies.

OPPORTUNITIES FOR PREVENTION AND FUTURE DIRECTIONS

The etiology of kidney cancer is largely unknown, although causes are thought to be multifactorial (Table 1). To date, a range of risk

Table 1. Risk Factors for Kidney Cancer

Risk Factor	Comment
Modifiable	
Tobacco smoking	Dose response with increased pack-years
Alcohol consumption	Inverse association with moderate intake
Excess body weight	Dose response with increased body mass index and other body size measures
Occupational exposure to trichloroethylene	Modest increased risk with exposure
Nonmodifiable	
Age	Dose response with increased age
Sex	Two-fold higher risk in men
Height	Dose response with increased height independent of weight
Geography	Higher risk in high-income countries and unexplained higher risk in some countries and regions
Ethnicity	Higher risk in black individuals than in white individuals, intermediate risk among indigenous (in the United States)
Genetic variants	Rare variants: von-Hippel-Lindau syndrome and other rarer syndromes; common variants: 13 loci identified
Medical history	
Hypertension	Dose response with increased blood pressure independent of weight
Chronic kidney disease	Dose response with declining renal function
Diabetes mellitus	Independent effect from obesity and hypertension not yet established

factors has been studied, some of which are modifiable and therefore offer an opportunity for primary prevention. Tobacco smoking abstinence or cessation, avoiding overweight/obesity, and control of hypertension are likely to be major players in keeping kidney cancer risk low. To this end, primary care providers and public health agencies play a significant role in the encouragement and adoption of healthy behaviors. On a broader scale, country-level factors related to geography and environmental exposures, including trichloroethylene and others yet to be identified, would require system-level interventions to influence not only kidney cancer risk, but population health overall. At the same time, kidney cancer is not generally considered an occupational cancer. Strong, consistent evidence for an association between environmental exposures in general and kidney cancer have not been reported.

It is clear that more evidence is needed to gain a more complete understanding of the etiology, epidemiology, and risk factors for kidney cancer. Future research must therefore ensure our improved understanding of the underlying mechanisms that are associated with kidney cancer. For example, although excess body weight has been demonstrated to be associated with an increased risk of kidney cancer in a dose-response manner, overweight and early obese states have also been associated with improved survival among patients with cancer. This obesity paradox in cancer, kidney cancer included, requires additional investigation.[26] The sex-ratio difference in patients with kidney cancer also requires additional mechanistic understanding.[6] Furthermore, any independent effects from diabetes mellitus, obesity, and hypertension require delineation.

Molecular epidemiology, including but not limited to metabolomics and tumor genomics, is an exciting new area of research that has yet to be fully used for the study of kidney cancer. Metabolomics can provide insight into metabolic derangements that underlie disease and lead to the discovery of new therapeutic treatments as well as the discovery of biomarkers for early diagnosis and/or prognosis.[82] Tumor genomics promises to causally identify individual tumors via mutational signatures that are specific to underlying exo- or endogenic causes.[69,83]

Finally, improvements along the diagnostic pathway can lead to earlier diagnosis and better prognosis. At present, evidence for blood- or urine-based biomarkers of kidney cancer is lacking. Identifying such biomarkers could have a major impact on overall survival and quality of life for patients worldwide, allowing for the detection of kidney cancer and recurrences at an earlier stage.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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