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European Association of Urology

Review – Kidney Cancer

Epidemiology of Renal Cell Carcinoma: 2022 Update

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Article info

Article history:
Accepted August 16, 2022

Keywords:
Kidney cancer
Tumors of the kidney
Epidemiology
Risk factors
Renal cell carcinoma

Abstract

Context: International variations in the rates of kidney cancer (KC) are considerable. An understanding of the risk factors for KC development is necessary to generate opportunities to reduce its incidence through prevention and surveillance.
Objective: To retrieve and summarize global incidence and mortality rates of KC and risk factors associated with its development, and to describe known familial syndromes and genetic alterations that represent biologic risk factors.
Evidence acquisition: A systematic review was conducted via Medline (PubMed) and Scopus to include meta-analyses, reviews, and original studies regarding renal cell carcinoma, epidemiology, and risk factors.
Evidence synthesis: Our narrative review provides a detailed analysis of KC incidence and mortality, with significant variations across time, geography, and sex. In particular, while KC incidence has continued to increase, mortality models have leveled off. Among the many risk factors, hypertension, obesity, and smoking are the most well established. The emergence of new genetic data coupled with observational data allows for integrated management and surveillance strategies for KC care.
Conclusions: KC incidence and mortality rates vary significantly by geography, sex, and age. Associations of the development of KC with modifiable and fixed risk factors such as obesity, hypertension, smoking, and chronic kidney disease (CKD)/end-stage kidney disease (ESKD) are well described. Recent advances in the genetic characterization of these cancers have led to a better understanding of the germline and somatic mutations that predispose patients to KC development, with potential for identification of therapeutic targets that may improve outcomes for these at-risk patients.
Patient summary: We reviewed evidence on the occurrence of kidney cancer (KC) around the world. Currently, the main avoidable causes are smoking, obesity, and high blood

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https://doi.org/10.1016/j.eururo.2022.08.019

pressure. Although other risk factors also contribute, prevention and treatment of these three factors provide the best opportunities to reduce the risk of developing KC at present.

1. Introduction

In 2020, there were an estimated 431 288 new cases of kidney cancer (KC) globally [1]. Although much of the epidemiologic data pertain to KC overall, histologically, renal cell carcinoma (RCC) accounts for the overwhelming majority (90%) of KC cases, predominantly including clear cell RCC (ccRCC; 70%), papillary RCC (pRCC; 10–15%), and chromophobe RCC (5%) [2]. The remaining subtypes are rare (each with total incidence of $\leq$1%) and are beyond the scope of this review. Although it has been shown that histologic subtypes differ in clinical features, outcomes, and genetic determinants, granularity within epidemiologic data limits further descriptive analysis.

Here we present an updated synthesis of the epidemiologic data for KC in adults, with a primary focus on the epidemiology of RCC. We summarize and evaluate the contemporary epidemiologic data detailing geographic and temporal variations in disease incidence, risk factors for KC, and emerging research on somatic and germline genetic factors associated with KC development. Although data highlighting risk factors have already been well summarized [3], our narrative review provides updated epidemiologic observations and a wider analysis of the previous RCC literature.

2. Evidence acquisition

The primary objective of the current review was to retrieve and summarize the most up-to-date data and recommendations regarding KC epidemiology and risk factors. A systematic review was conducted via Medline (PubMed) and Scopus. The search strategy included meta-analyses, reviews, and original studies on RCC, epidemiology, and risk factors from January 2015 to May 2022.The search used medical subject heading (MeSH) terms and free text words: ((“kidney cancer*”) [MeSH] OR (“renal cell*”)) AND ((“renal tumour”) [MeSH] OR (“RCC”)) AND ((“renal tumor”) [MeSH] OR (“renal cancer”)) AND ((“*kidney tumour”) [MeSH]) OR (“*renal cell”)).

In addition to standard MeSH terminology, articles were screened on Elicit.org via natural language processing to include the following “What are the risk factors for kidney cancer?” and “What is the incidence of kidney cancer?” Elicit is a generative pretrained transformer (GPT-3) search engine that leverages deep learning search algorithms via natural language text [4]. The results from the MeSH terminology and Elicit search were compiled into Rayyan-Intelligent Systematic Review [5]. A total of 477 retrieved articles were screened by title and abstract within Rayyan by the primary author (L.B.). Of these, 102 articles underwent full-text review by the primary author, with 59 articles finally included in the review. Figure 1 shows a flowchart of the study selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [6].

Although the literature review was performed using a systematic search strategy, the results are presented as a narrative review without evaluation of heterogeneity or bias among the studies.

3. Evidence synthesis

3.1. Epidemiology of KC

3.1.1. Geography

According to the Global Cancer Observatory, KC is the 14th most common malignancy globally, with an estimated 431 288 new cases in 2020 [1]. Owing to sexual dimorphism with respect to incidence, KC is the ninth most common cancer among men and the 14th most common among women [1].

KC incidence varies widely geographically, with generally higher rates in Europe and North America (Fig. 2). As seen in Figure 3, there is also significant geographic variability in incidence by income: higher KC incidence is associated with greater median income. However, it is hypothesized that this difference is largely due to higher prevalence of small renal masses in settings where abdominal imaging is more ubiquitous. Overall, Lithuania reported the highest overall rate of KC in 2020, followed by Czechia, with estimated age-standardized rates (ASRs) of 14.5/100 000 and 14.42/100 000, respectively. Overall, the worldwide ASR reported in 2020 was 4.6/100 000, with lowest rates reported for Belize (0.26/100 000) and Solomon Islands (0.12/100 000). To illustrate the cumulative risk of KC diagnosis during an individual’s lifetime, a person living in Czechia has a 2.83% chance of developing KC during their lifetime, compared to a risk of 0.02% for a person living in Comoros (Supplementary Table 1). Despite stable KC-associated mortality rates, the risk of developing KC has been slowly rising over the past decade, largely attributable to an increase in abdominal imaging with increased rates of incidental detection of otherwise asymptomatic small renal masses [7–9]. The classical KC triad of hematuria, flank pain, and flank mass is seen infrequently in modern medicine (<15%), as the majority of KC cases are incidentally detected on cross-sectional abdominal imaging obtained for other reasons before the development of symptoms [10].

The first worldwide ASR reported for KC was 7.1/100 000 in 1975, which steadily increased to a peak of 16/100 000 in 2008. In contrast to most of the globe, Sweden and Israel have reported steady rates of detection, while the majority of other countries have seen an increase in diagnosis since the early 2000s (Fig. 3). Although birth cohort and calendar period both play an important role in increasing rates, countries such as Japan, Italy, and the USA have seen a steady rise in ASR from 2000 to 2016 from 5.3, 12, and

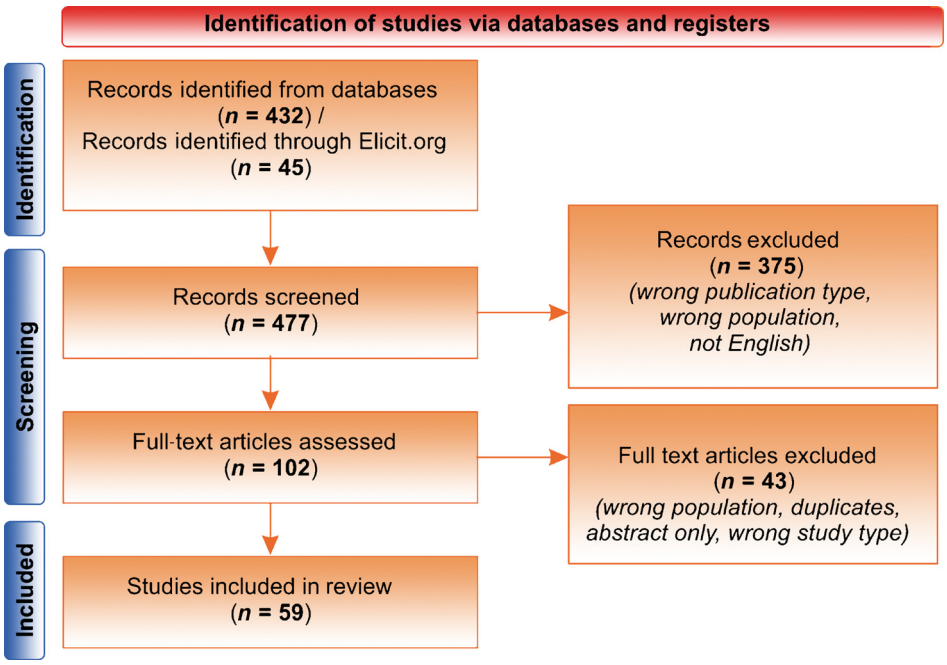

Fig. 1 – PRISMA flow diagram demonstrating the search methodology for this systematic review.

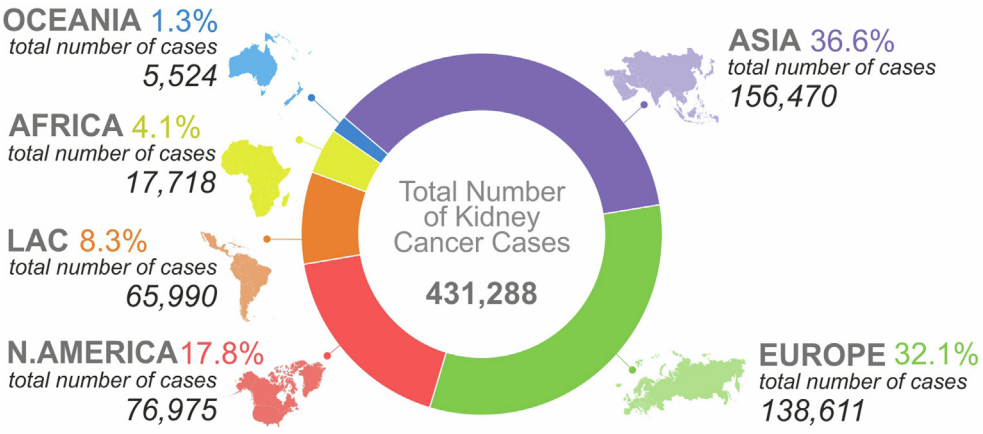

Fig. 2 – Kidney cancer incidence across continents represented as a percentage of the total, and number of cases per region for 2020. Data obtained from the International Agency for Research on Cancer/World Health Organization.

10.7/100 000 to 7.8, 13.7, and 13.3/100 000, respectively. The UK alone has experienced an 88% increase in KC incidence during this time [11].

3.1.2. *Age, sex, and ethnicity*

KC incidence increases steadily with age, with a worldwide median age at diagnosis of approximately 75 yr [12]. However, this largely depends on geographic region, as illustrated by variations in the peak age at diagnosis among the USA (64 yr), UK (74 yr), India (67 yr), and China and Italy (82 yr).

Regarding the differential risk of developing KC by sex, the incidence is approximately twofold higher for men than for women, a pattern that appears stable over time and across countries and age groups [13,14]. As seen in Figure 2, there are high fluctuations in the ASR among countries by sex, with the USA and Australia exhibiting highest discrepancy in incidence with ASR 16.1 vs 8.6 per 100,000 and 14.4 vs 6.4 per 100,000, across men and women, respectively. These differences are less pronounced in regions such as Eastern Africa (1.9 vs 1.4), and Western Africa (1.8 vs 1.6). The geographical variation in incidence by sex suggests that, while biologic differences between men and women exist, lifestyle as well as potential reporting of data, likely also contribute to observed disparities in incidence.

Comparison of KC incidence by ethnicity in the USA revealed that KC diagnosis among Black individuals has peaked at ASR 17.0/100 000, compared to 13.2/100 000 for White individuals, albeit with an identical mortality ASR of 3.2/100 000. In other words, while the Black population has a higher KC incidence rate in comparison to the White population, the mortality rate is largely unaffected.

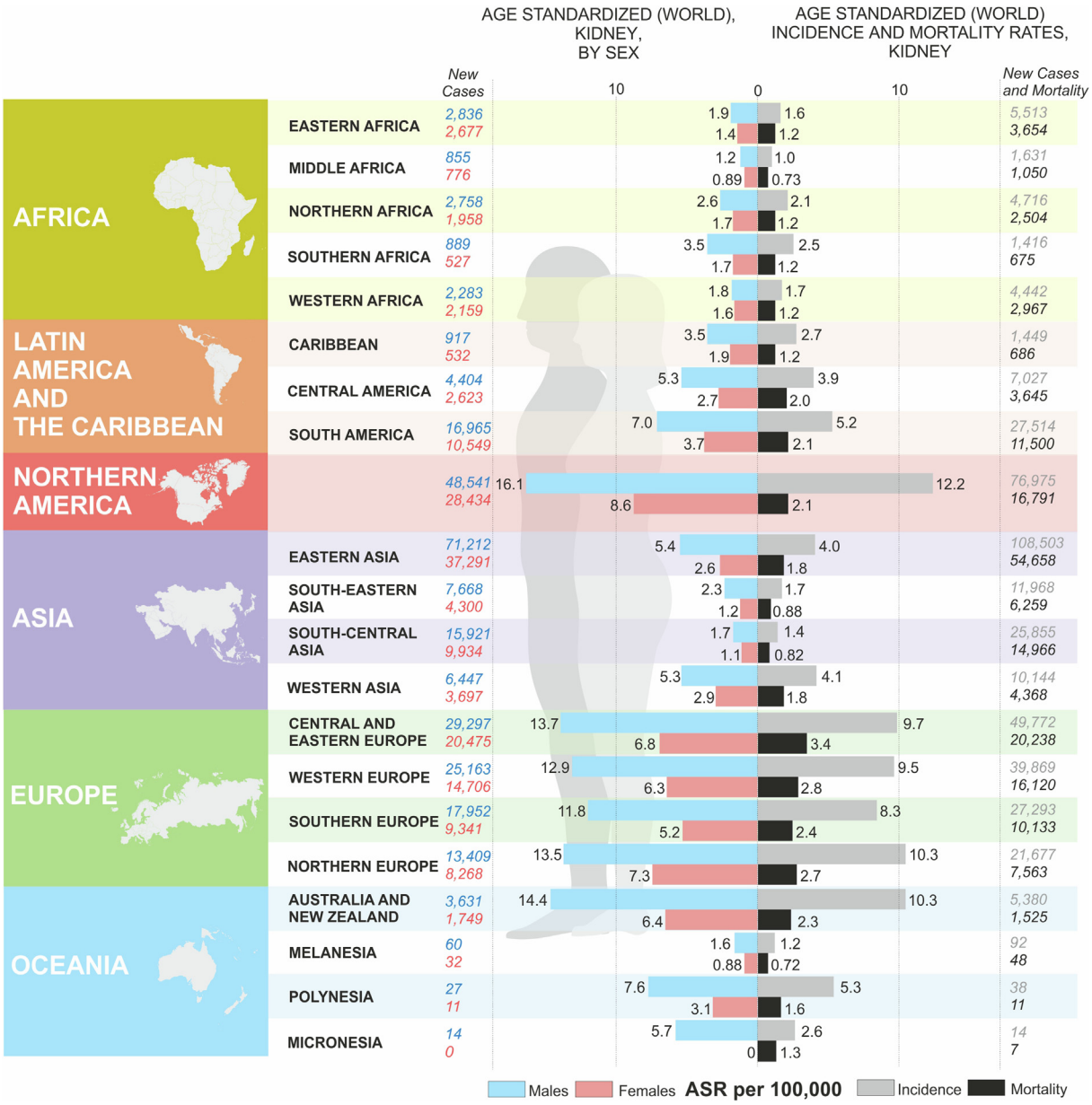

Fig. 3 – Age standardized rate (ASR) for kidney cancer incidence and mortality by World Health Organization (WHO) region and continent in 2020. Results are further stratified by sex. Data obtained from the International Agency for Research on Cancer/WHO.

3.1.3. *Mortality patterns*

In 2020 there were 179 368 deaths worldwide from KC (115 600 men and 63 768 women), with a calculated global ASR rate of 1.8/100 000. Regions with the highest age-adjusted population mortality rate were Central and Eastern Europe (ASR 3.4), Western Europe (ASR 2.8), and Northern Europe (ASR 2.7; Fig. 3). The lowest mortality rates were reported for South Central Asia (ASR 0.82), Melanesia (ASR 0.72), and Middle Africa (ASR 0.73). Unlike rates of KC diagnosis which have been steadily increasing since early 1970s, rates of KC mortality have been slowly declining. Countries such as Italy, Sweden, Japan, USA, and Australia, among others, have demonstrated a steady decrease in mortality. For example, in the USA, while KC incidence rose from 6.2/100,000 in 1975 to 13.3/100,000 in 2018, mortality peaked at 3.8 in 2002 but then slowly trended down to 3.1 in 2018. Countries such as Sweden have exhibited a more pronounced decline in KC mortality, reaching a peak in 1988 at 5.0/100,000, with most recent mortality rate almost halved to 2.9 in 2018 (Fig. 4). Many novel immunotherapy agents have contributed to a dramatic improvement in progression-free survival, and as such, may have contributed to the observed improvements in survival globally [15,16]. The increasing incidence of KC with declining mortality rates in developed countries is a well-described phenomenon; it has been hypothesized that this is because of overdiagnosis of small renal masses, which frequently demonstrate limited oncologic potential, as the utilization of cross-sectional abdominal imaging has increased [17,18].

Fig. 4 – Trends in the age-standardized rate for kidney cancer incidence (left) and mortality (right) in Israel, Italy, Sweden, Japan, France, USA, and Australia from 1960 (data when available) to 2020.

3.2. *Lifestyle risk factors*

KC incidence increases exponentially with age and is higher among men than among women. In the USA, predisposition by ethnicity has also been reported, with the highest rates observed for Native Americans, Indigenous Alaskans, and African Americans, and the lowest for Asian Americans and people of Pacific Island descent [19-21]. Previously established risk factors for development of KC include excess body weight, history of hypertension, and smoking, which are thought to contribute to up to 50% of KC pathogenesis [22,23].

3.2.1. *Smoking*

The International Agency for Research on Cancer (IARC) has classified tobacco smoking as a moderate carcinogenic risk factor for KC development [24]. According to a systematic review of 56 studies, the risk of KC development is 39% higher for current smokers. Furthermore, the authors reported that KC risk is 20% higher for former smokers and 26% higher for ever-smokers in comparison to never-smokers. The relationship between smoking and KC risk is dose-dependent, with the risk sharply increasing for individuals smoking up to 30 cigarettes/d. The relative risk (RR) was 1.18 (95% confidence interval [CI] 1.11–1.26), 1.36 (95% CI 1.22–1.52), 1.61 (95% CI 1.40–1.86), and 1.72 (95% CI 1.52–1.95) for individuals who smoked 5, 10, 20, and 30 cigarettes/d, respectively. KC risk linearly decreases with time since quitting cigarette smoking, with RR values for former versus current smokers of 0.94 (95% CI 0.87–1.01), 0.88 (95% CI 0.76–1.02), and 0.82 (95% CI 0.66–1.02) at 10, 20, and 30 yr after quitting, respectively [25]. However, it is notable that the RR does not ever return to the same level observed for never-smokers (RR for never vs current smokers 0.72, 95% CI 0.66–0.78) [25]. This observation is supported by additional studies showing that smoking cessation for >10 yr is associated with significant benefits in terms of lower KC incidence and disease-specific mortality. The results were applicable to both genders, implying that smoking cessation by KC patients even after diagnosis may potentially lead to better survival outcomes [26]. The exact mechanism for smoking-induced KC carcinogenesis has not been fully delineated; however, it is thought that individual carcinogens such as polycyclic aromatic hydrocarbons, aromatic amines, heterocyclic aromatic amines, and *N*-nitrosamines play a substantial role [26,27].

3.2.2. *Excess body weight and insulin resistance*

Numerous epidemiologic studies have shown that obesity is a strong risk factor for a number of cancers [28]. A 2016 report from the IARC Working Group on Body Fatness concluded that there is sufficient evidence to support a causal association between obesity and the risk of 13 cancers, including KC [29]. Nearly 20% of all KCs worldwide are attributed to excess body weight, with the highest reported association seen with higher central adiposity. The relationship is linear, with a 4% increase in KC risk for every 1-point increment in body mass index (BMI) [30]. Although excess BMI is associated with KC development, the relationship is less clear for KC survival. According to the "obesity paradox", while the risk of being diagnosed with KC increases with increasing BMI, higher BMI is associated with better KC-specific survival [31,32]. In other words, obesity is a well-established risk factor for KC development but is actually protective in the context of survival of patients with KC. Similar to localized disease, patients with metastatic renal cell (mRCC) and high BMI generally experience better overall survival with targeted therapy [33]. Biologically, some have argued that FASN pathway activation is associated with BMI and survival [33], suggesting an integral role for fatty acid metabolism in the prognosis of patients with mRCC [34]. However, critics of the obesity paradox contend that BMI is an inaccurate and nonspecific anthropologic measurement that does not reflect the presence of coexistent sarcopenia [35], and have noted that studies are often clouded by numerous unmeasured confounding factors. Indeed, residual confounding by tobacco smoking, which is related to lower weight, may account for the inverse asso-

ciation observed between obesity and smoking-related malignancies such as KC [36].

The main pathways linking obesity and adiposity to KC incidence include: (1) hyperinsulinemia or insulin resistance and abnormalities of the IGF-1 system and signaling; (2) biosynthesis of sex hormones and the associated pathway; (3) subclinical chronic low-grade inflammation and oxidative stress; and (4) alterations in the gut microflora and toxic metabolites.

The IGF pathway is a crucial and complex system composed of two growth factors (IGF-1 and IGF-2), along with many additional cell-surface receptors and proteases. In vitro and animal studies have demonstrated IGF-1 receptor overexpression by KC cells [37-39]. Thus, a state involving altered levels of serum IGFs and/or circulating levels of their binding proteins may potentiate neoplastic activity via promotion of cell cycle progression and inhibition of apoptosis [40].

Coupled with the pro-oncogenic state stimulated by dysregulated IGF-1 production, the effects of obesity on the gut microflora warrant further discussion. Diets high in fat are associated with changes in intestinal microbiome via the production of deoxycholic acid, which suppresses p53 by enhancing its degradation by the proteasome system [41]. Moreover, deoxycholic acid causes DNA damage via the formation of reactive oxygen species. This cancer-promoting microenvironment, in conjunction with dysregulated IGF-1 production, is associated with KC carcinogenesis and progression [42].

Obesity also represents a modifiable risk factor with respect to cancer-specific mortality, with reductions in the risk of cancer-associated death of 40–50% observed for obese patients who have undergone bariatric surgery [43]. Similarly, it has been shown that tight glucose control with metformin and lipid-lowering drugs such as statins reduce the risk of KC by 30%, highlighting the potential role of these drugs as cancer prevention agents [44,45]. Reversing obesity-associated dysfunction via lifestyle interventions, dietary modifications, or medical/surgical therapy could present a relevant public health contribution in decreasing the risk of KC development and progression.

3.2.3. *Hypertension and CKD*

There is strong evidence to suggest that hypertension increases the risk of KC development via dysregulation of HIF, lipid peroxidation, and the formation of reactive oxygen species [46]. A recent meta-analysis identified 18 studies that evaluated KC incidence among patients with hypertension, including ten with longitudinal analyses [47]. Of these ten studies, seven demonstrated an association between severity of hypertension and development of KC. The largest of these studies, from Sweden (n = 855) [48] and the USA (n = 759) [49], noted RR values of 1.2–2.2 in comparison to nonhypertensive control subjects [50]. While the majority of the studies evaluated hypertension as a binary categorical variable, several evaluated the severity of hypertension as a continuum of risk [51,52]. Although a history of hypertension, reported as a binary measure, was associated with 67% higher risk of KC development [53], a meta-analysis evaluating hypertension and KC risk reported that each 10-mm Hg increase in blood pressure was associated with an additional 10–22% increase in KC risk [54]. Conversely, other studies did not demonstrate an association between hypertension and KC. For example, in a cohort of 918 965 adolescent males, Leiba et al. [55] observed no association between an established diagnosis of hypertension and the risk of KC development after 17 yr of follow-up. Many critics contend that obesity may be the driver of KC development, with co-development of hypertension in obese patients who are already at elevated risk of KC. However, there is evidence suggesting that hypertension seems to be biologically independent from obesity, with a cumulative effect observed in patients presenting with both conditions [56]. Interestingly, the association between KC risk and hypertension was strongest for diastolic blood pressure (DBP) in a study of 289 135 Swedish construction workers. The authors observed a dose-response relationship, whereby men with DBP of $\geq$90 mm Hg had double the risk of men with DBP <70 mm Hg [56]. Treatment with antihypertensive therapy, particularly ace inhibitors and angiotensin II receptor blockers, was associated with 2% higher incidence of KC per year of use (RR 1.02) in a recent meta-analysis [57]. However, these findings may reflect the increasing severity and duration of hypertension rather than risk related to the medication itself.

Likewise, CKD and ESKD increase the risk of KC development by two- to threefold, particularly among African American patients [58,59]. ESKD also increases the risk of mortality, with a standardized mortality ratio of 12.5 for patients on dialysis and 7.8 for kidney transplant recipients (KTRs) [60]. KTRs are more likely to present with KC in their native kidney than in the transplanted kidney [61]. KC incidence and outcomes for KTRs have not improved over the past 30 yr because of increased cancer risks and adverse effects of contemporary therapies, including immune-related adverse events and rejection with immune checkpoint inhibitors [62,63]. Evidence suggests that some of the increase in risk for ESKD patients may stem from acquired renal cystic disease, a common finding in ESKD patients on hemodialysis [64].

3.2.4. *Physical exercise*

Although no causal relationship between exercise and KC risk has been demonstrated, research does show that improvements in lifestyle are associated with a reduction in cancer incidence overall. In a pooled data set reported by Moore et al. [65] that included 1.44 million participants, a higher level of physical activity during leisure time was significantly inversely associated with KC incidence (hazard ratio [HR] 0.77, 95% CI 0.70–0.85, 90th percentile vs 10th percentile). Even after adjustment for BMI, the relationship was still present (HR 0.84, 95% CI 0.77–0.91) [65]. While this study reported on the protective effects of physical exercise against KC development, many others have found little or no difference [66]. This is probably because of the difficulty in quantifying physical activity across epidemiologic studies, as few measurement methods have been appropriately validated, coupled with challenges in accounting for unmeasured confounding risk factors. While the data link-

ing physical activity to KC risk are still limited and conflicting, physical activity is associated with reductions in body weight and adiposity, as well as improved blood pressure control and insulin sensitivity, all known risk factors for KC [67].

3.2.5. Alcohol

The first exploratory study on the carcinogenic effect of alcohol dates back to the beginning of the 20th century, when an excess of cancer mortality due to alcohol consumption was reported [68]. Evidence indicating that alcohol use is a preventable risk factor for cancer has existed for some time [69,70] and the World Health Organization deemed alcohol a carcinogen more than 30 yr ago [71]. Although alcohol has been linked to cancers of the oral cavity, pharynx, esophagus, liver, and larynx, results for its association with KC have been conflicting [72-75].

Unlike smoking, several prospective studies found that mild to moderate alcohol consumption was protective against KC development in a dose-response manner. Collectively, alcohol consumption of at least 15 g, equivalent to slightly more than one drink per day, was inversely associated with KC development, with an estimated 28% reduction [76]. An extensive meta-analysis by Bagnardi et al. [77] evaluated alcohol consumption and the risk of cancer across 23 malignancies, noting a statistically significant inverse association between KC and alcohol consumption. The authors reported a lower risk across 24 studies, with RR of 0.92 (95% CI 0.86–0.99) and 0.79 (95% CI 0.72–0.86) for light and moderate alcohol consumption, respectively (Fig. 5).

3.2.6. Environmental exposures

Despite increasing awareness of the contribution of pollutants and environmental exposures to human disease, the impact of many is difficult to assess in epidemiologic studies owing to competing exposures, challenges in measurement and reporting, and variable geographic risk factors. Nonetheless, it has been consistently proven that several important chemicals are associated with KC development, including perfluorinated chemicals and aristolochic acid (AA) [78]. Furthermore, emerging research has shown that micropalstic or nanoplastic particle exposure causes toxicologic damage to the kidneys via oxidative stress and inflammation [79].

Trichloroethylene (TCE) and perchloroethelene (PCE) are two chlorinated solvents that are frequently used in industry as degreasers for metal parts and in dry-cleaning, among other industrial applications [80]. In 2012 the IARC classified TCE and PCE as carcinogenic to humans because of known strong associations with the development of non-Hodgkin's lymphoma, multiple myeloma, and KC [81]. Owing to their lipophilic nature, TCE and PCE rapidly accumulate in the kidney, where they can be metabolized to cysteine-*S*-conjugates, the metabolites thought to be responsible for the carcinogenic effects. Prolonged high-level exposure to TCE or PCE is associated with a significant increase in the risk of KC development (odds ratio 1.78, 95% CI 1.05–3.03) [82] and mortality. A recent epigenome-wide association study in TCE-exposed workers highlighted elevated genome-wide DNA methylation variation and differential expression of genes involved in cell matrix adhesion and interferon subtypes, known to be related to cancer development [83].

Exposure to AA, typically via ingestion of *Aristolochia* plants, has historically been linked to Balkan endemic nephropathy and carcinomas of the upper urinary tract [13]. Studies have demonstrated a positive association between AA and many cancers, including KC. Shortly after AA-containing Chinese herbal products were banned in Taiwan in 2000, the incidence of many urothelial cancers and KCs appeared to decrease [84]. The mechanism underlying AA-induced carcinogenesis involves AA-DNA adducts, which

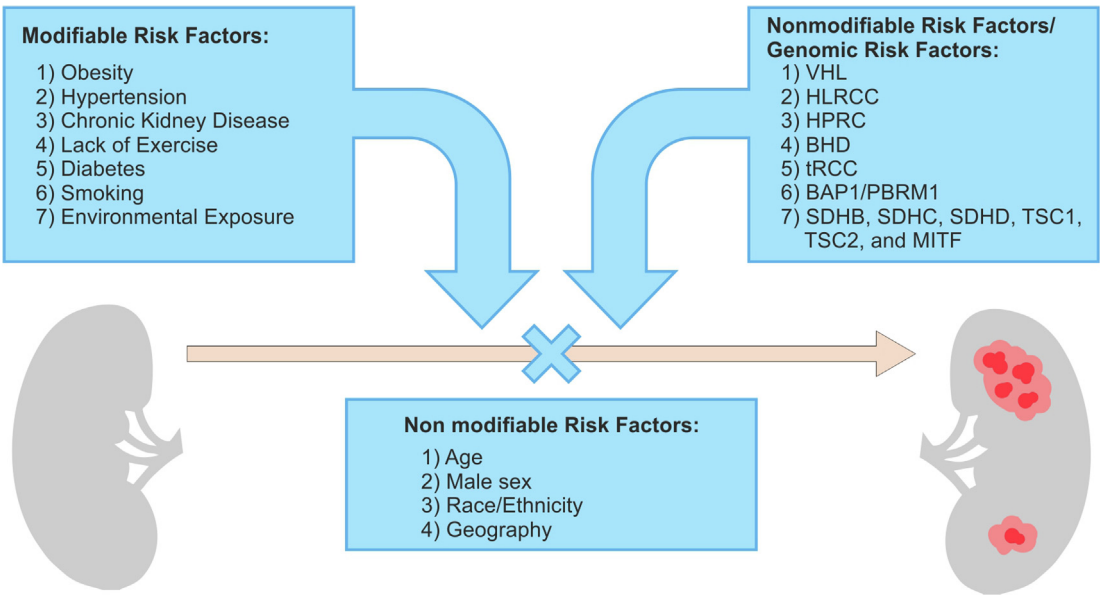

Fig. 5 – Schematic representation of modifiable and nonmodifiable risk factors contributing to the risk of kidney cancer development. VHL = von Hippel-Lindau syndrome; HLRCC = hereditary leiomyomatosis and renal cell carcinoma; HPRC = hereditary papillary renal carcinoma; BHD = Birt-Hogg-Dubé syndrome; tRCC = translocation renal cell carcinoma.

are typically repaired at high efficiency via the nucleotide excision repair mechanism [85]. Cells deficient in this DNA repair pathway accumulate higher levels of AA-induced DNA damage, leading to a higher risk of carcinogenesis [86].

3.3. Genomic risk factors

The genetic testing landscape in KC is continuing to evolve as we are better able to recognize germline and somatic mutations that predispose patients to KC development. It is estimated from The Cancer Genome Atlas analysis that nearly 6–9% of KC cases submitted had a germline alteration identified in a gene associated with cancer predisposition; however, owing to a lack of large population-wide studies, data on potentially strong autosomal recessive factors and polymorphisms that play a role in KC remain largely unknown [87].

Several autosomal dominant inherited cancer syndromes predispose patients to KC development, including von Hippel Lindau (VHL) syndrome, hereditary leiomyomatosis and RCC (HLRCC), hereditary pRCC (HPRC), and Birt-Hogg-Dubé (BHD) syndrome, caused by germline mutations in *VHL*, *FH*, *MET*, and *FLCN*, respectively [87]. There is also a higher risk of KC for patients with germline mutations in *BAP1*, *SDHB*, *SDHC*, *SDHD*, *TSC1*, *TSC2*, and *MITF* [88-91]. Here we describe established and several recently described hereditary syndromes associated with the development of KC.

3.3.1. VHL syndrome

VHL is an autosomal dominant syndrome associated with multifocal ccRCC, renal cysts, central nervous system hemangioblastomas, pheochromocytomas, and other tumors. The *VHL* gene is located on 3p25.3 and encodes the VHL protein, an essential component of the VHL complex, which targets HIF proteins for proteasomal degradation via ubiquitination. This results in accumulation of HIF-1 and HIF-2 and their downstream targets, including VEGF, GLUT1, PDGFB, and TGFA. These factors, in turn, predispose to the development of KC.

Among patients with a *VHL* mutation, deregulation of mTOR further correlates with both KC development and rapid progression. Recent work by Ganner et al. [92] points to common dysregulation of mTOR1 signaling via rapid degradation of RAPTOR, which promotes invasion and metastasis [93]. Despite common loss of 3p, there is significant interpatient and intrapatient variability in somatic variants and trinucleotide mutations among all the tumors, suggesting clonal independence following loss of VHL as the trigger event [94]. Although *VHL* mutations exhibit high penetrance (70–87%), the maximum prevalence in a large national UK cohort was estimated at approximately 1.4/100 000 [95]. The prevalence should be considered in the context of hereditary predisposition within a population, as many have reported much higher rates, such as national estimates for Denmark of 1/46 000 individuals [96].

3.3.2. HLRCC

HLRCC is an autosomal dominant syndrome associated with higher risks of cutaneous and uterine leiomyomas and type II papillary KC [97]. HLRCC is caused by mutations in the *FH* gene on chromosome 1p42.1, which encodes the Krebs cycle enzyme fumarate hydratase that catalyzes hydration of fumarate to malate [98]. Mutations shift glycolysis towards accumulation of fumarate, an oncometabolite, leading to HIF accumulation or genome-wide methylated status [99]. On loss of FH, fumarate further drives irreversible loss of mitochondrial respiration via inactivation of several core enzymes. Despite restoration of FH status, the inactivation is irreversible after the initial mitochondrial insult. Thus, mitochondrial dysfunction ultimately forces metabolic remodeling in HLRCC tumors that favors anabolic pathways crucial for tumor growth and metastasis [100].

Germline mutations across families are seen in 90% of HLRCC cases, but biallelic somatic activation of *FH* has also been reported in sporadic cases. KC, which is present in approximately 15% of HLRCC patients, may be solitary or multifocal, with a strong propensity to metastases, even with small primary tumors [97]. Given how common and often asymptomatic manifestations of HLRCC are (uterine fibroids, cutaneous leiomyomas, and adrenal nodules), it is thought that this syndrome is significantly underestimated in population studies. Although large population-wide studies have estimated that HLRCC prevalence in the USA is 0.024–0.181%, a recent analysis of germline records showed that *FH* variants were detected in 1.3% of individuals [101]. Furthermore, unlike previously reported high disease penetrance results for life expectancy of 70 yr, Shuch et al. [102] reported lifetime penetrance ranging from 3.9% to 17.3%.

3.3.3. HPRC

HPRC is a rare, autosomal dominant inherited disorder in which affected individuals are at risk of developing bilateral, multifocal type 1 pRCC [103]. Germline mutations in the *MET* proto-oncogene are located at 7q31, which encodes for tyrosine kinase receptor. Mutations in *MET* lead to uncontrolled activation of MET protein and aberrant cell growth [104]. HPRC has an estimated incidence of <1:1 500 000, and its rarity is highlighted by the fact that only approximately 35 affected families have been reported worldwide. Despite the rarity of the genetic mutation, it exhibits nearly 100% penetrance, with patients developing renal tumors between the fifth and sixth decades of life [105] (Fig. 6).

3.3.4. BHD syndrome

BHD syndrome is a rare genetic disorder caused by mutation in the *FLCN* gene located at 17p11.2 that causes the development of lung cysts, fibrofolliculomas, spontaneous pneumothorax, and renal tumors with various histologic subtypes, including chromophobe RCC, hybrid oncocytic/chromophobe tumor, ccRCC, pRCC, and oncocytoma [106,107]. It has been reported that bilateral, multifocal renal tumors develop in 29–34% of BHD-affected patients during the fifth decade of life [108]. The overall prevalence of BHD on the basis of the presence of a constellation of symptoms has recently been calculated as 2 per million for men and 1.75 per million for women in a meta-analysis of national data [109]. Recent evaluation of dysregulation leading to the formation of kidney cysts and cancer has elucidated the role of activation of RagC and RagD GTPases and mTORC1 kinase activity [110]. Napolitano et al. [111] suggested that the mTORC1 hyperactivity in

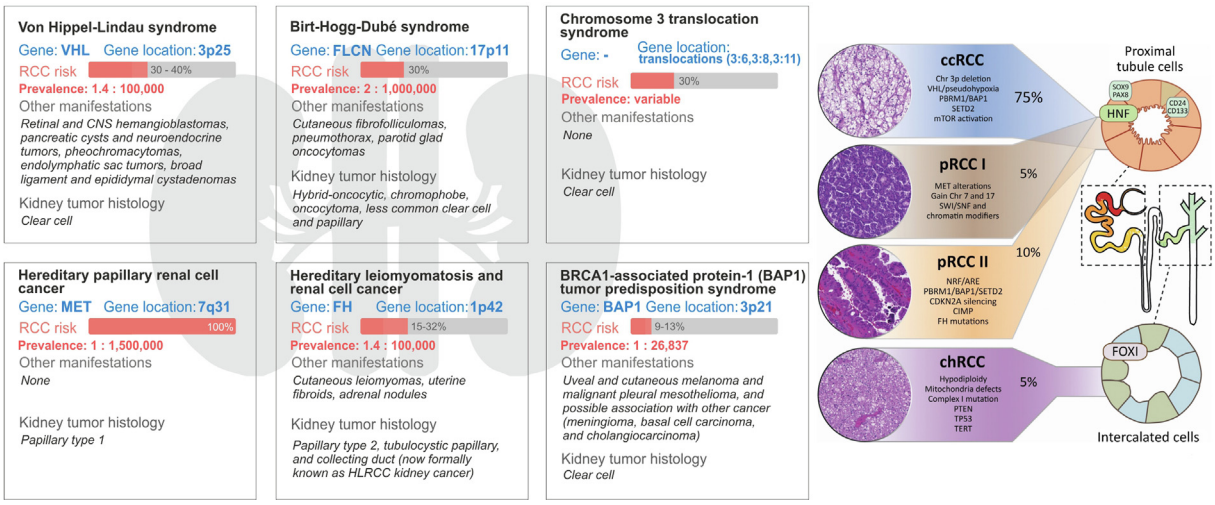

Fig. 6 – (A) Genomic risk factors, gene location, and prevalence of familial syndromes within the population. Other phenotypic manifestations and the RCC risk are also described. (B) Representative distribution of histopathologic variants of kidney cancer and kidney cell origin; reproduced with permission from Cell Trends in Cancer. CNS = central nervous system; RCC = renal cell carcinoma; HLRCC = hereditary leiomyomatosis and RCC; HPRC = hereditary papillary renal carcinoma; ccRCC = clear cell RCC; pRCC = papillary RCC; chRCC = chromophobe RCC.

BHD syndrome (a key step in cystogenesis and tumorigenesis) is not caused by a direct effect of FLCN on mTORC1 but rather by the substrates RagC and RagD (which are mutated in BHD). Phosphorylation of TFEB (a master regulator of lysosomal biogenesis and autophagy) is strictly dependent on RagC and RagD and leads to mTORC1 hyperactivation [110]. Depletion of TFEB in kidneys rescues the disease phenotype and associated lethality, while mTORC1 activity is normalized [111]. These findings not only identify a novel mechanism involving mTORC1 hyperactivation in BHD but also open a potential avenue for therapeutic targeting.

3.3.5. *Translocation RCC*

Although inactivation of a single oncogene does not predispose to KC development, double inactivation is a critical event triggering renal tumorigenesis [112]. Translocations associated with KC development have been described across multiple chromosomes, with varying degrees of penetrance and aggressiveness [105]. In general, translocation RCC (tRCC) is an aggressive subtype of non–clear-cell RCC that accounts for up to 5% of all RCCs among adults and up to 50% among children [113]. The most common subtype is characterized by Xp11.2 translocation, resulting in *TFE3* fusion with various partner genes (*PRCC*, *MED15*, and *ASPSCR1*, among others). Owing to the variety of fusion structures and genes, there is a high degree of tumor heterogeneity across genotypes and phenotypes at presentation. Specifically, while only 1–4% of adult RCCs have *TFE3* translocation, the true population prevalence is unclear. Unlike ccRCC, tRCC is distinct and characterized by younger age and advanced stage at presentation, as well as female predominance [114,115].

A recently published genomic profile of 74 tRCCs revealed that the genes most commonly involved include DNA damage response genes (*ATM*, 8.1%; *BRCA2*, 8.1%; and *WRN*, 4.4%), genes involved in ATP-dependent chromatin remodeling via the switch/sucrose nonfermentable complex (*ARID1A*, 5.4%; and *SMARCA4*, 5.4%), and *TERT* (6.8%; primarily noncoding mutations in the *TERT* promoter) [116]. Overall, the authors' analysis of arm-level copy-number alterations revealed that the most frequent translocations are located on chromosomes 3p (28.6%), 9p (23.5%), 18 (29.4%), and 22q (18.8%); they also noted a prevalent gain on chromosome 17q (20.0%) [116,117]. Currently, there are no molecular therapies targeting tRCC specifically. Of note, additional post hoc analyses highlighted that a heightened NRF2-driven antioxidant response in patients with tRCC was associated with significantly worse response to VEGFR inhibitors in comparison to treatment with immune checkpoint inhibitors [116].

3.3.6. *BAP1/PBRM1 cancer susceptibility*

BAP1-associated RCC is an autosomal dominant inherited disorder and patients are at risk of developing benign melanocytic tumors, malignant uveal and cutaneous melanoma, malignant mesothelioma, and RCC. Similar to other commonly mutated genes: *PBRM1* and *SETD2*, which are also located on chromosome 3, are chromatin modifiers contributing to DNA repair and transcriptional regulation [117]. BAP1 is a nuclear-localized deubiquitinating enzyme with tumor suppressor abilities [118]. Studies have revealed a strong link between BAP1 and HCF-1, a protein believed to regulate transcription [119]. Loss of BAP1 leads to cell proliferation and tumorigenesis via its interaction with HCF-1. Although BAP1 and PBRM1 are both considered chromatin modifiers, *BAP1*- and *PBRM1*-mutated tumors represent distinct gene expression signatures [120]. In comparison to *PBRM1* mutant tumors, *BAP1* mutation is associated with necrosis on histology, higher Fuhrman grade, and worse survival [121]. This might partly explain the poor outcomes associated with sarcomatoid and rhabdoid RCCs, as many harbor distinctive molecular features, including *BAP1* mutations [122].

3.3.7. *Other hereditary syndromes with a higher risk of KC*

SDH, comprising SDHA, SDHAB, SDHC, and SDHD subunits, is a ubiquitously expressed enzyme that acts as a tumor

suppressor via an unknown mechanism [123]. The importance of SDH subunit mutations has been highlighted across different malignancies, including KC, and a rare and aggressive subtype of RCC called SDH-deficient RCC has been identified [124]. Typically, patients present with co-occurring autonomic nervous system tumors (such as paragangiolomas) and pheochromocytoma [125]. The lifetime risk of RCC in *SDH* mutation carriers is not yet well defined, but it has been hypothesized that it is ~10% [126]. Although it is thought that the majority of tumors are indolent, approximately one in three undergoes malignant transformation, which is associated with a high risk of metastasis of up to 70% [127]. While the prevalence of hereditary SDH-deficient RCC is estimated to be anywhere between 0.05% and 0.5% of all kidney tumors, it is thought that underexpression of SDH subunits occurs in more than 80% of ccRCC cases [128]. Recently published data evaluating SDH-deficient RCC have highlighted that SDH downregulation is responsible not only for RCC pathogenesis but also for RCC progression [128]. The aggressive nature and risk of rapid progression may be secondary to immune-cell exclusion and T-cell exhaustion [123].

Similar to SDH-related inactivation of tumor suppressor genes, germline mutations in *TSC1* and *TSC2* in tuberous sclerosis complex (TSC) allow for frequent MTOR pathway activation and subsequent development of RCC in ~4% of patients [129,130]. Although angiomyolipoma and benign cysts are a more frequent manifestation of TSC, RCC can also occur with a wide spectrum of histopathologic morphologies and a propensity for bilateral or multifocal lesions [131].

A germline missense mutation in *MITF* confers genetic predisposition to melanoma and RCC [132,133]. While sporadic RCC mutations in *MITF* have been identified, this *MITF* variant is a germline alteration that increases susceptibility to multiple cancers. MITF is a master regular of melanocyte development, and Bertolotto et al. [134] reported that patients with the hereditary variant have a fivefold higher risk of melanoma and RCC incidence in comparison to the general population. However, a recent meta-analysis has questioned this early observation, noting that a common polygenic background and shared environmental factors may have contributed, at least in part, to this higher risk. In fact, according to the Surveillance, Epidemiology and End Results database, the risk of developing secondary melanoma is 2.31 times higher for patients with RCC than for the general population, attributed to common putative risk genes for RCC and melanoma, including *BAP1*, *CDKN2B*, and *MITF* [135]. The rarity of *MITF* variants contributes to the limited ability to characterize the relationship, limiting clinical utility at this time.

In addition to single germline mutations in hereditary RCC, many studies are now focused on elucidating polygenic susceptibility to KC from genome-wide association studies. Scelo et al. [136] identified single-nucleotide polymorphisms at six loci associated with risk of RCC for a population of European ancestry. As more KC susceptibility alleles are discovered, deciphering the biologic basis of risk variants will provide further mechanistic approaches to KC prevention, early detection, and intervention [136].

3.3.8. *Surveillance and treatment of familial KC syndromes*

In the hereditary RCC setting, young age at onset, bilateral/-multicentric tumors, and nonrenal manifestations of disease are well-recognized features and strong indications for genetic analysis. For patients with a high pretest probability of familial RCC, molecular testing will confirm the diagnosis, particularly for well-characterized mutations such as *VHL* [126]. As the mean age at diagnosis of symptomatic RCC in VHL is approximately 45 yr, germline mutation testing is generally recommended for patients with sporadic RCC who are younger than 46 yr. However, some centers have established a lower threshold (eg, age 40 yr) to minimize testing of patients with low clinical risk, which can often lead to diagnostic uncertainties because of identification of rare variants of uncertain molecular architecture and relevance [137].

The high likelihood of a detectable *VHL* mutation and well-defined genotype-phenotype has facilitated recommendations regarding surveillance for patients with VHL syndrome and asymptomatic family members. While screening for nonrenal manifestations is generally recommended within the first decade of life, magnetic resonance imaging (MRI) of the abdomen is indicated annually at the age of 16 yr to allow early intervention for small renal tumors [137]. While patients with VHL-associated renal tumors are prioritized for a nephron-sparing approach and active surveillance, treatment of patients with FH-associate renal lesions in HLRCC is prompt, with wide-margin surgical excision and consideration of retroperitoneal lymph node dissection [138]. Individuals with a *BAP1* mutation are encouraged to undergo biannual abdominal surveillance with ultrasound or MRI starting at age 30–35 yr [139].

For many patients, especially those with no established family history or early manifestations of hereditary RCC, a diagnosis is only made after presentation with metastatic disease. Some patients can be managed with active surveillance, particularly for individuals who remain asymptomatic for extended periods of time. Reig Torras et al. [140] recently explored the molecular genetic factors associated with failure of active surveillance for patients with mRCC. The authors highlighted that while *VHL* was the most frequently mutated gene (72%), *TP53*, *SMARCA4*, and *BAP1* mutations were associated with worse prognosis and rapid progression of disease without treatment. While *VHL* mutations increase significantly from 64% in primary to 75% in metastatic disease, *VHL* mutation presence itself was not a marker of worse prognosis.

Many of the benefits of surveillance protocols and surgical therapies are established according to decades of phenotypic data. However, continued development of novel diagnostic approaches in molecular testing will facilitate deeper knowledge of inherited RCC gene products and the consequences of mutations, allowing for patient-centered and personalized surveillance and treatment approaches.

4. Conclusions

KC incidence and mortality rates vary significantly by geography, sex, and age. Associations between the development of KC and modifiable and fixed risk factors such as obesity,

hypertension, smoking, and CKD/ESRD are well described. Recent advances in the genetic characterization of these cancers have led to a better understanding of the germline and somatic mutations that predispose patients to KC development, with potential for identification of therapeutic targets that may improve outcomes for these at-risk patients.

Author contributions: Sarah P. Psutka had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bukavina, Psutka.
Acquisition of data: Bukavina, Psutka.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bukavina, Psutka.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Psutka.
Other: None.

Financial disclosures: Sarah P. Psutka certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.08.019.

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