Chapter 1
Epidemiology and Risk Factors of Renal Cell Carcinoma

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Introduction

Renal cell carcinoma (RCC) is the most common tumor of the kidney, accounting for 2–3% of all adult malignant neoplasms [1]. Although the majority of cases are clinically localized at the time of initial detection, RCC is considered the deadliest of the common urologic cancers, with the highest ratio of annual deaths to number of incident cases [1, 2]. In this chapter, the epidemiology of RCC will be reviewed. Additionally, risk factors including demographics, lifestyle, comorbidities, and genetics will be discussed.

Incidence and Mortality

Worldwide, RCC is the 9th most common cancer in men and 14th most common in women [3]. The incidence of RCC varies globally, with the highest rates in Northern and Eastern Europe, North America, and Australia and the lowest rates in Africa and Southeast Asia [4]. In the United States, it is estimated that 63,990 new cases of RCC will be diagnosed in 2017 [5]. In 2012, there were approximately 84,000 new cases in the European Union and 338,000 worldwide [6, 7]. While increasing incidence has been reported worldwide, there is evidence of stabilization in most developed countries [4].

Based on data from the Surveillance, Epidemiology, and End Results registry, 65% of patients with renal tumors present with localized disease, 16% with regional

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disease, 16% with metastatic disease, and 3% with an unknown stage [8]. Over time, there has been a decrease in the size of newly diagnosed renal tumors, with the mean diameter of stage I tumors decreasing from 4.1 cm in 1993 to 3.6 in 2003 [9]. This has been attributed to an increasing number of incidentally detected renal tumors found on imaging performed for a wide variety of medical indications [10].

Despite the worldwide rise in the incidence of RCC, mortality rates have been more favorable. Mortality trends are stable in most countries and decreasing in Western Europe, the United States, Australia, and most Northern European countries [3]. It is estimated that the incidence of RCC has risen up to threefold higher than the mortality rate. Just as incidence varies globally, mortality varies as well. The highest mortality rates are in the Czech Republic and the Baltic countries [3]. In 2017, it is estimated that there will be 14,400 deaths from kidney cancer in the United States [5]. In 2008, the estimated kidney cancer-related deaths in the European Union were 39,3000, and globally this number reached 116,000 [6, 7].

Demographics

The incidence of RCC in Europe and the United States increases with age, occurring most commonly in the sixth to eighth decade of life, with a median age at diagnosis of 64 years and a plateau reached around age 70–75 [8, 11]. This lower incidence among the elderly has been attributed to less frequent use of diagnostic imaging [12]. RCC is infrequent in patients under 40 and rare in children [13].

The incidence of RCC is lower among Asians, both in the United States and within Asian countries [3, 11]. Interestingly, the incidence of RCC is low in African countries; however, within the United States, the incidence is highest among African Americans [11]. These racial disparities have been hypothesized to be due to a multitude of factors including access to health care, frequency of imaging, lifestyle or environmental risk factors, and genetics [12].

RCC is 50% more common in males than females worldwide, with 2/3 of new cases of RCC in the United States occurring in males in 2017 [3, 5]. Worldwide, comparison of incidence/mortality ratios revealed a higher case fatality among men, with male mortality rates threefold higher than for females [3].

Lifestyle

Lifestyle plays a significant role in development of RCC. For example, cigarette smoking is a well established risk factor for RCC [12], while the consumption of fruit, vegtables, and alcohol may have protective effects [14–16]. Additionally, the fact that RCC is more common in males than females may be related to lifestyle risk factors. Furthermore, the worldwide variation seen in incidence of RCC suggests that lifestyle plays a critical role in the development of this malignancy.

Smoking

Smoking is a significant risk factor for the development of RCC [12]. Tobacco contains a number of compounds (such as polycyclic aromatic hydrocarbons and aromatic amines) that promote DNA damage by bulky adduct formation, DNA breaks, and base modifications [17]. Furthermore, tobacco promotes the formation of oxygen free radicals further leading to DNA damage and promoting oncogenesis [17].

A 2016 meta-analysis that included 24 studies assessed the association between smoking and RCC [17]. Outcomes were reported for 17,245 patients with RCC and 12,501 controls. The pooled relative risk (RR) for developing RCC was significantly higher for all smokers (RR 1.31, 95% CI 1.22–1.40), current smokers (RR 1.36, 95% CI 1.19–1.56), and former smokers (RR 1.16, 95% CI 1.08–1.25) compared to nonsmokers. Furthermore, disease-specific survival was lower among patients with tobacco exposure. The risk of death from RCC was elevated for all smokers (RR 1.23, 95% CI 1.08–1.40), current smokers (RR 1.37, 95% CI 1.19–1.59), and former smokers (RR 1.02, 95% CI 0.90–1.15). A prior meta-analysis showed similar results, with a strong dose-dependent increase in risk and a higher risk among male smokers than female smokers [18]. Studies have shown that smoking cessation is associated with a decrease in RCC risk compared with current smokers, even after adjusting for confounders such as pack years; however, the benefit may not be seen until >10 years of cessation [18, 19].

Diet

The impact of diet on the development of RCC is the subject of current debate. Several case-control studies suggest that high meat consumption is associated with an increased risk of renal cancer; however results are largely inconsistent [14, 15]. A pooled analysis of prospective studies was performed to examine the association between meat, fat, and protein intake and the risk of RCC [14]. When adjusting for body mass index (BMI), fruit and vegetable intake, and alcohol intake, there was no association between intakes of fat, protein, and their subtypes and risk of RCC. The same group performed another pooled analysis to assess the relationship between fruit and vegetable consumption and the risk of RCC [15]. They found that compared to patients that consumed <200 g of fruits and vegetables a day, the pooled RR for patients that consumed ≥600 g of fruits and vegetables a day was 0.68 (95% CI 0.54–0.87). There have been inconsistent results regarding intake of vitamins and minerals and RCC risk [15].

The inverse relationship between fruit and vegetable intake and RCC risk may be related to carotenoids found in these food groups. Carotenoids protect cells against cancer by inhibiting oxidative damage to DNA, mutagenesis, malignant transformation, and tumor growth [20]. However, as mentioned above, results have been mixed when looking at intake of vitamins and minerals alone and RCC risk.

Alcohol

Alcohol consumption is associated with a decreased risk of development of RCC. A meta-analysis of 20 studies revealed this protective effect of alcohol [16]. Any alcohol drinking was associated with significantly decreased risk of RCC (RR 0.85, 95% CI 0.80–0.92). When assessing the dose-response relationship of alcohol, the RR was 0.90 (95% CI 0.83–0.97) for light drinking, 0.79 (95% CI 0.71–0.88) for moderate drinking, and 0.89 (95% CI 0.58–1.39) for heavy drinking. Results remained consistent when controlling for smoking, BMI, and hypertension.

Potential mechanisms of action that are hypothesized include the interplay between alcohol and insulin sensitivity, or the diuretic effect of alcohol, which increases urine volume and may reduce the time carcinogenic solutes are in contact with renal epithelium [21]. However, studies have shown that total fluid intake is not associated with RCC risk [22].

Medical Comorbidities

Hypertension

Several large prospective studies have shown that hypertension and/or its treatment is associated with RCC. A 2017 meta-analysis of 18 prospective studies revealed that a history of hypertension was associated with a RR of 1.67 (95% CI 1.46–1.90) for the development of RCC [23]. Results were similar after adjusting for BMI, hypertension, and smoking. Furthermore, each 10-mmHg increase in systolic and diastolic blood pressure was associated with 10% and 22% increased risk of kidney cancer, respectively. Given that most studies are based on diagnosis of hypertension, which is inevitably linked to use of antihypertensive medications, the relationship between hypertension, antihypertensives, and RCC is controversial. In a prospective study evaluating the risk of blood pressure, antihypertensives, and RCC, blood pressure was independently associated with RCC, and individuals taking antihypertensive agents were not at a significantly increased risk unless blood pressure was poorly controlled [24]. This supports the hypothesis that hypertension rather than antihypertensives increases RCC risk.

Potential biologic mechanisms underlying the relationship between hypertension and RCC are thought to involve high blood pressure leading to increased levels of lipid peroxidation by-products, which can cause DNA adducts, as well as hypertension leading to renal tubular damage making the kidney more susceptible to circulating carcinogens [25, 26].

Obesity

Several studies have shown that excess body weight is a risk factor for RCC. In a meta-analysis of prospective studies evaluating BMI and cancer incidence, the RR of developing renal cancer was 1.24 (95% CI 1.15–1.34) in men and 1.34 (95% 1.25–1.42) in women [27]. Furthermore, a large prospective cohort study of over 300,000 participants revealed that the risk for RCC increased with baseline BMI [28]. Compared to a reference group with a BMI of 18.5–22.5, the RR for men with a BMI of 25–27.5 was 1.43 (95% CI 1.07–1.92) and 1.57 (1.07–2.29) for women. Additionally, for patients with a BMI ≥35, the RR increased to 2.47 (95% CI 1.72–3.53) for men and 2.59 (95% CI 1.70–3.96) for women. Weight gain in midlife has also been shown to be associated with increased RCC risk [28, 29]. Interestingly, while excess body weight is associated with increased risk of developing RCC, it is also associated with higher overall and disease-specific survival in patients with newly diagnosed RCC, known as the obesity paradox [30]. This paradox may partly be explained by alterations in gene expression by obese patients. For instance, one genome-wide analysis performed in patients with RCC showed downregulation of fatty acid synthase, which may be associated with decreased RCC tumor growth [31].

While the mechanism of BMI leading to increased risk of RCC is not fully understood, it has been proposed that excess BMI can cause damage to the kidneys by a number of mechanisms that may predispose to RCC including oxidative stress (obesity can lead to an increase in lipid peroxidation by-products that can cause DNA adducts), renal atherosclerosis, and hormonal alterations including levels of insulin-like growth factor-1, vascular endothelial growth factor, and estrogen [32, 33].

Acquired renal cystic disease

Acquired renal cystic disease (ARCD) occurs in the setting of prolonged azotemia and therefore develops in patients with end-stage renal disease. ARCD is estimated to be present in 35–50% of patients on chronic dialysis [34]. There is up to 50-fold increased risk of RCC in ARCD than the general population [34]. There are several differences between renal cancers that develop in the setting of ARCD compared to the general population. ARCD patients are younger, predominantly male, and their tumors are often bilateral and multifocal. These tumors are also considered to be of low malignant potential [35]. Furthermore, the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia recognizes ARCD-associated RCC as a distinct epithelial tumor within the classification system [36].

Although transplantation and restoration of renal function are associated with regression of ARCD, the risk of RCC remains [37, 38].

While it is suggested that cysts in ARCD undergo malignant transformation, the mechanism of RCC development in patients with ARCD is largely unknown. Implicated factors include enhanced expression of growth factors and mutations in end-stage kidneys and the uremic milieu leading to immunosuppressive effects [39].

Kidney stones and urinary tract infections

There have been mixed data regarding the association between kidney stones and urinary tract infections and the development of RCC. To elucidate the relationship, a meta-analysis of seven observational studies was performed [40]. The pooled RR for RCC in patients with kidney stones compared to controls was 1.76 (95% CI 1.24–2.49). Interestingly, the association was only significant in males. The study, however, has major limitations including not controlling for confounding factors such as smoking and dietary habits. Furthermore, patients with kidney stones are more likely to undergo additional imaging, increasing detection of RCC. Other studies have shown a potential association between history of urinary tract infection and risk of RCC when confounders such as lifestyle and diet are controlled for; however, results of other studies are largely mixed [41].

The theorized mechanism for the potential increased risk of RCC in patients with kidney stones and urinary tract infections is related to the inflammatory response, which can promote the growth of neoplastic cells [42, 43].

Diabetes It is debated whether diabetes is an independent risk factor for development of RCC. A large retrospective study showed a significantly increased risk of RCC in diabetics in both men (RR 1.3, 95% CI 1.1–1.6) and women (RR 1.7, 95% CI 1.4–2.0), as well as higher risk of cancer mortality [44]. Another large retrospective cohort study also showed elevated risk of RCC in diabetic patients; however, this elevated risk declined after controlling for obesity [45]. Other studies have shown no significantly increased risk of RCC in patients with a history of diabetes [46]. Overall, the increased risk of RCC in patients with a history of diabetes appears to be linked to associated risk factors such as obesity and hypertension.

Hepatitis C A large cohort study of over 67,000 patients in a cancer registry tested for hepatitis C virus (HCV) showed that RCC was diagnosed in 0.6% of HCV-positive patients versus 0.3% of HCV-negative patients, with a RR of 1.77 (95% CI 1.05–2.98) in HCV-positive patients [47]. Additionally, HCV-positive patients were diagnosed at a younger age than HCV-negative patients ($p < 0.001$). In contrast, other large retrospective studies have shown no association between HCV and RCC [48]. However, in a recent prospective study, adults with RCC or newly diagnosed colon cancer were screened for HCV antibody, and RCC patients had a higher rate of HCV antibody positivity (8%) than colon cancer patients (1%) ($p < 0.01$) [49].

The mechanism for the potential association between HCV and RCC is not known. In HCV-mediated chronic kidney disease, HCV RNA and core protein have been isolated in kidney glomerulus and tubules [50]. Whether there is an oncogenic potential associated with these proteins is under exploration.

Exposures

Occupational exposure

Exposure to toxic compounds has been linked to the development of RCC. An international multicenter population case-control study evaluated the relationship between occupational exposures and RCC [51]. A number of exposures were significantly associated with RCC including employment in the blast furnace, coke oven, and iron and steel industries. Additionally exposure to asbestos, cadmium, dry cleaning solvents, gasoline, and other petroleum products was found to be associated with RCC. These analyses were adjusted for age, center, BMI, and cigarette use. Interestingly, for the majority of exposures, there was no clear dose-dependent increase in risk, except for other petroleum products. Overall, the literature on occupational exposures and RCC risk is conflicting with difficult to parse out confounding variables. Regardless, it is recommended to prevent exposure to carcinogens such as asbestos and cadmium, which are known to cause DNA damage [12].

Analgesic exposure

Evidence regarding the association between analgesic use and RCC is largely mixed. Two large prospective studies investigated the relationship with conflicting results [52, 53]. One study included data from the Nurses' Health Study and the Health Professionals Follow-up Study, which included 77,525 women and 49,403 men, respectively, with long-term follow-up [52]. This study found that aspirin and acetaminophen use were not associated with RCC risk; however, regular use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with increased RCC risk with a RR of 1.51 (95% CI 1.12–2.04), with a dose-response relationship between duration of nonaspirin NSAID use and RCC risk. This was consistent in both cohorts analyzed in the study. A multivariable model was used which adjusted for BMI, smoking, hypertension, physical activity, fruit and vegetable intake, alcohol use, and parity in women. Of note, the authors did not control for history of chronic kidney disease. The second study to evaluate the association of analgesic use and RCC included data from two large patient cohorts: the US Kidney Cancer Study and the Prostate Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [53]. The US Kidney Cancer Study included 1,217 RCC cases and 1,235 controls, and PLCO consisted of 98,807 participants. In this study,

acetaminophen use was associated with significantly increased RCC risk (OR 1.35, CI 1.01–1.83 in the US Kidney Cancer Study, and HR 1.68, 95% CI 1.19–2.39 in PLCO). This was further supported by a meta-analysis performed by the authors. Interestingly, in the US Kidney Cancer Study cohort, RCC risk was not associated with prescription acetaminophen use, and in the PLCO cohort elevated risk was absent among long-term users. Neither aspirin nor NSAIDs were associated with RCC risk in this study.

Overall, it is unclear if aspirin, NSAIDs, or acetaminophens are associated with an increased risk of RCC, particularly outside of development of chronic kidney disease. Potential biologic mechanisms for association do exist for each class. NSAIDs inhibit cyclooxygenases 1 and 2, which are important regulators of homeostasis. Renal damage with poor maintenance of homeostasis may contribute to carcinogenesis [54]. In the case of acetaminophen, the drug is converted to N-acetyl-p-benzoquinoneimine in the liver and kidney, which in excess levels can form protein adducts, bind to liver and kidney DNA, and disrupt homeostasis [55].

Genetics

The majority of cases of RCC are sporadic, with hereditary syndromes accounting for <5% incident cases [12, 56]. Hereditary syndromes include von Hippel-Lindau syndrome, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis renal cell carcinoma, and Birt-Hogg-Dube syndrome [57, 58]. Outside of hereditary syndromes, there is evidence that genetic factors impact susceptibility to RCC. For instance, the risk of RCC for a first-degree relative of a patient with RCC is increased twofold [12]. Furthermore, genome-wide association studies of RCC revealed that genetic variants increase the risk of sporadic RCC, including variants of genes encoding for hypoxia-inducible factor 2 alpha and telomere length [59, 60]. In patients with RCC, factors that favor hereditary contribution to RCC include patients with first-degree relatives with a renal tumor, early onset of disease (prior to age 40), and multifocal or bilateral disease [61].

Conclusions

RCC incidence has been increasing worldwide, with recent stabilization in developing countries. Despite this rise in incidence, mortality rates have largely been stable. RCC incidence varies globally, by sex and race. At least part of these trends can be attributed to exposure to risk factors in certain parts of the world. Lifestyle, medical comorbidities, and chemical exposures all appear to be linked to RCC development. While part of the growing incidence of RCC may be linked to the increased use of medical imaging, efforts such as smoking reduction may be contributing to declining mortality rates. With continued identification of risk factors for the development of RCC, progress can be made in disease prevention.

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