

Renal cell carcinoma: links and risks

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Abstract: This review provides an overview of the incidence of renal cell carcinoma (RCC) and a summary of the most commonly associated risk factors. A literature review was performed with a focus on recent studies with a high level of evidence (large prospective cohort studies and meta-analyses). The incidence rate of RCC varies globally, with the rate rising rapidly in more developed regions, demonstrating the effects of increased use of diagnostic imaging and prevalence of modifiable risk factors. Based on the current evidence, cigarette smoking, obesity, and hypertension are the most well-established risk factors for sporadic RCC worldwide. Acquired cystic kidney disease is also a significant risk factor, specifically in dialysis patients. There is increasing evidence for an inverse association between RCC risk and moderate alcohol consumption. Certain analgesics and occupational exposure have been linked to an increased risk of RCC, although data are limited. Diets rich in fruits and vegetables may provide a protective effect.

Keywords: renal cell carcinoma, risk factors, incidence, smoking, obesity, hypertension

Introduction

Kidney and renal pelvis cancer is among the top ten most common cancers in the world.^{1,2} The most frequent type of renal neoplasm is renal cell carcinoma (RCC), which accounts for ~85% of all renal malignancies. Urothelial carcinoma of the renal pelvis accounts for the remaining 10%.³

RCC arises from the renal parenchyma, particularly from the cells of the nephron and can be further specified into histological subtypes. Clear cell RCC (70%), which arises from the proximal convoluted tubule, is the most common histological subtype, followed by papillary (10%–15%) and chromophobe RCC (5%).⁴

Epidemiology Incidence and mortality

The incidence of RCC varies internationally. The incidence of renal cancer in more developed regions (eg, Europe and North America) is more than twice that of less developed regions (eg, Africa and South America). In Europe, an estimated 16/100,000 individuals were diagnosed with a renal malignancy, whereas in Africa, an estimated 1/100,000 individuals were diagnosed with a renal malignancy in 2012.¹ The regional variation is likely due to a combination of a higher amount of incidental tumors discovered on diagnostic abdominal imaging (computerized tomography scan, ultrasound, and magnetic resonance imaging) and modifiable risk factors such as smoking, obesity, and hypertension.⁵

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It is estimated that >320,000 new cases will be diagnosed in 2016 worldwide. The estimated number of deaths globally is 140,000 or 2.0/100,000 men and women. During the past 10 years, the incidence of RCC has increased worldwide, yet death rates have decreased or remained stable in most countries under study.¹ This could be explained by the fact that the size of renal tumors at diagnosis is decreasing with time in developed countries, such as the USA, which is characterized by better survival outcome.⁶

Survival

Based on a large epidemiologic analysis from the US National Cancer Institute, the overall 5-year survival for kidney and renal pelvis cancer is 73%. The earlier the tumor is discovered, the greater the chance at survival. The 5-year relative survival rate is 92% for localized tumors (confined to the kidney), 65% for tumors spread to regional lymph nodes, and 12% for metastasized tumors.⁷

Sex and age

Worldwide, RCC is twice as common in males as females after adjusting for age. In addition, >50% of RCC is diagnosed among people aged 55–74 years.¹

Race

Within the USA, renal malignancies are more common in African Americans, American Indians, and Alaska Native populations. The incidence of RCC is lower among Asians living in the USA and Asian countries. The highest incidence rates worldwide are observed in the Czech Republic (22/100,000 in men and 9.9/100,000 in women). The lowest rates are seen in most African and Asian populations, with the exception of Israel.⁸

Socioeconomic status

Population-based studies in the USA, Denmark, and the Netherlands show increased incidence of RCC with lower socioeconomic status.^{9–11}

Genetic predisposition

Multiple studies indicate that a family history of RCC is associated with a twofold increased risk of RCC.^{9,12,13} Although the majority of RCC occurs sporadically, several familial syndromes involving mutations in tumor suppressor genes and oncogenes have been identified. Hereditary RCC accounts for 4% of all RCCs. Familial forms of RCC develop at an earlier age and are often multiple and bilateral.¹⁴ von Hippel–Lindau (VHL) disease, which is due to

a tumor suppressor gene mutation of chromosome 3, is the most commonly inherited RCC. Other neoplasms associated with VHL include pheochromocytoma, retinal angiomas, and nervous system hemangioblastomas. There is a 69% chance of developing RCC before age 60 in VHL patients.¹⁵ Other genetic forms of RCC include tuberous sclerosis, hereditary papillary RCC, Birt–Hogg–Dube syndrome, and hereditary leiomyomatosis.

Established risk factors

Based on the current evidence presented later, cigarette smoking, obesity, and hypertension are the most well-established risk factors for sporadic RCC. Acquired cystic kidney disease (ACKD) is also a significant risk factor.

Cigarette smoking

Tobacco exposure is a major risk factor for RCC. According to the US Surgeon General and the International Agency for Research on Cancer, there is sufficient evidence from several cohort and case–control studies to support causality between tobacco smoking and development of RCC.^{16,17} The overall relative risk for ever-smokers compared to never smokers is ~1.38 for both sexes based on a comprehensive meta-analysis of 24 studies involving North America, Europe, and Australia.¹⁸ The relative risk is lower in former smokers as compared to current smokers. The risk is directly related to duration of smoking and increases with cumulative dose (number of cigarettes smoked per day) and decreases with long-term smoking cessation >10 years.¹⁸ In a large cohort study of ~250,000 US veterans >26 years, the relative risk for renal cancer increased significantly with the number of cigarettes smoked per day, from 1.31 for 1–9, 1.37 for 10–20, 1.6 for 21–39, and 2.06 for ≥40.¹⁹ There is evidence to support that never smokers exposed to environmental tobacco smoke at home or work are also at increased risk of RCC.^{20,21} With respect to histological RCC subtype, a prospective study comparing the relationship between smoking and RCC subtypes demonstrated that active smoking was significantly more common with clear cell (23%) and papillary RCC (26%) than benign histology (14%) and chromophobe RCC (6%).²²

Individuals who are current smokers or have a history of tobacco exposure present with more aggressive forms of RCC and experience worst cancer-specific survival and overall survival. In the USA, tobacco exposure is associated with higher pathological tumor, lymph node, and metastasis classification.²³ A North American study found a dose-dependent relationship between duration of smoking

and survival in individuals with nonmetastatic clear cell RCC: each pack-year of smoking was associated with a 1% increase in mortality. This suggests that smoking may have an ongoing effect on the progression of RCC. Compared to nonsmokers, smokers have a higher incidence of impaired performance status and medical comorbidities, including chronic obstructive pulmonary disease and coronary artery disease, which may explain why overall survival is worst in smokers.²⁴

There are multiple mechanisms that explain how tobacco exposure promotes the development of RCC. Cigarette smoke induces oxidative stress and injury in the kidney and causes renal impairment.^{25,26} The free radicals contained in cigarette smoke cause oxidative DNA damage, which may lead to the development of cancer.²⁷ For example, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is the most abundant *N*-nitrosamine present in cigarette smoke and a known carcinogen. It induces DNA damage and has been associated with increased risk of RCC.²⁸ Chromosome 3p aberrations are the most frequently identified genetic alterations in RCC. Benzo[α]pyrene diol epoxide, a major constituent of cigarette smoke, induced chromosome 3p aberrations in cultured peripheral blood lymphocytic cells from individuals with RCC, suggesting that chromosome 3p may be a specific molecular target of cigarette carcinogens.²⁹ Another major component of tobacco, nicotine, has been shown to stimulate pathological angiogenesis and accelerate tumor growth.³⁰ Furthermore, a study examining the histopathological changes brought about by 6 weeks of cigarette smoke in rat kidneys showed lymphocytic infiltration of the interstitium and intraluminal hyaline deposition in specifically the proximal tubules, which is predominantly where RCC originates.³¹

Obesity

Obesity, which in adults is defined by the World Health Organization as a body mass index (BMI) ≥ 30 kg/m², increases the risk of RCC among both men and women.³² The prevalence of overweight (BMI ≥ 25 to < 30 kg/m²) individuals and obesity has been on the incline in the past 3 decades, particular in developed countries.³³ In the USA, more than one-third of adults and almost 17% of children and adolescents are obese.³⁴ The increasing prevalence of obesity is likely a contributor to the increasing incidence of RCC.

There are various methods to assess obesity. BMI and body weight are measures of total body fat, whereas waist and hip circumference are measures of central adiposity. A large prospective cohort study of $> 340,000$ Europeans demonstrated that increased BMI, body weight, and hip and

waist circumference were related to an increased risk of RCC in females. However, among males, a low rather than high hip circumference was related to an increased RCC risk after accounting for body weight. This suggests that body fat distribution may be more predictive in males, particularly hip circumference.³⁵ Obesity follows a dose-response pattern between increasing obesity and increasing magnitude of risk. A quantitative summary analysis of 14 studies from Australia, the People's Republic of China, Canada, the USA, Italy, and France revealed a relative risk of 1.07 per unit increase in BMI in both sexes.³² Bjørge et al demonstrated a similar relationship in a large cohort of Norwegian men and women. In their study, they calculated a relative risk of 1.05 per unit increase in BMI.³⁶ Morbidly obese (BMI ≥ 35 kg/m²) individuals were shown to be at 71% increased risk compared to normal weight individuals in the USA.³⁷ Obesity early in adulthood along with obesity near diagnosis of RCC are both associated with an increased risk of renal cancer.^{38,39}

Obese patients are technically more challenging surgically as there are significant increases in blood loss and operative time with increasing BMI.⁴⁰ Although obesity is an established risk factor in the development of RCC, the relationship between obesity and overall or cancer-specific survival of individuals with RCC is inconsistent. A large prospective cohort study consisting of $> 900,000$ US adults demonstrated a dose-dependent relationship between increasing body weight and overall death rates in patients with RCC.⁴¹ Since tumor stage at the time of diagnosis predicts survival outcome,⁴² one may hypothesize that increased BMI may be associated with advanced tumor stage. However, data indicate that obese patients are not at a greater risk of advanced tumor stage at the time of diagnosis.^{39,43} Surprisingly, two American studies show improved disease-specific survival for obese patients.^{44,45} Furthermore, Korean and German studies suggest that being underweight at the time of surgery worsens cancer-specific survival by more than four times that of normal weight individuals.^{46,47} BMI is an imperfect measurement of body fat as it does not distinguish between fat and muscle and between visceral and subcutaneous fat. Based on the results of multiple Japanese studies, visceral obesity rather than BMI may be a more useful predictor of disease-recurrence survival rather than BMI since high visceral fat has been associated with longer cancer-specific survival and overall survival.⁴⁸⁻⁵⁰

Multiple mechanisms linking obesity to increased risk of RCC have been proposed. Adipose tissue secretes molecules known as adipokines into the blood stream, which play a role in energy balance, macromolecule metabolism,

and signaling to the rest of the body. Adipokines such as leptin and interleukin-6 support tumor growth and circulate at higher levels in obese patients. In contrast, obese patients have lower levels of adiponectin, which has tumor suppressive effects.⁵¹ Aberrations in hypoxia-detecting pathways underlie most cases of sporadic RCC.⁵² Obesity induces renal damage and tissue hypoxia that may predispose to tumor formation.⁵³ In vitro experiments show that RCC expresses elevated amounts of insulin and insulin-like growth factor-1 receptor protein, which have been shown to play a significant role in the development and progression of RCC.⁵⁴ In addition, lipid peroxidation that has been shown to promote renal tumorigenesis in vitro is increased among the obese.⁵⁵

Hypertension

Hypertension is a significant risk factor for RCC. Several studies conducted in the USA and in the People's Republic of China show a dose-dependent increase in RCC with increasing blood pressure measurement taken at baseline clinic visit.^{37,56–58} An 18-year follow-up of a Norwegian cohort revealed that compared to the reference systolic pressure of <130 mmHg, the relative risk in women with systolic pressure 130–149 mmHg was 1.7, with levels 150–169 mmHg the risk was 2.0, and with levels \geq 170 mmHg, the risk was 2.0.⁵⁹ In a large prospective European cohort study, both elevated systolic and diastolic blood pressures were associated with a two- to threefold increased RCC risk that was independent of sex, BMI, smoking, and use of antihypertensives.⁶⁰ Multiple studies consisting of patients from Europe and the USA report similar results.^{61–63} The risk decreases with reduction in blood pressure over time, which suggests that the risk of RCC can be modified with better blood pressure control.^{64,65} Antihypertensives, namely diuretics, have been implicated in earlier studies, but current evidence suggests that it is the underlying disorder of hypertension rather than the treatment that increases the risk of RCC.^{66–70} Perioperative blood pressure \geq 150/100 mmHg negatively affects the overall survival in Korean patients with RCC.⁴⁶ Yet, in a study of RCC cases in the USA, a self-reported history of hypertension was associated with a better overall survival.⁷¹ The biological mechanism underlying the relationship between elevated blood pressure and increased risk of RCC remains unknown. One theory suggests that the chronic renal hypoxia accompanying hypertension promotes tumor cell proliferation and angiogenesis by a transcription factor known as hypoxia inducible factor.⁷² Similar to individuals with elevated BMI, patients with essential hypertension

also exhibit increased lipid peroxidation, which has been implicated in the pathogenesis of RCC.⁵⁵

Acquired cystic kidney disease

ACKD occurs in patients with end-stage renal disease on dialysis. The frequency of ACKD increases with the duration of dialysis.⁷³ Over 50% of patients on dialysis for >3 years will develop renal cystic changes.⁷⁴ A comprehensive review of the literature shows that there is up to a 50-fold increased risk of RCC in patients with ACKD compared to the general population. ACKD-associated RCC tumors tend to be more common in males and often bilateral and multicentric.^{75,76} RCC can develop at any time in patients on dialysis with ACKD, even after renal transplantation, although RCC is more likely to involve the native kidney than the transplanted kidney.^{77,78} The prevalence of RCC in patients with ACKD is 19%, whereas the prevalence in native kidneys after renal transplantation is 5%. This suggests that renal transplantation may reduce risk of RCC in dialysis patients.⁷⁹

Risk factors with conflicting or limited evidence

Alcohol

Multiple well-conducted systematic reviews examining several studies from Europe, North America, Australia, and Asia suggest that moderate alcohol consumption reduces the risk of RCC.^{80–83} Although the majority of the literature supports a link between alcohol consumption and risk of RCC, some American and Japanese studies suggest there is no association.^{37,56,84} A large prospective cohort study of >100,000 American participants showed an inverse relationship between alcohol consumption and RCC risk in both males and females with all types of alcoholic beverages, including wine, beer, and liquor.⁸⁵ Two large international meta-analyses summarized a specific dose–response relationship and found that 5–12 g/d increment of alcohol intake corresponded to at least a 5% statistically significant decreased risk of RCC. When these associations were examined separately by sex, alcohol specifically from wine reduced the risk of RCC in females whereas alcohol from beer and liquor reduced the risk of RCC in males. This suggests sex-specific and alcoholic beverage-specific differences in the association between alcohol intake and RCC risk.^{86,87}

Analgesics

There is mixed evidence supporting analgesics as a risk factor for RCC.^{88–91} A recent large meta-analysis of 20 studies from North America, Europe, and Australia including >8,000

cases of renal cancer showed that the use of acetaminophen and nonaspirin nonsteroidal anti-inflammatory drugs was associated with an increased risk of renal cancer. No overall increased risk was found for aspirin, but a significant risk was found when the analysis was restricted to non-US countries. Although the majority of studies specifically address RCC, some studies grouped RCC and urothelial carcinoma of the renal pelvis together.⁹²

Diabetes mellitus

A history of diabetes mellitus is reported to be associated with increased risk of RCC in some North American, Asian, and European studies^{93–99} but not in other studies in the USA and Italy when correcting for confounding factors, such as BMI, smoking, and hypertension.^{37,62}

Diet

Epidemiologic studies evaluating dietary habits and risk of RCC are inconsistent. The majority of studies performed in North America, Europe, and Australia suggest that high consumption of fruits and vegetables may be associated with reduced risk of RCC, but not all.^{37,100–105} A meta-analysis of seven North American and European studies indicates that the risk of RCC is inversely associated with dietary fiber intake in the form of vegetable and legume fiber but not with fruit and cereal fiber intake.¹⁰⁶ Another meta-analysis of 12 studies performed in North America, Europe, Australia, and Russia specifically focusing on cruciferous vegetable intake found that increased intake may reduce the risk of RCC.¹⁰⁷ Asian and North American studies indicate that excess risk may be associated with heavy meat consumption^{108–111} and high fat dairy products,¹¹² although data are limited.

Occupation exposure

There are numerous studies examining the risk of RCC in relation to occupational exposures worldwide; however, the data remain limited and inconclusive. Table 1 lists the

Table 1 Occupational exposures associated with risk of RCC

Asbestos
Dusts – glass fiber, mineral wool, and brick
Chemicals – polycyclic aromatic hydrocarbons
Fumes – silica and solder
Metals – cadmium and lead
Mineral oils
Organic solvents – benzene and trichloroethylene
Paints
Rubber

Abbreviation: RCC, renal cell carcinoma.

various occupational exposures that have been connected to an elevated risk of RCC.^{113–127}

Summary

The overall incidence of RCC internationally continues to trend upward. The liberal use of diagnostic abdominal imaging detecting incidental renal tumors is likely a contributor along with established risk factors, such as smoking, obesity, and hypertension. Several studies support a dose-dependent increase in the risk of RCC for all three major risk factors and a decrease in risk with smoking cessation, weight loss, and blood pressure control. Thus, a focus on these modifiable risk factors may help prevent future cases of RCC. Moderate alcohol consumption may be associated with a decreased risk of RCC. Certain analgesics and occupational exposure have been linked to increased risk, although data are limited. Diets rich in fruits and vegetables may provide a protective effect. Additional studies are needed to explain all factors that may play a role in the development of RCC.

Disclosure

The authors report no conflicts of interest in this work.

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