6

The Etiology of Renal Cell Carcinoma and Upper Tract Urothelial Carcinoma

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Abstract: Renal cell carcinoma accounts for most malignant renal cancers, with clear cell as the most common subtype. Nowadays, the typical presentation of loin pain, frank hematuria, and palpable mass of renal cell carcinoma are seen less frequently. The advancements in medical imaging, in particular abdominal imaging, have significantly increased the number of small renal masses detected incidentally. Urothelium lining of upper urinary tract starts from the calyces and run the entire length of the ureter till the vesico-ureteric junction. Urothelial carcinoma is the malignancy of this urothelium tract. Established risk factors for renal cell carcinoma, and to some extent to upper tract urothelial carcinoma, include male gender, smoking, hypertension, obesity, and end stage renal diseases. This chapter provides an overview of the etiology of renal cell carcinoma and upper tract urothelial carcinoma.

Keywords: etiology of kidney cancer; etiology of renal cell carcinoma; etiology of upper tract urothelial carcinoma; risk factors for etiology of upper tract urothelial carcinoma; risk factors for renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for most malignant renal cancers. The subtypes of RCC include clear cell (most common), papillary, chromophobe, multilocular cystic, medullary, and collecting duct RCC. With the advancements in medical imaging and easily accessible abdominal imaging facilities, increasing numbers of small renal masses are being detected with majority of patients diagnosed incidentally when they are imaged for other non-urological reasons or symptoms. This has certainly led to an increasing detection rate of renal cancers, leading to earlier intervention and better treatment pathways for localized small renal cancers. This is supported by the latest Global Cancer Statistics report, as there were 431,288 new renal cancers diagnosed worldwide in 2020 alone. This incidence rate accounted for 6.1/100,000 age standardized rate (ASR) in males and 3.2/100,00 in females (1). Following early detection of incidental small renal cancers, effective treatment options have been successful in the last few decades. These treatment options range from minimally invasive percutaneous laparoscopic cryoablation and radiofrequency ablation to open or robotic assisted partial/total nephrectomy. The success of these modalities of treatment have transformed and improved the prognosis of patients with these incidental early detected small renal cancers.

The upper urinary tract urothelium is the innermost lining of the urinary tract starting from renal calyces collating towards renal pelvis and running the entire length of the ureters till its termination in the vesico-ureteric junction. Upper tract urothelial carcinoma (UTUC) is the malignant change that can occur anywhere along the entire length of the urothelium. Typical clinical presentation of UTUC include hematuria, loin pain and less commonly, palpable mass. Clinical outcome usually depends on the clinical stage at presentation, grade, and presence of muscle invasion of the urothelial carcinoma. UTUC affects the older population with a peak incidence between 70 and 90 years of age (2). Approximately 40–50% of patients present with non-muscle invasive UTUC, 50–60% present with muscle invasive, locally advanced stage, and 25% present with metastases (3). This chapter provides a snapshot of the etiological factors of RCC and UTUC.

RENAL CELL CARCINOMA

The incidence of renal cancers worldwide has an age standardized rate of 4.6 per 100,000 with a morality rate of 1.8 per 100,000 in 2020 (4). Incidence rates vary regionally, largely due to healthcare accessibility for the local population and data acquisition in terms of data reporting. The highest incidence of renal cancers in 2020 was recorded in Northern America (ASR 12.2 per 100,000) with the lowest incidence observed in Middle Africa (ASR 1 per 100,000) (4). Clearly this high incidence detected in Northern America compared to the rest of the world reflects the early detection of incidental renal cancers due to easy access to radiological abdominal imaging facilities in their healthcare system coupled with robust clinical disease reporting. In Europe, the ASR is 8.3–10.3 per 100,000 persons, depending on the different regions of Europe, comparable with Australia and New Zealand (ASR 10.3). In Asia, the range of ASR is 1.4–4.1 (4).

Certainly, demographic factors account for the incidence rates throughout the world and this also reflects the Human Development Index (HDI) of the countries, with the incidence and mortality rates increasing with increasing HDI status. HDI reflects the standard of living, health and knowledge aspects of a country population, with positive correlation towards incidence of cancers.

Despite the increasing trend of early detection of renal cancers leading to earlier treatment options, the mortality rates are still high at a steady rate. In fact, there were 179,368 deaths in 2020 with an ASR of 2.5 in 100,000 males and 1.2 in 100,000 females based on the GLOBOCAN 2020 report (1). This is due to the fact that RCC is still a lethal disease when diagnosed at a locally advanced stage and unfortunately a significant proportion of patients (17%) still present late in the metastatic stage (5). Mortality rates were noted to be higher in Europe (ASR range 2.4–3.4) compared to Asia (ASR 0.8–1.8) while lowest were recorded for regions of Africa (ASR 0.7–1.2) (4).

Age and gender

The risk of developing renal cancer increases with age, with a peak incidence of 60–70 years, an ASR of 0.5 in those below 40 years old and rising to 35 in those who are more than 75 years of age (5). However, there is a rising trend in the detection of incidental small renal cancers in the younger age groups as there is increased public awareness and easier access to routine abdominal imaging. In the latest GLOBOCAN 2020 report, the risk of developing renal cancer in males is close to double (ratio of 1.9 :1) compared to females with an ASR of 6.1 and 3.2 respectively (1). This rate has remained the same across all age groups, signifying the male predominance. In fact, men are more likely to have larger tumors, more aggressive histological types and grades, present at later advanced stages, and poorer prognosis (6). Numerous theories have been proposed for this gender propensity – androgenic hormonal cancer promotion (7) and biomolecular pathways with influences from inflammatory and immune mediated genes (8).

Genetic factors

The alterations in the genetic landscape for the development of RCC have been extensively studied in the last few decades. Perhaps the most influential genetic aberration in clear cell RCC (ccRCC) is the tumor suppressor gene von Hippel Lindau (vHL). The inactivation of vHL gene leads to the upregulation of hypoxia inducible factors leading to tumor neo-angiogenesis and proliferation (9). Numerous other genetic alterations have also been shown to contribute along with inactivation of vHL gene in the development of ccRCC. These are polybromol (PBRM1), BRCA1 associated protein-1, SET domain containing 2 (SETD2) and lysine K-specific demethylase 6A (KDM6A) (10). Hereditary RCC syndromes have been also well documented. The common familial RCC syndromes include von Hippel Lindau syndrome (affected gene vHL, autosomal dominant disease with risk of pheochromocytoma, pancreatic tumors and central nervous system tumors), Birt-Hogg-Dube syndrome (affected gene folliculin, autosomal dominant disease with risk of chromophobe RCC and papillary RCC) and hereditary leiomyomatosis renal cell cancers (affected gene fumarate hydratase, autosomal dominant disease with risk of papillary RCC) (11).

Smoking

Positive history of smoking has long been associated with the risk of developing RCC. Numerous carcinogens from active or passive smoking have been linked to development of cancers including renal cancers. These carcinogens include multiple chemical classes, including polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, aldehydes, volatile organic hydrocarbons, and metals. The carcinogenic pathways starts with inhalation of carcinogens from smoking leading to covalent bond formations between carcinogens and DNA resulting in somatic mutations in critical oncogenes and tumor suppressor genes (12). The risk of renal cancers increases with increasing exposure to smoking leading to higher grade diseases, while cessation of smoking led to decrease in relative risk. A meta-analysis by Cumberbatch et al. confirmed pooled relative risk of RCC incidence of 1.31 for all smokers, 1.36 for current smokers, and 1.16 for ex-smokers (13).

Hypertension

Another modifiable risk factor in the development of renal cancers include history of hypertension. Previous studies have concluded the positive association of hypertension as an independent risk factor for renal cancers (14, 15). This association was further confirmed by a meta-analysis of 18 prospective studies which showed a 67% increased risk with history of hypertension and with every 10 mmHg increase in blood pressure led to a 10–22% increased risk of developing RCC (16). Possible explanations for this association include chronic renal hypoxia and lipid peroxidation leading to development of hypoxia-inducible factors which promotes malignant angiogenesis and tumor cell proliferation (17).

Obesity

Obesity has been commonly linked to risk of developing various cancers including renal cancers. A study on 77,620 participants by Macleod et al. revealed a significant association of obesity and RCC risk with a 1.7 hazard ratio (95% CI 1.06–2.79) in those with body mass index greater or equal to 35 kg/m^2 versus those with less than 25 kg/m^2 (18). With 5 kg increases in weight, there was a relative risk increase in RCC risk of 25% in males and 35% in females (19). Theories supporting the proposed association of obesity and RCC center around circulating sex-hormones, insulin-like growth factors and adipokines (leptin, adinopectin) and cellular events relating to chronic inflammation (19, 20). This led to the proposal of use of statins to decrease RCC risk, but a meta-analysis revealed no association between statins usage and RCC risk (21). However, increased levels of physical activity may decrease the risk of RCC by reducing obesity and improving blood pressure. In the same meta-analysis, Zhang et al. showed inverse association of RCC risk with physical activity (relative risk 0.88) (21).

Diet

A healthy diet combined with active lifestyle will prevent obesity and decrease the risk of RCC. Diet consisting of high fruit and vegetable intake, particularly

cruciferous vegetables, have been associated with decreased risk of developing RCC (22). However, the large EPIC study of 375,851 participants revealed no significant association between fruit and vegetable intake with RCC risk (23). In terms of alcohol intake and association with RCC risk, various studies have found mixed results with some studies showing a reduction in risk with alcohol intake while others showed no association (18, 24).

Concomitant diseases

A meta-analysis which studied the association of renal stones with RCC risk showed that there was pooled relative risk of 1.76 (95% CI 1.24–2.49) in patients with RCC and renal stones. A further subgroup analysis noted a significantly increased risk of RCC only in males and not in females with renal stones (25). End stage renal failure often leads to pathological degenerative cystic changes which is termed as acquired cystic kidney disease. These end stage kidney diseases have a positive correlation with RCC risk, with at least a ten-fold increased risk of developing RCC in their lifetime (26).

Analgesia use

Regular use of analgesia, particularly nonsteroidal anti-inflammatory drugs (NSAIDS), has been long studied in regard to its association with development of RCC risk. A meta-analysis revealed that there was an increased risk of RCC with regular use of acetaminophen and non-aspirin NSAIDS (pooled RR 1.51) (27).

UPPER TRACT UROTHELIAL CARCINOMA

The incidence of UTUC has been difficult to quantify and validate as most UTUC that arise in the renal calyces or pelvis get collated together with the rest of renal cancers. UTUC is relatively uncommon as it represents only 5% of urothelial cancers and less than 10% of renal tumors (3). Data from Western countries estimate the incidence of UTUC at 2 new cases per 100,00 person-years (2). The last few decades have seen improvement in detection of UTUC due to better imaging modalities in the form of computed tomogram and magnetic resonance urography and smaller flexible ureteroscopes that allow better visualization and subsequent tissue biopsy opportunities. This has led to early detection and thus influenced the incidence of UTUC. Furthermore, the advancements in bladder cancer surveillance and treatment have also influenced the diagnosis and earlier treatment of UTUC.

Gender

UTUC is more common in males compared to females, with studies showing that men are affected 2–3 times more than women (28, 29). This higher risk of UTUC in men is somewhat similar to higher bladder cancer risks in men too. Mortality and survival rates of UTUC have not been shown to be

dependent on gender. A study by Shariat et al. on patients who underwent radical nephroureterectomy for UTUC did not show any association between gender of patients with pathologic features, prognosis, recurrence of disease or cancer-specific mortality (28).

Smoking

Smoking is a well-known risk factor for urothelial cancers including UTUC. The estimated relative risk of developing UTUC from smoking is 2.5 to 7-fold (30). Another study involving 864 patients who underwent radical nephroureterectomy for UTUC revealed that current and long-term heavy smokers had more aggressive disease, presented at advanced later stages, were prone to disease recurrences, and had a higher cancer specific mortality rate. It was also shown in that same study, patients who stopped smoking >10 years prior to surgery for UTUC had a better oncologic outcome compared to patients who were still smoking or ceased <10 years prior to surgery (31).

Other risks

A significant risk factor for the development of UTUC is hereditary non-polyposis colon cancer (Lynch syndrome). This is an autosomal dominant disease characterized by a spectrum of malignancies (colon cancer, endometrial cancer, UTUC, ovarian cancer, gastric, and hepatobiliary cancers which occur in younger age groups). The main genetic problem arises from the germline mutation of DNA mismatch repair genes (MMR genes) or in the hEPCAM genes, which result in microsatellite instability in regions of DNA (32). The reported lifetime risk of developing UTUC in Lynch syndrome patients is between 0.4 and 20%, which translates to about 22 times higher risk than the average population (33, 34)

The risk of Balkan endemic nephropathy is another disease entity noted to increase the risk of developing UTUC which was initially discovered to be endemic in rural areas of Southeastern Europe near the Balkan peninsula. It is a tubulointerstitial disease that leads to chronic end stage kidney disease with high risk of developing UTUC. This is due to the phytotoxin of aristolochic acid (AA) which are in the common plant *Aristolochia clematitis* that grow alongside wheat fields, and therefore consumed in homemade bread (35). A meta-analysis showed that exposure to AA led to overall increased risk of urothelial tract cancers and RCC (OR 6.085) (36).

Kidney stones in renal calyces and renal pelvis can lead to chronic irritation leading to a cascade of chronic inflammation and have been shown to be associated with increased risk of development of UTUC. A Netherlands Cohort Study showed that history of kidney stones was significantly associated with an increased risk of UTUC (HR 1.6) (37).

Association with bladder cancers

Concomitant urothelial carcinoma of the bladder with UTUC is about 8–17% (2). Three popular theories have been widely recognized for this phenomenon—monoclonality, intraluminal seeding from upper tract tumor into bladder (38) and

field cancerization change. In monoclonality theory, a single genetically abnormal cell has spread through the length of urothelium; in field change theory, there is independent development of synchronous nonrelated tumors in different parts of the urothelium (39, 40). It is a well-accepted diagnostic algorithm that patients presenting with hematuria will usually require upper tract imaging to rule out renal cancers and UTUC, and a flexible cystoscopy to rule out urothelial carcinoma of bladder. Similarly, post treatment for bladder urothelial carcinoma or UTUC, there is a regime of surveillance to rule out recurrence and metachronous urothelial carcinoma. The incidence of metachronous UTUC following diagnosis of urothelial carcinoma of bladder is 0.7–1.7% with a median of 4.1 years (41), whereas the incidence of metachronous bladder urothelial carcinoma following UTUC is higher at approximately 15–50% —usually 1–2 years after diagnosis of UTUC (42).

CONCLUSION

RCC and UTUC are important cancers of the upper urinary tract. Both disease entities still carry a high mortality rate particularly if presented at later stages. There exist some common risk factors for the development of both cancers. Over the last few decades, improvement in imaging techniques, enhanced biopsy techniques, and robotics instrumentations have led to earlier detection of such tumors and earlier treatment pathways. Further understanding of the etiology of these RCC, UTUC, and increasing public awareness can lead to prevention strategies in hope of reducing the development of these cancers.

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