

Reverse onconeurology: Cancer risk in patients with chronic kidney disease

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Abstract *Introduction:* Chronic kidney disease (CKD) is a growing global health concern that significantly increases the risk of developing certain malignancies, including kidney cancer. Various etiological factors contribute to this elevated cancer risk in CKD patients. *Methods:* A non-systematic literature search was conducted using PubMed and Google Scholar to gather updates on cancer risk factors, the impact of CKD on malignancy development, renal oncology, and the cancer risk in patients undergoing dialysis. *Results:* Several risk factors were identified. CKD weakens the immune system, impairing the body's ability to combat cancer cells. Patients with chronic renal failure, especially those undergoing hemodialysis or who have received renal transplants, are at an increased risk of developing renal malignancies, skin cancer, and certain types of lymphoma. Additionally, CKD treatments such as dialysis and specific medications may further elevate cancer risk. *Conclusion:* These findings highlight the importance of rigorous evaluation and cancer screening in CKD patients to mitigate their heightened cancer risk.

Key words: chronic kidney disease, chronic renal failure, chronic inflammation, malignancy risk, cancer contributing factors

Background

Cancer and its treatments can profoundly impact kidney health in several ways. Chemotherapy can lead to renal damage, while tumors themselves may cause injury to the kidney. The treatment process can also result in significant electrolyte imbalances, further complicating renal function (1, 2). Cancer patients can experience a range of kidney-related disturbances, including acute kidney injury, electrolyte abnormalities, kidney stones, and several complications related to tumor infiltration to the renal tissue (3-5). Onconeurology, a new field of nephrology, is dedicated to the

diagnosis and treatment of kidney diseases in cancer individuals (6, 7). This field includes the diagnosis and management of renal complications that arise as a result of cancer or its treatment, such as chemotherapy-induced kidney damage, tumor-related kidney dysfunction, electrolyte imbalances, and renal complications from immunotherapy (1, 3). In this context, the collaboration of nephrologists and oncologists to manage kidney-related disease in cancer patients is crucial. Therefore, this field focuses on the intersection between nephrology and oncology. Conversely, cancer in kidney disease refers to the development of cancerous tumors in chronic kidney disease (CKD). Therefore,

the term “reverse onconeurology” could be applicable in conditions where cancer occurs in patients with chronic kidney disease. We also have the same term as reverse cardio-oncology as the cancer in individuals with cardiovascular disease (8, 9). This narrative review aims to study the risk factors associated with cancer development in individuals with CKD.

Search strategy

For this review, we conducted a search across several databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase, using various keywords such as chronic kidney disease, CKD, chronic renal failure, cancer risk factors, cancer treatment, chronic inflammation, and pro-inflammatory cytokines. We screened 4,336 articles related to the topic and included 39 original articles and review articles that specifically focus on the relationship between CKD and the incidence of various cancers.

Association between cancer and renal diseases

The relationship between cancer development and renal disease is intricate and multifaceted. Numerous factors can contribute to the development of both cancer and renal disease and there are instances, where one condition can predispose an individual to another one (10-12). Certain risk factors, such as smoking, obesity, and hypertension, are known to increase the risk of both cancer and renal disease. Moreover, chronic inflammation plays a role in the development of various cancers and also renal disease (13, 14). Conditions like chronic renal failure can lead to persistent inflammation, which may promote the development and progression of cancer. In addition to genetic syndromes, such as von Hippel-Lindau (VHL) disease, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis, and renal cell cancer syndrome, are associated with a strengthened risk of both kidney cancer and other types of malignancies (15, 16). Moreover, certain cancer treatments, such as chemotherapy drugs and radiation therapy, can cause kidney damage and lead to

the development or exacerbation of renal disease (17). Likewise, certain cancers can produce substances that affect the kidneys or other organs, leading to the development of paraneoplastic syndromes. These syndromes can manifest as a range of renal disorders, including glomerulonephritis and electrolyte imbalances (3, 18). Conversely, patients with chronic kidney disease may face an elevated risk for certain types of cancers, such as kidney, bladder, prostate, urinary tract, pancreatic, digestive, genitourinary tumors, and also skin cancer (19). Factors influencing cancer risk in CKD patients include the male gender and the elderly population (20). Previous investigations showed that the prevalence of CKD is strengthening in cases with kidney carcinoma, urinary tract malignancies, and pancreatic tumors (19, 21). In contrast, the prevalence of chronic renal failure is higher among individuals with cancer compared to those without cancer, regardless of the type of malignancy (22). Patients with genitourinary cancers are more likely to develop CKD compared to those without cancer (3, 22).

Mechanism of cancer development in CKD

Compared to patients without CKD, chronic renal failure is a risk factor for cancer by itself. Notably, the risk of malignancy in patients with chronic renal failure increases with decreasing kidney function, with the highest risk in individuals on dialysis (23). The correlation between CKD and cancer can be related to numerous factors like oxidative stress, changes in intestinal microbiota, impairment of DNA repair, excessive parathyroid hormone, accumulation of carcinogenic compounds and chronic inflammation (24). Accordingly, CKD is also associated with worse cancer outcomes, including higher mortality rates and decreased response to cancer treatment (25).

The mechanisms linking CKD and cancer

The possibility of early-stage CKD as a risk factor for cancer development is not well-known, nevertheless, some previous studies have investigated cancer-related death or incidence in cases with and without chronic

renal failure (23). These studies have shown a rise in malignancy-related deaths across those with reduced kidney function. Importantly an enhanced risk of malignancy related to moderate chronic renal failure was also demonstrated in previous investigations, however, this finding was restricted to the male gender (3, 26). It should be noted that this association appears to be site-specific for pulmonary and urinary tract malignancies.

A brief overview of reverse onconeurology

The coexistence of cancer and CKD can have several mechanistic impacts, as both conditions can influence each other in complex ways. Certain cancers, such as kidney carcinoma can directly affect renal function. Tumors in or near the kidney can obstruct the urinary tract, leading to decreased kidney function (11, 19, 24). Furthermore, certain malignancy treatments, such as chemotherapy or radiation therapy, can also have nephrotoxic effects, potentially exacerbating the coexisting CKD or causing acute kidney injury. Therefore, both cancer and CKD can have metabolic implications (3, 27). Cancer-related factors, such as increased energy expenditure, altered metabolism, and systemic inflammation, can further strain the already compromised metabolic balance in CKD patients. This can lead to malnutrition, muscle wasting, and metabolic derangements (28, 29). Likewise, cancer can trigger an immune response, leading to systemic inflammation. Previous studies showed that CKD patients, often have dysregulated immune function, which causes magnification of inflammatory responses (30, 31). Accordingly, chronic inflammation in CKD can accelerate the progression of kidney damage which may contribute to the development or progression of cancers (32). Moreover, managing cancer in the setting of CKD is a challenge in clinical medicine. Some cancer treatments, such as certain chemotherapeutic agents, necessitates to be adjusted or avoided in CKD patients to prevent further kidney damage (33). The presence of CKD can also complicate the dosing and tolerability of cancer therapies (34). Notably, both cancer and CKD are associated with an increased risk of cardiovascular disease. The combination of these two conditions can further elevate the risk of cardiovascular events, such as

heart attacks or strokes (35, 36). Likewise, certain risk factors, such as age, obesity, smoking, and hypertension, are common to both cancer and CKD. Notably the occurrence of one disorder could intensify another one, creating a complex interplay between cancer and kidney disease (37). To find the risk of malignancy in individuals with CKD, one study examined a group of adult CKD cases with a glomerular filtration rate below $60\text{ml/min}/1.73\text{m}^2$. This study consisted of 13,750 individuals with a diagnosis of chronic renal failure. In their cohort, around 20% were diagnosed with a malignancy. The risk factors connected with cancer development in their patients consisted of increasing age and male gender.

On the other hand, this study showed diabetics were related to a lower risk of malignancy. They also showed that the parameters associated with enhanced mortality in their group who developed malignancy comprised elderly cases, diabetes, and lower renal function. This study also showed the median period to develop of a cancer upon the diagnosis of chronic renal failure was about 8.5 years (23).

Risk factors for developing cancer-associated nephropathy

Cancer can develop in the kidneys or be linked to specific kidney diseases, some kidney which may increase the risk of developing certain types of cancer (20). As mentioned above, the risk factors for developing cancer-associated nephropathy include smoking, obesity, high blood pressure, certain inherited genetic conditions such as Hereditary Papillary Renal Carcinoma (HPRC), long-term dialysis, and a strong family history of kidney cancer (38). Exposure to cadmium, working with batteries, paints, or welding materials, and overuse of certain medications have also been linked to both kidney cancer and renal failure (39, 40). Previous investigations showed simple kidney cysts are fluid-filled sacs that form in the kidneys and are usually benign. However, complex kidney cysts or cystic kidney diseases such as Autosomal Dominant Polycystic Kidney Disease (ADPKD) may have an increased risk of kidney cancer, particularly renal cell carcinoma (41, 42).

Table 1 - Important Points of Reverse Onconephrology.

Probable mechanisms	Risk factors	Associated malignancies
<ul style="list-style-type: none"> Chronic inflammation Oxidative stress Intestinal microbiota Change Impaired DNA repair Excessive parathyroid hormone Metabolic implications 	<ul style="list-style-type: none"> Smoking Obesity Hypertension Eldery Male Long-term dialysis Family history Genetics disease (VHL, HPRC, ADPKD) Exposure to carcinogens 	<ul style="list-style-type: none"> Kidney Bladder Prostate Urinary Tract Pancreas Gastrointestinal Genitourinary Skin Pulmonary Lymphoma/Leukemia

Additionally, VHL disease, a genetic disorder, is characterized by the development of multiple tumors and cysts in various organs, including kidneys. Several studies showed cases with VHL disease have an increased risk of developing renal cell carcinoma. While not directly linked to kidney cancer, some types of glomerulonephritis may be associated with an increased risk of certain types of lymphoma or leukemia (43, 44). Moreover, patients with end-stage renal failure who have been on long-term dialysis may have an increased risk of kidney cancer compared to the general population, and finally chronic kidney disease due to prolonged exposure to several factors that can promote cancer development (24, 45, 46,47).

Table 1 provides a summary of the key points in Reverse Onconephrology.

Conclusion

Chronic renal failure and cancer are interconnected through immunologic mediators, hormonal changes, and genetic markers. Cancer can either directly or indirectly initiate CKD through the adverse effects of cancer treatments, while CKD itself may serve as a risk factor for malignancy, as both conditions share common risk factors. Therefore, patients with CKD should be closely monitored for cancer risk and receive appropriate cancer screening and treatment.

List of abbreviations

CKD: Chronic Kidney Disease

HPRC: Hereditary Papillary Renal Carcinoma

VHL: Von Hippel-Lindau

ADPKD: Autosomal Dominant Polycystic Kidney Disease

DOAJ: Directory of Open Access Journals

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