

Chemical Carcinogenesis in Clear Cell Renal Cell Carcinoma: A Comprehensive Review of Environmental Risk Factors, Mechanisms, and Clinical Implications



Chinyere Pamugo¹, Rishita Dave², Yousra Merdjana³, Yalemwork Muluye Gethenh⁴, Monica Haydée Santos⁵, Ghazala Anjum⁶, Emmanuel Adjei-Wiafe⁷, Philip Obiri Ankomah⁸, Sahithya Ekasi⁹, Anushka Mantina¹⁰ and Maria Isabel Gomez-Coral¹¹

¹DNP, PMHNP University of Texas Health Science, Houston USA

²MD, MBA. University of Medicine and Health Sciences, Saint Kitts

³MD, Medical Institute of Tambov State University named after G.R. Derzhavin, Russia

⁴MD, VHC health, VA, USA

⁵Latin American School of Medicine, Cuba

⁶MD. Liaquat College of Medicine & Dentistry, Karachi, Pakistan

⁷MBChB. University of Ghana Medical School. Ghana

⁸MBChB. University of Cape Coast School of Medical Sciences, Ghana

⁹MBBS. Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation

¹⁰MVJ Medical College and Research Hospital, Bengaluru, India

¹¹Universidad del Valle, México.

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***Corresponding author:** Maria Isabel Gomez-Coral, Universidad del Valle, México.

Abstract

Renal cell carcinoma (RCC), particularly clear cell renal cell carcinoma (ccRCC), presents a growing global health burden with increasing incidence. While established risk factors exist, environmental and occupational chemical exposures are increasingly recognized as significant contributors. This review systematically synthesizes literature on the association between chemical exposures (e.g., trichloroethylene, cadmium, asbestos, pesticides, PFAS, benzene) and ccRCC development. Epidemiological evidence reveals elevated ccRCC incidence in exposed populations, often with distinct geographic and occupational clusters, and demographic disparities. Mechanistically, chemical carcinogens drive ccRCC through direct DNA damage, epigenetic alterations (DNA methylation, miRNA dysregulation), chronic inflammation, fibrosis, and disruption of the VHL-HIF pathway, leading to metabolic reprogramming. Chemically induced tumors often exhibit more aggressive biological behavior and distinct molecular signatures (e.g., VHL, PBRM1, SETD2, BAP1 mutations; NRF2-KEAP1 activation), influencing prognosis and treatment responsiveness. Prevention strategies include stricter occupational regulations, but challenges remain in early detection due to long latency and lack of specific biomarkers. Comprehensive occupational health surveillance and integrated therapeutic approaches targeting these mechanistic pathways are crucial for mitigating the impact of chemical carcinogenesis on ccRCC.

Abbreviations: RCC: Renal Cell Carcinoma; ccRCC: Clear Cell Renal Cell Carcinoma; VHL: Von Hippel-Lindau; HIFs: Hypoxia-Inducible Factors; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor; GLUT1: Glucose Transporter 1; TME: Tumor Microenvironment; TAMs: Tumor-Associated Macrophages; TCE: Trichloroethylene; DDR: DNA Damage Response; MHC: Major Histocompatibility Complex; PFAS: Per- and Polyfluoroalkyl Substances; IARC: International Agency for Research on Cancer; PFNA: Perfluorononanoate; PFOS: Perfluorooctane Sulfonate; ROS: Reactive Oxygen Species; miRNA: microRNA; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha; CXCLs: Chemokines (C-X-C motif ligand); TGF-β: Transforming Growth Factor-beta; EMT: Epithelial-to-Mesenchymal Transition; EPO: Erythropoietin; IGF-2: Insulin-like Growth Factor 2; LDHA: Lactate Dehydrogenase; MCT4: Monocarboxylate Transporter 4; NRF2: Nuclear Factor Erythroid 2-Related Factor 2; KEAP1: Kelch-like ECH-associated protein 1; PBRM1: Polybromo 1; SETD2: SET Domain Containing 2; BAP1: BRCA1 Associated Protein 1; KDM5C: Lysine Demethylase 5C; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; C/EBP: CCAAT/Enhancer-Binding Protein

Keywords: Clear Cell Renal Cell Carcinoma; Chemical Exposure; Environmental Carcinogenesis.

Introduction

Renal cell carcinoma (RCC) is the most prevalent type of kidney cancer in adults, accounting for nearly 90% of all kidney malignancies. Its global incidence has been rising steadily, particularly in industrialized nations, and RCC now constitutes approximately 2 to 3% of all adult cancers. The disease poses a considerable global health burden, with an estimated 431,000 new cases and over 179,000 deaths each year [1]. While well-established risk factors include cigarette smoking, obesity, hypertension, and certain genetic predispositions, there is growing interest in the potential role of environmental and occupational exposures in RCC development [2].

Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype of RCC, accounting for approximately 70 to 80% of cases [3]. It is distinguished histologically by cells with clear cytoplasm, resulting from high intracellular lipid and glycogen content, and typically arises from the epithelial cells of the proximal convoluted tubule. ccRCC is frequently linked to mutations in the VHL gene and is notable for its highly vascularized tumor microenvironment, which plays a key role in both disease progression and therapeutic strategies. Clinically, ccRCC generally demonstrates a more aggressive course, especially when metastatic, compared to other subtypes like papillary or chromophobe RCC [3].

Given the increasing incidence and aggressive behavior of ccRCC, there is a compelling need to investigate the potential contribution of environmental and occupational chemical exposures to its development. Several chemicals such as trichloroethylene (TCE), cadmium, and various herbicides and industrial solvents have been associated with renal carcinogenesis due to their nephrotoxic and possibly genotoxic properties [4]. Individuals working in sectors like metalworking, dry cleaning, agriculture, and rubber manufacturing may face heightened risk from prolonged exposure to these substances. Gaining a clearer understanding of these risk factors is essential for guiding public health measures and shaping effective regulatory policies [4]. This review aims to critically assess the existing scientific literature on the relationship between chemical exposures especially those occurring in environmental and occupational settings and the development of clear cell renal cell carcinoma (ccRCC). By integrating evidence from epidemiological studies, mechanistic research, and toxicological data, the review seeks to evaluate the strength of the association between these exposures and ccRCC, while also highlighting key knowledge gaps that require further exploration.

Methodology

This review article systematically synthesizes existing literature to explore the association between chemical exposure and clear cell renal cell carcinoma (ccRCC). A comprehensive search strategy was employed across multiple electronic databases, including PubMed, Scopus, Web of Science, and Embase, to identify

relevant studies. Google Scholar was also utilized for supplementary searches to ensure broad coverage of both peer-reviewed and grey literature where appropriate. The inclusion criteria for articles focused on studies investigating a direct or indirect link between specific chemical exposures (occupational, environmental, or lifestyle-related) and the development, progression, or molecular mechanisms of ccRCC in humans or relevant animal and in vitro models. This encompassed a range of study designs, including epidemiological investigations such as cohort studies, case-control studies, and cross-sectional analyses, as well as mechanistic studies detailing cellular and molecular pathways. Review articles and meta-analyses were also considered to provide a broader perspective and consolidate existing evidence. Articles were excluded if they did not specifically address ccRCC or a directly related renal cancer subtype, if the chemical exposure was not clearly defined or quantifiable, or if they were purely clinical management guidelines without etiological insights.

A wide array of keywords and search terms were used, strategically combined with Boolean operators (AND, OR) to maximize the retrieval of pertinent literature. Key terms included “clear cell renal cell carcinoma,” “ccRCC,” “renal cancer,” “kidney cancer,” combined with terms such as “chemical exposure,” “environmental carcinogens,” “occupational exposure,” “toxicology,” “nephrotoxicity,” and specific chemical names like “trichloroethylene,” “cadmium,” “arsenic,” “pesticides,” “herbicides,” “PFAS,” “mycotoxins,” and “solvents.” Variations and synonyms of these terms were also incorporated into the search strings. The literature review covered studies published from the inception of each database up to June 2025, ensuring that the most recent findings were captured while also providing a historical context of research in this area.

Pathogenesis and Molecular Biology of Clear Cell RCC

Genetic Alterations: VHL Mutation and HIF Pathway

The Clear Cell Renal Cell Carcinoma (ccRCC) is triggered by genetic alterations, most notably in the von Hippel-Lindau (VHL) tumor suppressor gene [5]. According to Liao et al. (2024), VHL mutations occur in approximately 70–80% of sporadic clear cell renal cell carcinoma (ccRCC) cases and lead to the stabilization of hypoxia-inducible factors (HIFs) [7], particularly HIF-2 α , under normoxic conditions [6]. This dysregulation promotes transcription of genes involved in angiogenesis, cell proliferation, and metabolic reprogramming, including VEGF, PDGF, and GLUT1 [8]. The HIF pathway thus acts as a central oncogenic driver in ccRCC, and recent therapies such as belzutifan target HIF-2 α directly, showing promising clinical efficacy in renal Ca treatment [6].

Tumor Microenvironment and Angiogenesis

The tumor microenvironment (TME) in clear cell renal cell carcinoma (ccRCC) is characterized by extensive vascularization

and infiltration of immune cells [9]. HIF activation leads to the overexpression of angiogenic factors, such as VEGF, facilitating neovascularization and tumor growth [9]. Additionally, the TME, which includes tumor-associated macrophages (TAMs), regulatory T-cells, and myeloid-derived suppressor cells, contributes to immune evasion and resistance to immunotherapy [9,10]. Rac1 signaling has been implicated in priming the TME for angiogenic switching, further enhancing endothelial cell recruitment and VEGF-mediated paracrine signaling [9]. These interactions highlight the need to target both angiogenesis and immune modulation in the treatment of ccRCC [9].

3.3. Relevance to Chemical-Induced Molecular Damage.

In Chemical-induced molecular damage, especially to DNA, a role is played in ccRCC pathogenesis [11]. Alterations in DNA damage response (DDR) pathways, including mismatch repair and homologous recombination, are observed in over 50% of clear cell renal cell carcinoma (ccRCC) cases [11]. These mutations, through complex processes, form neoantigens and are presented by major histocompatibility complex (MHC) proteins to T cells, resulting in genomic instability and sensitization of tumors to immunotherapy [12]. Furthermore, exposure to environmental toxins and metabolic reprogramming, such as bile acid dysregulation, can lead to oxidative stress and lipid peroxidation, hence promoting ferroptosis and exacerbating DNA damage [13]. Understanding these mechanisms gives a broad avenue for DDR-targeted therapies and biomarker-driven treatment strategies [13].

Epidemiology of Chemical Exposure and RCC

The epidemiology of clear cell renal cell carcinoma (ccRCC) exhibits notable patterns related to chemical exposure, with distinct trends, geographic variations, and demographic disparities. The global incidence of RCC has been steadily increasing, and while factors like improved diagnostic imaging play a role, environmental and occupational chemical exposures are increasingly recognized as significant contributors [14,15]. Populations with known or suspected high chemical exposure often demonstrate elevated ccRCC incidence and unique trends. For instance, workers in specific industries that handle certain chemicals, such as trichloroethylene (TCE), cadmium, benzene, herbicides, pesticides, and vinyl chloride, have shown an increased risk of developing ccRCC, with the risk often correlating with the duration and intensity of exposure [16-18]. The incidence trends in these populations can reflect past exposure levels, with latency periods often spanning years to decades before cancer diagnosis [16]. Studies on agricultural workers, for example, have identified associations between lifetime use of specific pesticides like 2,4,5-T, chlorpyrifos, chlordane, atrazine, and cyanazine with an increased risk of RCC [19]. Similarly, the presence of per- and polyfluoroalkyl substances (PFAS) in blood serum has been linked to a higher risk of kidney cancer, including ccRCC, particularly in populations with high environmental contamination [16,19].

Geographic or occupational clusters of ccRCC have provided

compelling evidence for the role of chemical exposure. Historically, areas with significant industrial activity or specific environmental contamination have sometimes shown elevated rates of kidney cancer. For example, some studies have explored the link between TCE exposure and RCC in regions with high industrial use of the solvent, such as the Arve Valley in France, finding increased risk associated with high cumulative doses [20,21]. Occupational settings, where individuals experience higher and more prolonged exposure, are particularly prone to forming such clusters. Workers in chemical manufacturing, commercial printing, construction, electronics manufacturing, and agriculture are among those identified with a heightened risk [16]. While the International Agency for Research on Cancer (IARC) previously noted iron and steel founding as an occupational setting for kidney cancer risk, other areas, including those with significant solvent exposure, have shown evidence of increased risk [22]. Furthermore, recent research has identified mutational signatures in kidney tumors that suggest widespread, geographically variable, and as-yet-undiscovered mutagenic exposures, indicating that environmental factors contribute significantly to global kidney cancer rates [23].

Demographic differences in ccRCC incidence also highlight the potential influence of chemical exposure. Globally, ccRCC incidence is approximately twofold higher in men compared to women, a pattern that remains largely unexplained by traditional risk factors like smoking or obesity alone, suggesting potential biological differences or differential occupational exposures [24,25]. Indeed, some studies on occupational chemical exposure to agents like cadmium, lead, and organic solvents have reported higher excess risks in women compared to men, indicating potential gender-specific susceptibilities to certain nephrocarcinogens [22]. In the United States, while overall RCC incidence has shown a slight decline among Caucasian populations, it has rapidly increased among African Americans, who disproportionately suffer from adverse effects related to RCC [26]. This disparity may be linked to a complex interplay of socioeconomic status, healthcare access, and potentially higher exposure to certain environmental or occupational chemicals in these communities. For instance, higher blood levels of perfluorononanoate (PFNA), another frequently detected PFAS, have been associated with an increased risk of kidney cancer, with the association being strongest among African American participants, a group that also exhibits higher concentrations of PFNA and perfluorooctane sulfonate (PFOS) [27]. Additionally, the disease most commonly appears in individuals between 50 and 70 years of age, reflecting the long latency period often associated with chemical carcinogenesis [29].

Key Chemicals Implicated in RCC Development

Occupational exposure to such compounds as Trichloroethylene, Asbestos and Cadmium has been found to have an increased association with the development of Renal Cell Carcinoma. [29-31]. In a multicenter study of over 1700 patients with Renal Cell Carcinoma and 2300 controls, It was observed that there was an increased risk of cancer in asbestos exposed individuals (RR

1.3,95% CI 1.1-1.8), cadmium (RR 2, 95% CI 1-3.9) and gasoline (RR 1.6 CI 1.2-2.2) [29].

Trichloroethylene (TCE)

Trichloroethylene; a petroleum byproduct used as a metal degreasing solvent and cleaner, also used in the production of other metals. It was also used in the past as a grain fumigant and anesthetic agent. Studies have shown that exposure to Trichloroethylene has been linked with pathogenic variants of the von Hippel-Lindau (VHL) tumor suppressor gene. Toxic metabolites derived from TCE are reported to induce chronic renal tubular lesions and may exert genotoxic effects on the proximal convoluted tubule. The relationship between pathogenic variants of the VHL tumor suppressor gene and exposure to TCE was evaluated in 44 patients with RCC and known exposure to the toxin, 107 with RCC but no known exposure, and 97 controls [32]. A specific mutational hot spot in the VHL gene was found in 39 percent of individuals who were exposed to the toxin (TCE) [32].

Cadmium

Cadmium is also implicated in the development of RCC. It is found in metals as Copper, Zinc, and Steel, and can be found in cement, phosphate fertilizers, batteries, and some paints and plastics. Individuals who work in the smelting, welding, and mining industries are also at high risk of cadmium exposure. Cadmium workers who smoke particularly have a high incidence of RCC [33]. Inhalational cadmium toxicity tends to be a contributing factor in renal injury [34,35]. Its diagnosis is based solely on clinical presentation and a history of cadmium exposure. Cadmium toxicity is confirmed by evaluating the blood level of cadmium as well as urine levels of cadmium. An estimate of the ratio of urine cadmium to creatinine levels suggests kidney injury from cadmium exposure [36,37]. The earliest sign of cadmium nephrotoxicity is tubular proteinuria. It can be present as glycosuria, aminoaciduria, hypercalciuria, polyuria, reduced glomerular filtration, and mild metabolic acidosis. Rarely, a patient may present with end-stage kidney disease. Risk factors for cadmium toxicity are iron deficiency, increasing age, and diabetes mellitus [33-37].

Cadmium induces the production of reactive oxygen species, leading to oxidative damage to cellular components such as DNA, lipids, and proteins. This contributes to the development of cancer. It also breaks strands of DNA and causes mutations, thereby activating oncogenes and suppressing tumour suppressor genes. Cadmium also accumulates in the proximal tubules of kidney cells and directly damages them [33-37].

Asbestos

Asbestos is a fibrous silicate mineral, carcinogenic to humans, used in construction, fireproofing, and insulation. Epidemiological evidence suggests it is one of the causes of renal cell carcinoma. This is complex because the physicochemical characteristics of asbestos fibers, their size, surface reactivity, chemical composition,

exposure time, and dose vary among patients. Other factors such as genetics, alcohol, smoking, a sedentary lifestyle, and environmental factors such as solvents (mainly trichloroethylene), pesticides, dust, and medications also influence this type of cancer. Renal fibrosis is observed in patients exposed to asbestos, where these fibers can be transported through the blood to kidney cells, where they can cause inflammatory processes and, therefore, genetic alterations. Asbestos fibers have also been observed in urine [38,39].

Industries that process plastics, dyes, synthetic fibers, and lubricants use benzene, an organic hydrocarbon that, like gasoline, is a pollutant and is considered a Group 1 carcinogen by the International Agency for Research on Cancer. Prolonged exposure can cause kidney, urinary, and bladder cancers. However, the carcinogenesis of benzene is debatable, as is asbestos. Benzene is metabolized in the liver to benzene oxide and several reactive metabolites, which can reach the bone marrow and other organs such as the kidney. They are excreted in the urine, damaging the urinary tract and causing carcinogenicity through two main mechanisms: covalent binding to DNA (genotoxicity) and the generation of reactive oxygen species through oxidative damage [40,41].

Other Chemicals

Regarding the chemical carcinogenesis of kidney cells, it is essential to mention environmental factors such as pesticides and herbicides. Thirty-eight pesticides associated with kidney cancer have been studied, with an increased risk in people exposed to the herbicide 2,4,5-T and with years of exposure to three herbicides (atrazine, cyanazine, and paraquat) and two insecticides (chlorpyrifos and chlordane) [42,43]. Renal cell carcinoma is the most common form of kidney cancer. Its incidence has been increasing in the United States. Previous studies have found associations between renal cell carcinoma and pesticide use in agriculture [42].

Mechanistic Insights into Chemical Carcinogenesis in ccRCC

Clear cell renal cell carcinoma (ccRCC) develops through a complex interplay of genetic, epigenetic, inflammatory, and metabolic changes, often triggered by environmental carcinogens like cadmium, arsenic, nitrosamines, and polycyclic aromatic hydrocarbons. These substances drive ccRCC by causing DNA damage, disrupting epigenetic regulation, inducing chronic inflammation and fibrosis, and interfering with the hypoxia-inducible pathway, particularly via the Von Hippel-Lindau (VHL) tumor suppressor gene [43-47]. The process typically begins with direct DNA damage, where environmental carcinogens form adducts, oxidative lesions, and strand breaks, primarily in proximal renal tubular cells. Chemicals like arsenic and cadmium further hinder DNA repair mechanisms by inhibiting key enzymes, increasing mutations that inactivate tumor suppressor genes (e.g., VHL, SETD2) and activate oncogenes, promoting clonal expansion [48,57].

Beyond direct DNA damage, chemical exposures profoundly influence epigenetic changes. DNA methylation, a major alteration, silences crucial tumor suppressor genes like VHL, RASSF1A, CDKN2A, and TIMP3 by adding methyl groups to their promoters. VHL promoter methylation, seen in up to 70% of sporadic ccRCC cases, functionally mimics VHL mutations, disrupting hypoxia signaling [46,53]. Global hypomethylation can destabilize the genome, while specific hypermethylation further silences anti-proliferative genes. Carcinogens also alter microRNA (miRNA) expression, for instance, by reducing DICER expression, which impairs miRNA processing. This leads to the downregulation of tumor-suppressive miRNAs (e.g., miR-9, miR-124-3) and upregulation of oncogenic miRNAs (e.g., miR-21, miR-17-5p, miR-210), collectively promoting cell proliferation, survival, immune evasion, and angiogenesis [45,56]. Notably, miR-2355-5p, responsive to HIF-2 α , targets multiple tumor suppressors [44].

Chronic inflammation and fibrosis exacerbate these changes, fostering a pro-tumor microenvironment. Environmental factors elicit sustained immune responses, releasing inflammatory cytokines (IL-6, TNF- α) and chemokines that attract immune cells, generating reactive oxygen species (ROS) that inflict further DNA damage and epigenetic alterations. Pro-fibrotic cytokines, like TGF- β , drive epithelial-to-mesenchymal transition (EMT) and extracellular matrix deposition, enhancing tissue remodeling, angiogenesis, and invasive potential, ultimately contributing to metastasis [51].

Central to ccRCC development is the disruption of the hypoxia-inducible pathway due to VHL gene inactivation. Normally, pVHL ubiquitinates HIF- α subunits (HIF-1 α , HIF-2 α) for degradation. Loss or silencing of VHL, through mutation, methylation, or miRNA repression, stabilizes HIF proteins even under normal oxygen. This “pseudohypoxic” state drives transcription of genes promoting angiogenesis (VEGF, PDGF), glycolysis (GLUT1, LDHA), and cell survival (EPO, IGF-2) [47,49]. HIF-2 α is particularly critical, promoting oncogenic transcription, upregulating oncogenic miRNAs (miR-210, miR-2355-5p), and altering enhancer landscapes to amplify gene expression [55]. HIFs also stimulate histone demethylases, supporting an active oncogenic program.

Mutations in chromatin-modifying enzymes (PBRM1, SETD2, BAP1, KDM5C) are also significant, often co-occurring with VHL mutations. Loss-of-function in these genes disrupts transcriptional regulation, leading to persistent abnormal gene expression. For example, SETD2 loss impairs DNA mismatch repair, while BAP1 loss is linked to dedifferentiation and poor prognosis [54].

A key downstream effect of VHL and HIF dysregulation is metabolic reprogramming. HIF activation induces the Warburg effect (glycolysis even with oxygen), upregulating glucose transporters (GLUT1) and glycolytic enzymes (hexokinase 2, LDHA). This allows tumor cells to thrive in low-oxygen conditions while suppressing mitochondrial oxidative phosphorylation, reducing ROS production, limiting apoptosis, and acidifying the microenviron-

ment, promoting invasion and immune evasion [50,52].

These interconnected pathways DNA damage, epigenetic dysregulation, inflammation, hypoxia signaling, and metabolic reprogramming form a self-reinforcing loop. For instance, ROS-induced DNA damage can epigenetically silence DNA repair genes, which in turn stabilize HIF activity, promoting inflammatory cytokines and fibrosis. This inflammatory microenvironment perpetuates hypoxia and oxidative stress, with miRNAs acting as crucial intermediaries. This results in a highly adaptable tumor capable of resisting apoptosis, promoting angiogenesis, remodeling its environment, and metastasizing [44-57].

Chemical carcinogenesis in ccRCC is a multifaceted process driven by environmental toxins, initiating DNA mutations, epigenetic silencing, inflammatory signaling, and hypoxia-driven transcription. Understanding this intricate network clarifies how environmental exposures lead to ccRCC and reveals diverse opportunities for prevention, early detection, and personalized therapy [44-57].

Clinical Features and Prognostic Implications

Clear cell renal cell carcinoma (ccRCC) is the most common histologic subtype of renal malignancy, accounting for over 75% of all kidney cancers. While genetic predispositions and lifestyle factors such as smoking, obesity, and hypertension are well-established risk contributors, increasing attention has been given to the role of environmental and occupational exposures particularly to carcinogenic chemicals such as trichloroethylene (TCE), benzene, cadmium, and petroleum-based solvents. TCE, a volatile chlorinated solvent used in metal degreasing and dry cleaning, has been classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC), with substantial epidemiologic evidence linking long-term exposure to an elevated risk of ccRCC [58,59].

Evidence suggests that ccRCC associated with chemical exposure may demonstrate distinct clinical behaviors. While tumor stage at diagnosis is generally similar between exposed and non-exposed patients, some studies have reported increased tumor aggressiveness in the former group. Case-control studies involving TCE-exposed workers have shown a higher frequency of Fuhrman grade 3 and 4 tumors, more frequent sarcomatoid differentiation, and increased vascular invasion all of which are associated with worse prognosis [60,61]. Moreover, transcriptomic profiling studies have demonstrated that exposure-related tumors are more likely to belong to the ccB molecular subtype, which is characterized by increased angiogenic, proliferative, and inflammatory signatures and correlates with inferior survival outcomes compared to the more indolent ccA subtype [62]. These findings suggest that while tumor burden may not initially appear greater, the biological behavior of chemically induced tumors tends to be more aggressive, with shorter progression-free and overall survival [63].

Treatment responsiveness in chemically associated ccRCC remains an area of active research. Although clinical trials have not yet stratified ccRCC patients by chemical exposure history, molecular features of these tumors suggest potential differences in therapy sensitivity. Tumors with high HIF pathway activation and VEGF expression may be more responsive to VEGFR tyrosine kinase inhibitors such as sunitinib or axitinib [64]. However, the co-occurrence of mutations in tumor suppressor genes like BAP1 frequently observed in exposure-associated tumors has been linked to poor outcomes and resistance to both targeted and immunotherapeutic agents [65]. The absence of prospective, exposure-stratified therapeutic trials represents a significant gap in the current literature. Molecularly, exposure-related ccRCC is characterized by a distinctive mutational landscape. The VHL gene, a tumor suppressor inactivated in over 90% of ccRCC cases, frequently shows mutation patterns in exposed individuals that are consistent with chemical-induced genotoxicity, including G-to-A transitions and base substitutions linked to oxidative damage [66]. Beyond VHL, genes involved in chromatin remodeling and epigenetic regulation such as PBRM1, SETD2, and BAP1 are often mutated. Among these, BAP1 mutations are particularly notable, as they correlate with high-grade, aggressive tumors and reduced cancer-specific survival [67,68]. Epigenetically, exposure-related ccRCC demonstrates global DNA hypomethylation and promoter hypermethylation of tumor suppressor genes, contributing to widespread enhancer remodeling and oncogenic transcriptional reprogramming [69]. Inflammatory pathways including NF- κ B and C/EBP are often activated, promoting immune evasion and metastasis [70].

Recent research has also highlighted oxidative stress-related pathways as key players in chemical carcinogenesis. The NRF2-KEAP1 signaling axis, typically repressed in ccRCC, is paradoxically activated in a subset of chemically induced tumors, potentially reflecting an adaptive mechanism to chronic oxidative stress from environmental toxins [71]. While NRF2 activation can promote tumor survival, it may also contribute to therapy resistance, particularly against anti-angiogenic agents and immune checkpoint inhibitors. These insights suggest that chemical exposure history is not only a risk factor for tumor initiation but also a determinant of tumor biology, therapeutic vulnerability, and prognosis [71].

In conclusion, ccRCC arising from chemical carcinogenesis, especially due to agents like trichloroethylene, presents with unique clinical and molecular features. While tumor stage at diagnosis may be similar to sporadic cases, these tumors tend to be biologically more aggressive, exhibit distinct mutational signatures, and activate transcriptional programs associated with inflammation and oxidative stress.

Prevention, Screening, and Public Health Strategies

Regulatory responses to chemical carcinogenesis in ccRCC have focused primarily on establishing occupational exposure limits and implementing protective workplace standards. Studies

have shown that males considered as 'substantially exposed to organic solvents' showed a significant excess risk for RCC leading to stricter regulations on solvent exposure in industrial settings [72,73]. International agencies have developed exposure limits for known nephrotoxic substances, including heavy metals like cadmium, lead, and arsenic, which have been associated with increased renal cancer risk. The International Agency for Research on Cancer (IARC) has classified crystalline silica as a Group 1 human carcinogen, prompting workplace safety regulations to limit dust exposure through engineering controls, personal protective equipment, and regular monitoring. However, regulatory gaps remain for emerging chemicals and combined exposures, where occupational exposures to specific types of dusts, specifically glass fibre, mineral wool fibre, and brick dust have shown increased RCC risk, yet comprehensive workplace standards for these materials are still evolving [73].

Early detection of chemical-induced ccRCC faces substantial obstacles due to the long latency period between exposure and cancer development, often spanning decades. The relationship between renal cancer risk and these occupational dust exposures was examined allowing for a 20-year lag between exposure and diagnosis, highlighting the extended timeframe that complicates screening efforts [74]. Biomonitoring for chemical exposure presents technical challenges, as many carcinogenic substances are metabolized quickly, making it difficult to establish causative links between past exposures and current cancer risk. The lack of specific biomarkers for chemical-induced renal carcinogenesis means that screening programs must rely on imaging techniques like contrast-enhanced CT scans, which are expensive and may not detect early-stage disease [75]. Additionally, the heterogeneous nature of chemical exposures in occupational settings makes it challenging to develop standardized screening protocols that account for multiple simultaneous exposures and their synergistic effects.

Effective occupational health surveillance for chemical carcinogenesis requires comprehensive exposure assessment and long-term worker follow-up programs. Expert-based exposure assessment teams reviewed all occupational questionnaires, rating frequency and intensity of occupational exposure to 72 specific agents, demonstrating the complexity of surveillance systems needed to track chemical exposures accurately [76,77]. Surveillance programs must account for the fact that substantial exposure to metals and solvents may be nephrocarcinogenic, with evidence for gender-specific susceptibility, requiring tailored monitoring approaches for different worker populations. Modern surveillance systems integrate occupational history databases, exposure matrices, and health outcome tracking to identify at-risk workers and implement preventive measures [78]. However, challenges remain in standardizing exposure assessment methods across different industries and countries, particularly in developing regions where industrial hygiene practices may be less stringent. The effectiveness of surveillance is further complicated by worker mobility between industries and the need for lifelong

health monitoring to capture the delayed effects of chemical carcinogenesis [77].

Conclusion

Clear cell renal cell carcinoma (ccRCC) arising from chemical carcinogenesis, particularly due to agents like trichloroethylene, cadmium, and various industrial and environmental toxins, presents with unique clinical and molecular features that distinguish it from sporadic cases. While tumor stage at diagnosis may be similar, these chemically induced tumors tend to be biologically more aggressive, exhibit distinct mutational signatures—especially in VHL, PBRM1, SETD2, and BAP1 and activate specific transcriptional programs associated with inflammation, oxidative stress, and metabolic reprogramming. The pervasive influence of environmental and occupational chemical exposures on ccRCC underscores the critical need for a deeper understanding of the underlying molecular mechanisms, which encompass direct DNA damage, widespread epigenetic dysregulation, the fostering of pro-tumor inflammatory microenvironments, and profound alterations in the VHL-HIF pathway. Despite advancements in understanding these complex pathogenic pathways, significant challenges persist in prevention and early detection due to the prolonged latency periods and the absence of specific biomarkers for chemically induced renal carcinogenesis. Current regulatory responses, while beneficial in establishing occupational exposure limits, must evolve to address emerging chemicals, complex mixed exposures, and global disparities in safety practices. Future efforts must focus on developing targeted screening tools, refining exposure assessment methods, and implementing robust, long-term occupational health surveillance programs. Clinically, recognizing the distinct molecular profiles of exposure-related ccRCC is paramount, as these features may dictate differential responses to targeted therapies, immunotherapies, and metabolic inhibitors. By integrating a comprehensive understanding of chemical carcinogenesis with advanced diagnostic and therapeutic strategies, we can move closer to more effective prevention, earlier detection, and personalized management for patients affected by environmentally induced ccRCC.

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