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Renal Cell Carcinoma (RCC) Epidemiology and Genetic Variation, Risk Factor-Based Primary and Secondary Prevention with Early Detection with a Focus on Biomarkers

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Abstract

Renal cell carcinoma (RCC), with 400,000 diagnoses and 180,000 deaths in 2020, represents 2.4% of all cancer diagnoses globally industrialised nations with the greatest rates of sickness, particularly in Europe and North America. As more nations adopt Western lifestyles, incidence is expected to rise in the future. In addition to intervening variables like smoking, obesity, hypertension, diabetes, nutrition, and alcohol, RCC risk factors also include fixed characteristics like gender, age, and inherited disorders. The development of early diagnostic techniques, knowledge of prenatal risk factors, and intervening measures in primary prevention are crucial for RCC. The epidemiology of RCC, risk factors, and biomarkers implicated in lowering incidence and enhancing survival will all be covered in this review.

Keywords: Renal cell carcinoma; Epidemiology; Prevention; Genetic illness

Introduction

According to GLOBOCAN data [1], renal cell carcinoma (RCC) accounts for around 2.4% of all malignancies in adults, with more than 400,000 new cases being diagnosed and roughly 180,000 people dying from it globally in 2020.The widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) has led to an increase in the discovery of early RCC lesions in many individuals, and the 5-year survival rate for early RCC detection is as high as 93% [2,3]. For RCC patients with metastases, the 5-year survival rate is only 12%, and at least half of them need systemic medication therapy [4]. RCC is typically regarded as an immunogenic tumour because to its overall resistance to cytotoxic chemotherapy and radiation treatment and earlier immunotherapies have had some effectiveness, but insufficiently [5]. The only alternatives for treating RCC 20 years ago were surgery and ineffective immunotherapy. Today, there are many more options for treating RCC. A wealth of options are now available for RCC treatment options, including anti-vascular endothelial growth factor (VEGF) antibodies, VEGF receptor tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) pathway inhibitors, and immune checkpoint inhibitors (ICIs). The outlook for patients is improving [6].

Even with pharmaceutical advancements, the prognosis for advanced RCC is probably only going to improve to a certain extent. As a result, learning how to decrease the prevalence of RCC and diagnose it early may help lessen the burden of illness, encourage timely treatment, and increase survival rates for this condition that claims 180,000 lives each year [1]. Overviews of the epidemiology, genetic variation, primary prevention including risk factors, and secondary prevention involving early identification will all be covered in this session.

Epidemiology

RCC has been on the rise recently and is currently the ninth most prevalent malignant neoplasm in the United States (U.S.) [4]. The number of RCC patients globally is anticipated to rise as a result of changing lifestyles in Asia and Africa. Patients with RCC are particularly prevalent in Europe and North America. The incidence and mortality of RCC are described in this section.

Frequency

Based on 2020 projections from GLOBOCAN statistics, RCC is the 12th most prevalent malignant neoplasm overall, excluding blood cancers, with around 431,000 newly diagnosed cases, of which roughly 271,000 are in men and 160,000 are in women [1]. In the globe as a whole, the age standardised rate (ASR) is 4.6; for men and women, it is 6.1 and 3.1, respectively [1]. The incidence rate was 12.2 in North America, 10.2 in Australia and New Zealand, and 9.5 in Europe. At 2.8 and 1.8, respectively, the ASRs in Asia and Africa were low [1]. With scores of 7.6, 7.5, and 6.5, respectively, Japan, Israel, and South Korea had the highest levels [1]. The high values in industrialised nations imply that lifestyle, in addition to race, influences incidence.

Mortality

RCC accounted for around 180,000 deaths in 2020, or 1.8% of all cancer patients. GLOBOCAN data shows that of the fatalities, 64,000 were female and 116,000 were male [1]. ASR was 1.8 overall, 2.5 for males, and 1.2 for women [1] by comparison Slovakia had a death rate of 4.7, whereas Eastern Europe and Latin America had higher mortality rates, 4.4 for Uruguay and 4.3 for Latvia [1]. 2.1 was the 2020 U.S. death rate, down from 2.4 in 1999. 4.3/10,000 between 1992 and 1994, which might be a result of advancements in diagnosis and therapy.

RCC Risk Factors

There have been several documented risk factors for RCC, such as genetic alterations. The risk factors that cannot be modified are discussed in this section.

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Age, gender, and race

As RCC is often a disease of the elderly, it is common to find many sporadic cases among them. In the United States, diagnosis occurs on average at 64 years old. Clear cell RCCs (ccRCC), papillary cell RCCs (pRCC), and chromophobe RCCs (chRCC) make up more than 90% of all RCCs that are formed from tubular tissue [7,8]. The prognosis for the two other kinds is better than that of ccRCC, the most prevalent RCC (75%). The age for pRCC diagnosis was noticeably older than that of ccRCC, although chRCC did not vary from ccRCC [7].

The GLOBOCAN data demonstrates that most neoplasms are more frequent in men, and RCC is no exception, with 1.5 times as many instances in men as in women [1]. This could be as a result of the fact that males are more likely than women to engage in the lifestyle behaviours listed below that promote carcinogenesis. In terms of histology, women have more chRCCs and fewer pRCCs, however the reason for this is unclear [7]. Incidence of RCC varies by ethnic group in the U.S., with Asian Americans having a lower risk of RCC than Native Americans and African Americans [3]. In addition to ethnic disparities, lifestyle factors including food and exercise, education, and access to healthcare may also play a role in this result.

Genetic Illness

While sporadic in nature, some cases of RCC are caused by certain germline gene alterations. Due to their link with RCC, inherited illnesses caused by such genetic abnormalities are risk factors.

VHL (Von Hippel–Lindau Disease): The most typical kind of RCC, known as ccRCC, develops from tubular epithelial tissue and frequently metastasizes hematogenously to the lungs or bone. 90% of ccRCCs have chromosome 3 von Hippel-Lindau (VHL) mutations. The most well-known genetic condition linked to RCC, VHL illness, accounting for 5% of instances of ccRCC and increases the risk of bilateral RCC in young children. Hypoxia-inducible factor (HIF)-1, 2, a hypoxia-inducible factor that stimulates angiogenesis into the tumour microenvironment and promotes tumour growth, is expressed more frequently as a result of decreased gene products linked to VHL mutations. Growth factors like transforming growth factor- and platelet-derived growth factor, as well as glucose metabolism factors like glucose transporter, are all involved in how increased HIF advances malignancies [8].

Chemicals and drugs

The use of over-the-counter painkillers has been linked to an increased risk of RCC and is widespread around the world. An aspirin research revealed no difference overall but a higher risk in non-US studies. However, acetaminophen usage was linked to a higher incidence of RCC and other NSAID use was as well [9]. Things like bladder cancer and malignant mesothelioma that have been linked to particular occupational exposures are not linked to kidney cancer. However, trichloroethylene, an organic solvent, has a potent degreasing effect and has been utilized in the past for cleaning, particularly semiconductor cleaning. It has been linked to kidney cancer, according to reports. This drug is extremely carcinogenic and increases the likelihood of developing lymphoma, liver cancer, and RCC [10].

Initial defense

According to the extensive Vitamins and Lifestyle (VITAL) research conducted in the United States, lifestyle diseases like smoking, hypertension, and obesity raise the chance of developing RCC. The risk of developing RCC may also be increased by high levels of male obesity, hypertension, and hyperglycemia as well as female body mass index (BMI). This section discusses primary prevention in terms of dietary practises and smoking, which are thought to raise the likelihood of developing RCC, as well as risk factors including obesity, diabetes, and hypertension, which are characteristic of illnesses linked to lifestyle.

- **Tobacco Smoking:** RCC is one of the many prevalent malignancies that smoking has been connected to. A variety of carcinogens associated with the pathogenesis of RCC are present in tobacco smoke. There is epidemiologic data linking tobacco use to disease, including a dose-response association between risk and daily cigarette use and a risk reduction with more years of smoking cessation.

- **Alcohol Use:** Compared to abstinence, moderate alcohol consumption has been shown to have a protective impact on the incidence of RCC.

- **Eating Patterns:** In terms of food, the group with a median consumption of 62.7 g of red meat per 1000 kcal had a higher risk of cancer than the group with a median intake of 9.8 g, with an HR of 1.19 (95% CI, 1.01-1.40).Consuming fruits and vegetables, particularly cruciferous ones, has been linked to a lower risk of developing RCC. However, despite a large range of consumption in the EPIC trial [11] and the important study, no conclusive link between fruit or vegetable intake and RCC risk was discovered.

- **Keeping a Healthy Body Weight:** Obesity has been proven to be strongly linked to the risk of RCC.

Second-Line Defense

By identifying and treating RCC in its earliest, treatable stages, screening programmes increase survival rates. Although it has been hypothesised that screening for RCC may be a cost-effective strategy by downstaging the disease, lowering the prevalence of metastatic tumours, and lowering associated costs related to systemic therapies, the ideal screening modalities have not yet been established, and there are currently no diagnostic modalities for the early detection of RCC other than incidental radiological discovery. Recent searches of serum microRNAs, urinary proteins, or metabolomics, proteomics, and amino acid profile analysis have revealed several potential compounds in blood and urine as RCC biomarkers. They have not yet developed to a usable level and there are no outcomes or adequate evaluations of screening in a sizable general population.

Biomarkers in the Blood and Urine as a Screening Method

The use of tumour markers with high sensitivity and specificity is preferred instead of radiologic screening, although there are currently no easily accessible and clinically validated biomarkers for RCC screening. Nevertheless, a number of blood and urine biomarkers have been suggested as suitable screening instruments. Due to its rapid, simple, and non-invasive manner in clinical practise, the collection of this biological fluid might also be appealing. Urine biomarkers aquaporin 1 (AQP1) and perilipin 2 are the most promising (PLIN2). These concentrations serve as sensitive and accurate indicators for the early non-invasive identification of RCC's papillary or clear cell subtypes. Both indicators had 87-100% and 85-92% sensitivity and specificity, respectively.

Metabolomics

Utilizing tissue samples analysed using the Global Metabolomics technique, previous investigations were able to identify the metabolites of ccRCC. Glutathione, tryptophan, and glycolysis are a few of the pathways linked to these metabolites that have been identified to be

important for the diagnosis and prediction of cancer. In addition, whereas the tricarboxylic acid cycle, nucleotide sugars, and inositol pathways are linked to cancer, the glycoglycerolipid, carnitine, and tocopherol pathways are possibly diagnostic.

Because low molecular weight substances (such low molecular weight metabolites) may be readily filtered out, urine is potentially a suitable instrument for the research of urinary tract illnesses. As a result, urological cancer metabolic profiling and biomarker development may benefit from urine metabolomics. The metabolite p-cresol glucuronide can serve as a diagnostic marker for RCC, according to a recent untargeted metabolomic investigation of urine samples from RCC patients and healthy individuals. Also discovered through study of urine samples taken from RCC patients a year after nephrectomy were the potential prognostic markers isobutyryl-Lcarnitine and L-proline betaine [12].

Proteomics

Numerous types of materials, including tumour cell lines, serum, tissue, and urine, have been used in proteomics investigations of RCC utilising a range of mass spectrometry (MS) methods. The plasma levels of fibronectin 1 (FN1), a high molecular weight extracellular matrix protein, are considerably higher in patients with localised and metastatic RCC compared to a control group. FN1 is a key player in cellular attachment and cell dissemination. A different research showed that FN1 mRNA expression may be used as a marker for the aggressiveness of RCC since it is more prevalent in RCC than in normal renal tissue and is correlated with advanced illness [13].

Lipidomics

Deficiencies in lipid metabolism have been linked to the aetiology of several disorders, including ovarian cancer, prostate cancer, and breast cancer. Lipidomics is an autonomous and developing subject within metabolomics. Numerous additional cancer types (colorectal, bladder, and RCC) have also shown significant changes in linoleic acid metabolism that are linked to inflammatory conditions, immunological responses, and cell proliferation. 39 lipids were shown to be the most discriminatory between tumour and healthy tissue or between tumour recurrence and non-recurrence status in a global lipid profile investigation by MALDIFT-ICR MS [14].

Analysis of the amino acid profile

Serum amino acid levels have been extensively studied to see whether they might serve as a biomarker for RCC. According to one research, there were statistically significant changes in the concentrations of 15 amino acids, with a drop in 13 and an increase in two, in serum taken preoperatively from 189 RCC patients and 104 age- and sex-matched controls. Additionally, a logistic regression model containing eight amino acids yielded an AUC value of 0.81. (cysteine, ornithine, histidine, leucine, tyrosine, proline, valine, and lysine). Serum amino acid levels may be beneficial as a screening tool for identifying individuals with RCC and predicting outcome. This same model also had predictive value in terms of overall survival and tumour recurrence in patients with RCC [15].

Conclusion

RCC mortality and incidence rates differ greatly from country to country. Hereditary risk factors cannot be changed, however comorbidities, behavioural risk factors, and environmental risk factors may all be improved. Therefore, it is crucial to focus prevention efforts on smoking, obesity, hypertension, diabetes, and occupational exposure.

In addition to the prevention of epidemics, secondary prevention, particularly early diagnosis, is crucial. RCC mortality may be decreased with proper genetic disease monitoring and early discovery of sporadic instances, which make up the bulk of cases.

RCC biomarkers have been extensively researched and published for both diagnostic and prognostic reasons. None, however, are currently reliable enough to be applied widely in clinical practise. None, nevertheless, are currently reliable enough to be extensively applied in clinical practise. Therefore, more study is needed to understand novel RCC indicators.

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Conflict of Interest

Author declares no conflict of interest.

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