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Review – Kidney Cancer – Editor's choice

Epidemiology of Renal Cancer: Incidence, Mortality, Survival, Genetic Predisposition, and Risk Factors

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Abstract

Background and objective: Renal cancer (RC) is a common malignancy. Its incidence and mortality rates vary by geographic area and sex, and are projected to increase in the future. This review aims to describe global epidemiology of RC examining its incidence, mortality, survival, genetic predisposition, and risk factors.

Methods: We obtained national estimates of the current and projected incidence and mortality from the Global Cancer Observatory of the International Agency for Research on Cancer. Incidence and mortality were defined as the number of new cases and deaths for the year 2022, respectively. Future estimations from 2022 to 2050 were based on the projected population growth and aging. We have assessed all the global metrics and stratified the data according to geographic area and sex. We evaluated survival from international or national registries, systematic reviews and meta-analyses, or original reports. Additionally, we updated epidemiological reviews on genetic predisposition and risk factors.

Key findings and limitations: Globally, 434,840 individual cases and 155,953 individual deaths were recorded in 2022. Incidence and mortality varied according to geographic

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area and sex. In total, 745,791 new cases (+72%) and 304,861 (+96%) new deaths are expected in 2050. The 5-yr overall survival rate ranged from 40% to 75% according to geographic area. Pathogenic variants in the alleles, *VHL*, *ELOC*, *TSC1/2*, *MET*, *FLCN*, PRDM10, *SDHA/B/C/D*, *MiTF*, *CDC73*, *FH*, *PTEN*, *BAP1*, *SMARCB1*, *CHEK2*, *MUTYH*, *BRCA2*, *ATM*, and *APC*, predispose to RC. Nonmodifiable risk factors include sex, geography, ethnicity/ancestry, and family history. In contrast, modifiable risk factors include obesity, insulin resistance/diabetes, hypertension, chronic kidney disease, smoking, environmental exposure, and lack of physical exercise.

Conclusions and clinical implications: The current and projected incidence and mortality rates empower patients, clinicians, and policymakers. Data on RC epidemiology, genetic predisposition, and risk factors may facilitate early detection, aid selective genetic testing, and guide risk-adapted prevention and screening strategies.

ADVANCING PRACTICE

What does this study add?
This study adds information on up-to-date incidence, mortality, survival, genetic predisposition, and risk factors of renal cancer.

Clinical Relevance
This comprehensive review of renal cancer epidemiology highlights the substantial and rising global burden of disease, with projected incidence and mortality increases of 72% and 96%, respectively, by 2050. For the uro-oncology community, these findings underscore the imperative for risk-adapted prevention strategies, including genetic testing for hereditary syndromes and targeted screening of high-risk populations based on modifiable and non-modifiable risk factors. Incorporating these epidemiological insights into clinical and policy frameworks can guide early detection initiatives and inform equitable allocation of healthcare resources across diverse geographic settings. Associate Editor: Gianluca Giannarini, M.D.

Patient Summary
Renal cancer (RC) is a common malignancy with notable geography and sex-specific differences. Out of ten patients diagnosed with RC, four to seven are alive 5 yr after the diagnosis, depending on the cancer and patient characteristics. Genetic testing is indicated for some patients with RC. Individuals with a higher risk of developing RC can be identified by specific, well-defined risk factors. Management of body weight, diabetes, hypertension, and renal dysfunction control, along with smoking cessation, may reduce the risk of developing RC.

1. Introduction

Globally, renal cancer (RC) ranks as the sixth and ninth leading new cancer diagnosis for men and women, respectively [1]. The World Health Organization classification of RC comprehends renal cell carcinoma (RCC) subtypes such as clear cell (ccRCC), papillary (pRCC), and oncocytic and chromophobe (chRCC) RCC; moreover, it also includes metanephric, mixed epithelial and stromal, mesenchymal, and embryonal tumors of the kidney [2–5].

Given the critical role that cancer epidemiology plays in informing patients, clinicians, and policymakers, the aim of this report is to update the *European Urology* 2019 [6] and 2022 [7] epidemiology studies with contemporary data. Specifically, we describe herein the global epidemiology of RC based on regional- and sex-specific cases and deaths, the available survival estimates, and, for the first time, the projected rates for the year 2050. We also review and summarize the current available evidence regarding genetic predisposition and risk factors associated with the development of RC.

2. Methods

2.1. Incidence and mortality

We retrieved data on the incidence and mortality of RC from the CANCER TODAY tool [8] of the Global Cancer Observatory, an interactive web-based platform presenting global cancer statistics [9,10] developed by the International Agency for Research on Cancer of the World Health Organization. RC was defined as malignant neoplasms of the kidney, except for renal pelvis or lymphoid, hematopoietic, and related tissues, based on the code C64 of the International Classification of Disease, tenth revision. Incidence and mortality were defined as the number of RC cases and deaths due to RC in 2022, respectively. The estimates were assembled at the national level using the best available

sources of cancer incidence and mortality data within a given country [9].

We described incidence and mortality by reporting the total number of cases/deaths; crude rates per 100,000 persons; age-standardized rates (ASRs), defined as weighted average of the age-specific rates per 100,000 persons based on the 1966 Segi-Doll standard population [11]; and, finally, cumulative risk, defined as the number of newborn children out of 100, who would be expected to develop/die from RC before 75 yr, assuming the absence of competing causes of death. We analyzed all the metrics globally after stratification according to geographic areas and sex. Finally, with the purpose of assessing the impact of differences in infrastructures and health care systems on the observed incidence and mortality, we analyzed, for each country, the incidence and mortality ASRs stratified according to the human development index, a summary metric of three key dimensions of human development, namely, life expectancy at birth, education based on years of schooling, and gross national income per capita. We assessed the association between the human development index and incidence and mortality with linear regression. The statistical tests were two sided, with a significance set at $p < 0.05$.

2.2. Survival

We retrieved the survival data from international, national, or subnational population-based cancer registries, when available. Alternatively, in the absence of the former, systematic reviews and meta-analyses as well as original reports were considered. We reported overall survival and relative survival, assuming the absence of competing causes of death. We described survival in terms of the rate and 95% confidence interval for patients with RC alive at 1, 5, and 10 yr after diagnosis.

2.3. Future estimation

We retrieved the data on incidence and mortality from the CANCER TOMORROW tool [12] of the Global Cancer Observatory. We have described future incidence and mortality by reporting the total number of RC cases expected in the year 2050, the projected annual increase, and the percentage increase from 2022 up to 2050. The prediction is based on the assumptions that the 2022 rates do not change in future years and that the population change projections are correct for these years [13,14]. These estimations do not consider any changes in the prevalence of risk factors or improvements in cancer treatments, but rather reflect the growth and aging of the population only.

2.4. Genetic predisposition and risk factors

We have updated the 2019 [6] epidemiology report and 2022 [7] systematic review by performing a narrative review on the risk factors and genetic predisposition for RC (Supplementary material), and we have qualitatively summarized the available evidence.

We have summarized the current criteria for selecting RC patients for genetic testing, as well as the actionable genes for RC, defined as genes that confer a higher risk for cancer phenotype in the setting of hereditary RC. For each gene, we have described the frequency of germline pathogenic/-likely pathogenic variants in RCC patients, and we have classified the associated hereditary RC syndromes according to the ORPHANET inventory and classification [15]. For each hereditary syndrome, we have described the prevalence, risk of RC development, RC histology, prognosis, and extrarenal clinical manifestations. Finally, we have classified risk factors as nonmodifiable and modifiable, and we have reported the potential underlying biological mechanism, magnitude of risk increase, and efficacy of preventive measures.

3. Results

3.1. Incidence and mortality

Fig. 1 illustrates the global incidence of RC. In 2022, 434,840 individual cases were indexed. The heatmap describes the ASR ranging from 0.04 per 100,000 individuals in Sierra Leone to 14.1 in Belarus. Approximately 35% (151,276) of the cases were recorded in Asia, 34% (145,721) in Europe, 18% (79,769) in North America, 8% (35,927) in Latin America, 4% (17,129) in Africa and 1% (5,018) in Oceania.

Fig. 2 illustrates the global mortality of RC. In 2022, 155,953 individual deaths were indexed. The heatmap describes the ASR for each country, ranging from 0.01 per 100,000 individuals in Sierra Leone and 4.6 in Uruguay. About 38% (59,239) of the deaths were recorded in Asia, 34% (52,347) in Europe, 11% (16,977) in North America, 10% (15,678) in Latin America, 6.5% (10,173) in Africa and 1% (1,539) in Oceania.

RC region- and sex-specific incidence and mortality are depicted in Fig. 3 and Fig. 4, respectively.

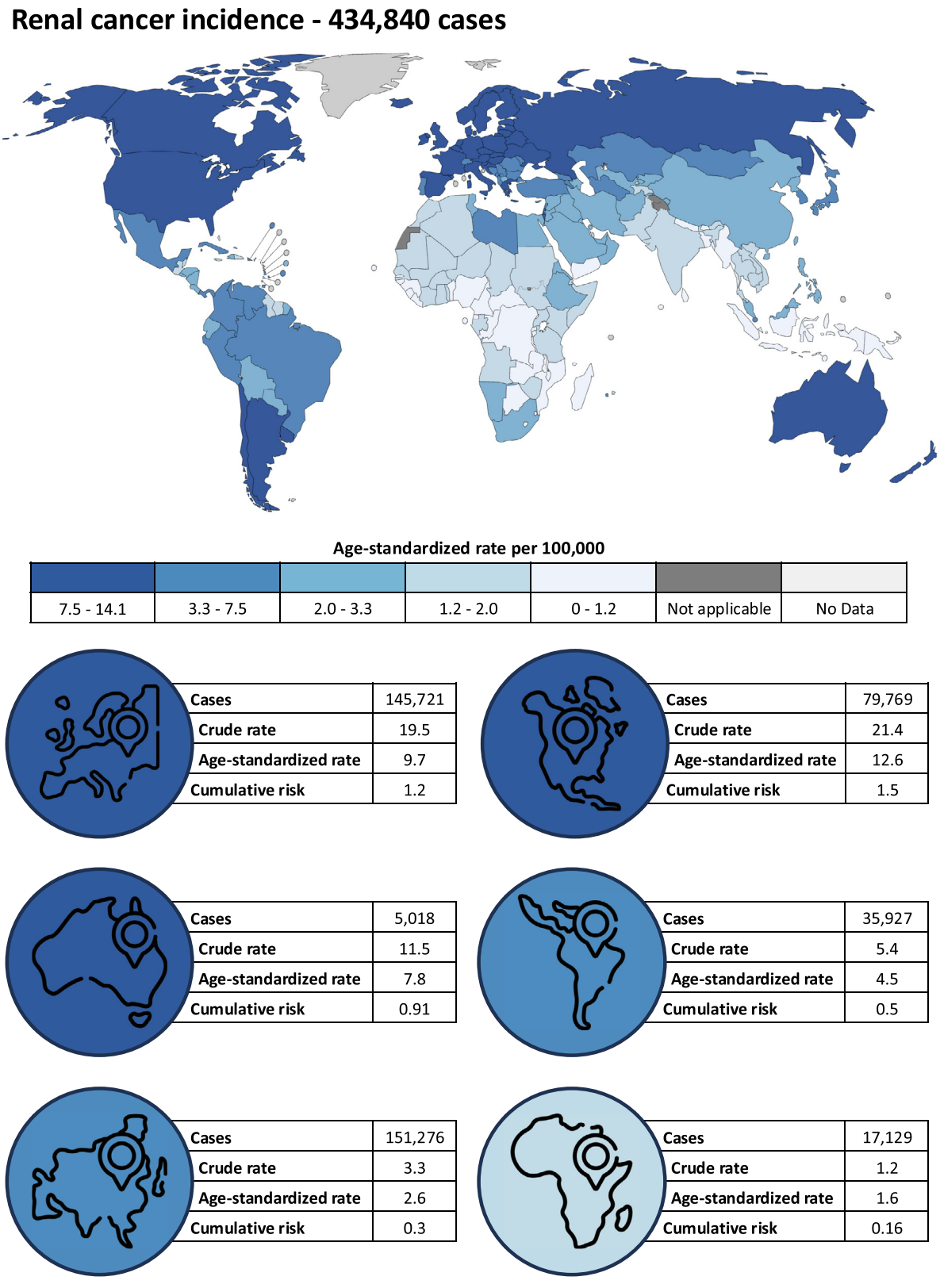
Fig. 5 illustrates RC incidence and mortality ASR stratified according to human development index for each country. Geographic areas and individual countries with higher level of human development index have elevated higher incidence and mortality ASR (all p<0.0001).

3.2. Survival

The survival estimates are reported in Table 1. Based on the registry data, the 5-yr overall survival rate was 66% in Europe [16], 67% in North America [17], and 75% in Oceania [18]. Based on systematic reviews and meta-analyses, the 5-yr overall survival rate was 69% in Asia [19]. Based on original reports, the 5-yr overall survival rate ranged from 40% to 63% in Africa [20,21]. In Latin America, the 5-yr overall survival rate was 86% for patients with nonmetastatic RC [22]. Based on the registry data, the 5-yr relative survival rate ranged from 67% to 76% in Europe [16,23], was 75% in North America [24], and was 82% in Oceania [18].

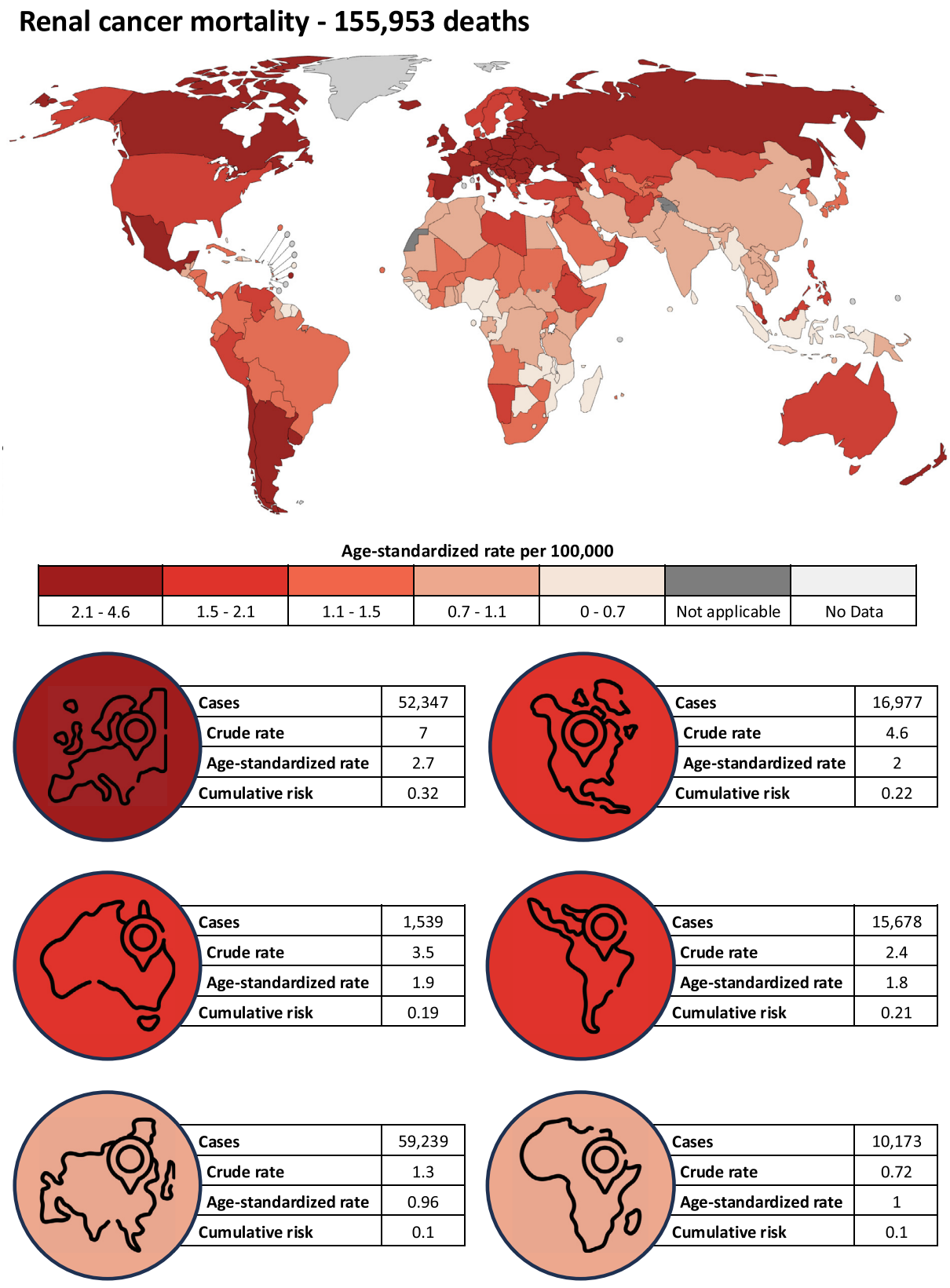
3.3. Future estimation

Fig. 6 depicts the projected new cases over the next years, as based on the expected population growth and aging. Globally, 745,791 new cases are predicted by the year



Source: Cancer Today - IARC; https://gco.iarc.who.int/today; Data version: Globocan 2022 (version 1.1) - 01.03.2025

Fig. 1 – Global renal cancer incidence in 2022. The heatmap depicts age-standardized rates of renal cancer cases for each country. The tables outline total cases, crude rates, age-standardized rates and cumulative risk for each geographic area.



Source: Cancer Today - IARC; https://gco.iarc.who.int/today; Data version: Globocan 2022 (version 1.1) - 01.03.2025

Fig. 2 – Global renal cancer mortality in 2022. The heatmap depicts age-standardized rates of renal cancer deaths for each country. The tables outline total cases, crude rates, age-standardized rates and cumulative risk for each geographic area.

Renal cancer region- and sex-specific incidence

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Africa	F	1.1	1.3	0.12
	M	1.2	1.8	0.18
Middle Africa	F	0.92	1.0	0.09
	M	1.1	1.5	0.12
Northern Africa	F	1.7	1.8	0.18
	M	2.2	2.5	0.27
Southern Africa	F	1.7	1.8	0.17
	M	2.6	3.3	0.36
Western Africa	F	0.82	1.0	0.10
	M	0.91	1.2	0.11

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Europe	F	13.8	7.0	0.84
	M	23.0	14.5	1.8
Northern Europe	F	14.3	6.8	0.77
	M	25.8	13.7	1.6
Southern Europe	F	12.3	5.1	0.58
	M	26.0	12.5	1.5
Western Europe	F	15.4	6.2	0.70
	M	28.0	13.0	1.5

Region	Sex	Crude rate	ASR	Cumulative risk
Northern America	F	14.8	8.5	0.96
	M	28.1	16.9	2.0

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Asia	F	4.4	2.4	0
	M	8.1	4.8	0
South-Eastern Asia	F	1.3	1.1	0
	M	2.4	2.3	0
South Central Asia	F	1.0	1.0	0.11
	M	1.6	1.7	0
Western Asia	F	2.7	2.8	0
	M	4.5	5.1	0

Region	Sex	Crude rate	ASR	Cumulative risk
Caribbean	F	2.9	2.3	0
	M	4.4	3.5	0
Central America	F	2.8	2.6	0
	M	5.5	5.7	0
South America	F	4.3	3.2	0
	M	8.0	6.7	0

Region	Sex	Crude rate	ASR	Cumulative risk
Australia-New Zealand	F	8.9	5.0	0
	M	22.7	13.7	1.6
Melanesia	F	0.58	0.79	0.08
	M	1.0	1.6	0
Micronesia	F	0.00	0.00	0.00
	M	4.6	4.8	0
Polynesia	F	2.6	2.4	0
	M	6.8	6.3	0

Source: Cancer Today - IARC; https://gco.iarc.who.int/today; Data version: Globocan 2022 (version 1.1) - 01.03.2025

Fig. 3 – Region- and sex-specific incidence of renal cancer. The tables report crude rates, age-standardized rates and cumulative risk according to United Nations Regional Groups and sex.

2050. The estimated increase is consistent across sexes, with an additional 71.6% in males and 71.4% in females. The estimated increase varies considerably by geographic area, ranging from an additional +19% in Europe to +106% in Africa.

Fig. 7 depicts the projected new deaths in the next years as based on the expected population growth. Globally, 304,861 new deaths are expected by 2050. The estimated increase is consistent across sexes, with an additional 94.5% in males and 97.3% in females. The estimated increase varies considerably by geographic area, ranging from an additional +39% in Europe to +103% in Africa.

3.4. *Genetic predisposition*

3.4.1. *Indications for genetic testing*

Hereditary factors play a significant role in determining genetic predisposition to RC, with an estimated 5–8% of RC cases being indexed as hereditary [25,26]. Hereditary RC syndromes are often suspected based on early onset, synchronous multifocal or bilateral tumors, a personal or family history of RC or other cancers, and presence of other syndrome-specific lesions [7,25,26].

Several guidelines are available to select candidates for genetic testing following an RC diagnosis [4,27–31]. Testing may be conducted either as primary genetic testing, defined as the initial test performed on an individual without a known pathogenic variant in the family, or as cascade testing, which targets a specific known variant in family members of an individual diagnosed with a genetic condition or mutation.

Indications for testing include young age at diagnosis, with specific thresholds identified at $\leq$46 and $\leq$50 yr of age; a multifocal or bilateral tumor; a family history of at least another first- or second-degree relative diagnosed with RC; and histological features associated with hereditary RC [4,27–31]. Specific criteria based on a personal history of extrarenal features suggestive of hereditary RC syndrome (Fig. 8) must also be contemplated [27–31]. Pathogenic variants in specific genes are often linked to extrarenal manifestations in the context of a hereditary RC

Renal cancer region- and sex-specific mortality

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Africa	F	0.95	0.71	0.09
	M	1.3	0.80	0.14
Middle Africa	F	0.75	0.60	0.07
	M	1.2	0.71	0.10
Northern Africa	F	0.91	0.87	0.09
	M	1.3	1.1	0.13
Southern Africa	F	0.80	0.75	0.08
	M	1.5	1.1	0.16
Western Africa	F	0.69	0.51	0.07
	M	0.85	0.57	0.09

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Europe	F	1.8	4.6	0.21
	M	5.0	8.6	0.62
Northern Europe	F	1.6	5.0	0.17
	M	3.5	8.5	0.38
Southern Europe	F	1.3	4.5	0.13
	M	3.5	9.1	0.39
Western Europe	F	1.5	5.6	0.16
	M	3.9	10.6	0.42

Region	Sex	Crude rate	ASR	Cumulative risk
Northern America	F	1.2	3.1	0.13
	M	2.9	6.1	0.32

Region	Sex	Crude rate	ASR	Cumulative risk
Eastern Asia	F	0.59	1.4	0.
	M	1.4	2.7	0
South-Eastern Asia	F	0.58	0.71	0.06
	M	1.3	1.3	0
South Central Asia	F	0.57	0.56	0.06
	M	1.0	0.93	0.12
Western Asia	F	0.92	0.94	0.10
	M	2.2	1.8	0

Region	Sex	Crude rate	ASR	Cumulative risk
Caribbean	F	0.78	1.2	0.
	M	1.4	1.9	0
Central America	F	1.3	1.5	0
	M	2.9	2.9	0
South America	F	1.2	1.8	0
	M	2.7	3.3	0

Region	Sex	Crude rate	ASR	Cumulative risk
Australia-New Zealand	F	1.2	3.2	0
	M	3.0	6.4	0
Melanesia	F	0.32	0.21	0.03
	M	0.98	0.54	0.10
Micronesia	F	0.00	0.00	0.00
	M	1.5	1.4	0
Polynesia	F	0.61	0.88	0.00
	M	2.5	2.9	0

Source: Cancer Today - IARC; https://gco.iarc.who.int/today; Data version: Globocan 2022 (version 1.1) - 01.03.2025

Fig. 4 – Region- and sex-specific mortality of renal cancer. The tables report crude rates, age-standardized rates and cumulative risk according to United Nations Regional Groups and sex.

syndrome. Table 2 summarizes individual genes associated with RC together with any related hereditary RC syndrome.

3.4.2. *Von Hippel-Lindau Disease*

Von Hippel-Lindau disease is caused by a germline pathogenic variant in one *VHL* allele. In line with the two-hit hypothesis, any somatic event disrupting the other *VHL* allele induces loss of function, hypoxia inducible factor accumulation, and oncogenesis [32,33]. A Von Hippel-Lindau–like phenotype has also been described as result of an *ELOC* variant [34]. The incidence ranges from one per 27,000 to one per 43,000 individuals, and the prevalence is one to nine per 100,000 individuals [35,36]. In RCC patients, the frequency of pathogenic/likely pathogenic variant ranges from 0.1 to 0.5 [37–43]. Affected individuals develop multiple tumors in multiple organ sites at metachronous time points [44,45]. Prototypical tumors include hemangiomas of the retina and hemangioblastomas of the central nervous system, pancreatic cystadenomas and neuroendocrine tumors, pheochromocytomas/paragangliomas, and ccRCC [44,45]. Management involves close surveillance until intervention becomes necessary to prevent local or systemic cancer progression or to alleviate symptoms [46,47]. Historically, local treatment with surgery or ablation was the only available option to treat ccRCC [48,49];, however, hypoxia inducible factor inhibitors have shown activity in clinical trials [50–52] and have been approved by regulatory agencies. As such, current management is based on the combination of local and systemic therapies [53].

3.4.3. *Tuberos sclerosis complex*

Tuberos sclerosis complex is associated with a germline pathogenic variant in either *TSC1* or *TSC2* allele [54]. These variants cause activation of the mTOR pathway and multifocal tumor formation [55]. The incidence is one per 18,000 and the prevalence is one to nine per 100,000 individuals [56]. In RCC patients, the frequency of pathogenic/likely pathogenic variant ranges from 0.1 to 0.3 [37–43]. Affected

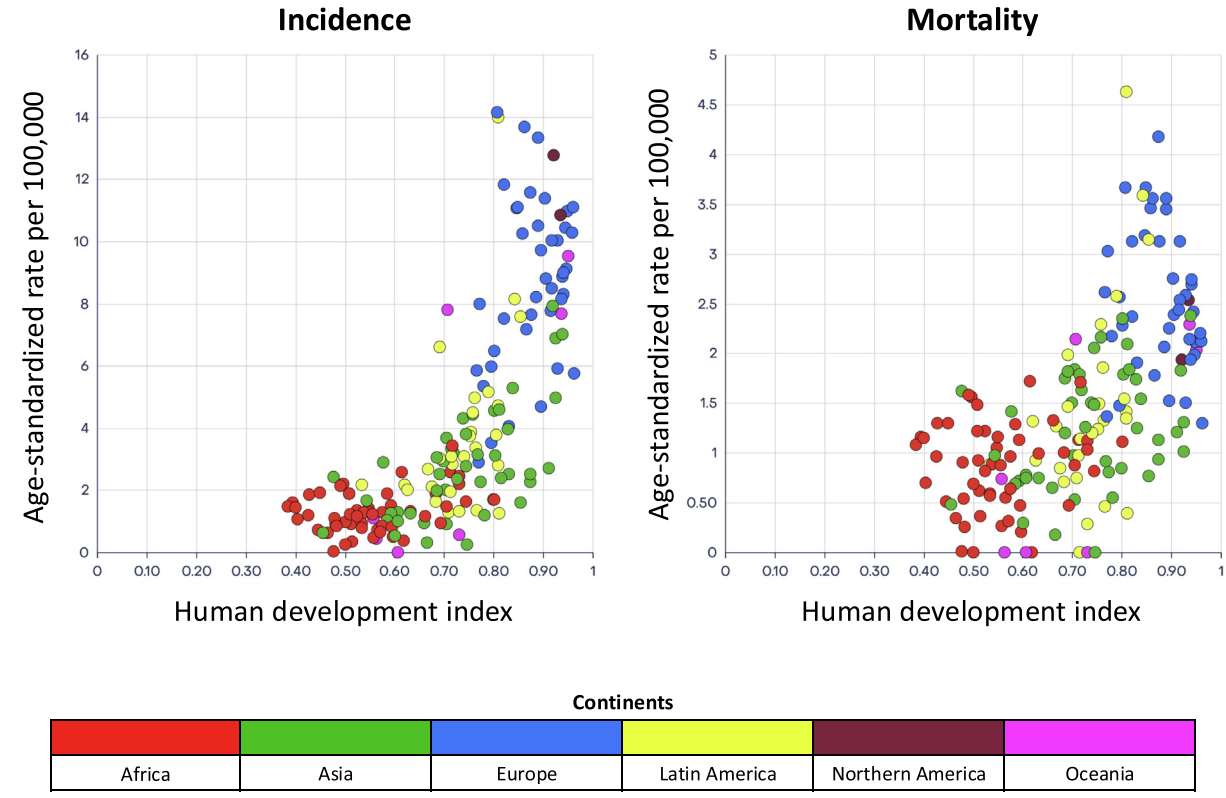


Fig. 5 – Renal cancer incidence and mortality according to human development index. The figures present country-specific age-standardized incidence and mortality rates stratified by human development index, which is a summary metric of three key dimensions of human development: life expectancy at birth, education based on years of schooling and gross national income per capita.

individuals develop multisystem hamartomas, most commonly involving the skin, brain, eye, lung, and heart, and often present with epilepsy and neuropsychiatric disorders [54]. RC occurs in <5% of cases, while angiomyolipoma and benign cysts are more frequent [57]. Available therapies include surgery and ablation of renal tumors, systemic and local mTOR inhibitors, antiseizure medications, and dermatological surgery [58].

3.4.4. *Hereditary papillary renal cell carcinoma*

Hereditary pRCC stems from an activating missense pathogenic variant in the proto-oncogene *MET*, encoding the hepatocyte growth factor–responsive tyrosine kinase receptor [59]. The activation promotes cell proliferation and inhibition of apoptosis. The incidence is unknown, the estimated prevalence is one per 100,000 persons [60], and the frequency of pathogenic/likely pathogenic variant ranges from 0% to 0.2% in RCC patients [37–43]. Affected individuals are at risk of multifocal pRCC, and, unlike other hereditary RC syndromes, extrarenal manifestations have not been described [61,62]. The management of pRCC includes active surveillance and surgery [60]. For unresectable diseases, dual MET/VEGFR2 kinase inhibitor and tyrosine kinase inhibitors have shown promising results [63].

3.4.5. *Birt-Hogg-Dubé*

Birt-Hogg-Dubé syndrome is associated with a loss-of-function pathogenic variant in an *FLCN* allele responsible for mTORC1 hyperactivation [64,65]. A Birt-Hogg-Dubé–like phenotype has been described as a result of a *PRDM10* variant [66]. The incidence is unknown, and the estimated prevalence is one to nine per 1,000,000 individuals, although this figure might underestimate the true rate [67]. In RCC patients, the frequency of pathogenic/likely pathogenic variant ranges from 0.1 to 1.8 [37–43]. Patients may present with fibrofolliculomas, lung cysts leading to spontaneous pneumothoraxes, and multifocal renal tumors [68–70]. RC in this setting is heterogeneous, but largely indolent, with mixed histologies, including hybrid tumors, chRCC, oncocytoma, and, rarely, ccRCC and pRCC [71].

3.4.6. *Other rare hereditary syndromes*

Other RC hereditary syndromes with a prevalence of fewer than one per 1,000,000 individuals or uncertain data

Table 1 – Renal cancer survival by geographic area [a]

Region	Source	Type	Follow-up	Year(s) from diagnosis	Overall survival (95% CI)	Relative survival (95% CI)
Europe	NORDCAN, The Association of the Nordic Cancer Registries. Data version 9.3 – October 2, 2023 [23]	International population-based cancer registry	2021	1	NA	88.4 (87.2–89.4)
				5	NA	75.9 (74.1–77.9)
				10	NA	NA
Europe	Cancer Survival in England, National Health System; Cancers diagnosed during 2016–2020, followed up to 2021. Data version February 16, 2023 [16]	National population-based cancer registry	2021	1	78.8 (78.4–79.2	80.8 (80.2–81.4)
				5	65.6 (65.0–66.2)	66.8 (65.7–68.0)
				10	NA	NA
North America	Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: incidence, 22 registries (excluding IL and MA), November 2023 Sub (2000–2021). Data version April 2024 [17]	Subnational population-based cancer registry	2021	1	84.4 (84.3–84.6)	86.2 (86.1–86.3)
				5	67.1 (67.0–67.3)	74.7 (74.6–74.9)
				10	53.0 (52.8–53.2)	67.4 (67.2–67.7)
Oceania	Cancer Data in Australia 2024 web report, Australian Institute of Health and Welfare. Data version December 9, 2024 [18]	National population-based cancer registry	2020	1	89.5 (89.0–89.9)	91.1 (90.6–91.5)
				5	75.2 (74.5–75.8)	82.3 (81.6–83.0)
				10	61.6 (60.8–62.4)	75.6 (74.6–76.5)

CI = confidence interval; NA = not applicable.
[a] Net survival is reported assuming the absence of a competing cause of death.

include *MiTF*-related melanoma and RCC predisposition syndrome, hyperparathyroidism-jaw tumor syndrome, fumarate hydratase–deficient RCC, phosphatase and tensin homolog hamartoma syndrome, *BAP1*-related tumor predisposition syndrome, renal medullary carcinoma, and chromosome 3 translocation syndrome [72]. Finally, besides the already known genes and the associated hereditary RC syndromes described above, the frequency of germline pathogenic or likely pathogenic variants in the genes *CHEK2*, *MUTYH*, *BRCA2*, *ATM*, and *APC* was >1% in three large, contemporary case-control investigations of RC susceptibility in patients with RCC [38,40,41]. Other less frequent variants [73] or different genome regions [74] are currently under scrutiny.

3.5. Risk factors

3.5.1. Nonmodifiable risk factors

The risk factors for RC are summarized in Fig. 9. The nonmodifiable risk factors are age, male sex, geography, ethnicity/ancestry, and family history [4,7]. These risk factors deserve consideration for the purpose of primary prevention strategies. The RC incidence and mortality rise consistently with age [6,7,75]. Males have a higher risk of developing RC, are diagnosed with more aggressive disease, and have worse oncological outcomes relative to their female counterparts [1,76]. Sexual dimorphism is largely affected by geographic factors; for instance, the difference is more pronounced in Europe, North America, and Oceania, and less pronounced in Africa, as noted in Figs. 3 and 4. Geography is also associated with incidence and mortality regardless of sex, as depicted in Figs. 1 and 2. Finally, other factors linked to genetic predisposition such as ancestry/ethnicity [40] and family history [77] increase RC risk. Specifically, Native American/Alaska Native and Black/African Americans have the highest risk, White individuals have intermediate risk, and Asian and Native Hawaiian/Pacific Islanders have the lowest risk [1,7].

3.5.2. Modifiable risk factors

Modifiable risk factors for RC are obesity, insulin resistance/diabetes, hypertension, chronic kidney disease, smoking, environmental exposure, and lack of physical exercise [4,7]. More than 50% of RC cases and deaths are attributable to potentially modifiable risk factors [78], and these determinants identify high-risk individuals who may benefit from screening policies for secondary prevention.

3.5.2.1. Excess body weight

Excess body weight is a recognized risk factor for RC [7,79,80], and the relationship between overweight/obesity and RC is causal [81,82]. The mechanisms linking obesity to RC incidence include sex hormone biosynthesis, inflammation and oxidative stress, and dysfunction of the gut microbiota, and are cross-linked to hyperinsulinemia or insulin resistance [7]. These conditions may facilitate mitogenic, antiapoptotic, and proangiogenic effects [7,79]. Up to 34% cases of RC are attributable to excess body weight [78], and the relative risks (RRs) were 1.35 (1.27–1.43) in overweight and 1.76 (1.61–1.91) in obese individuals compared with the normal-weight individuals in a meta-analysis [83]. Surprisingly, obesity has a protective effect on RC mortality [84,85], and body mass index is associated with improved outcomes in patients treated with immunotherapy [86];

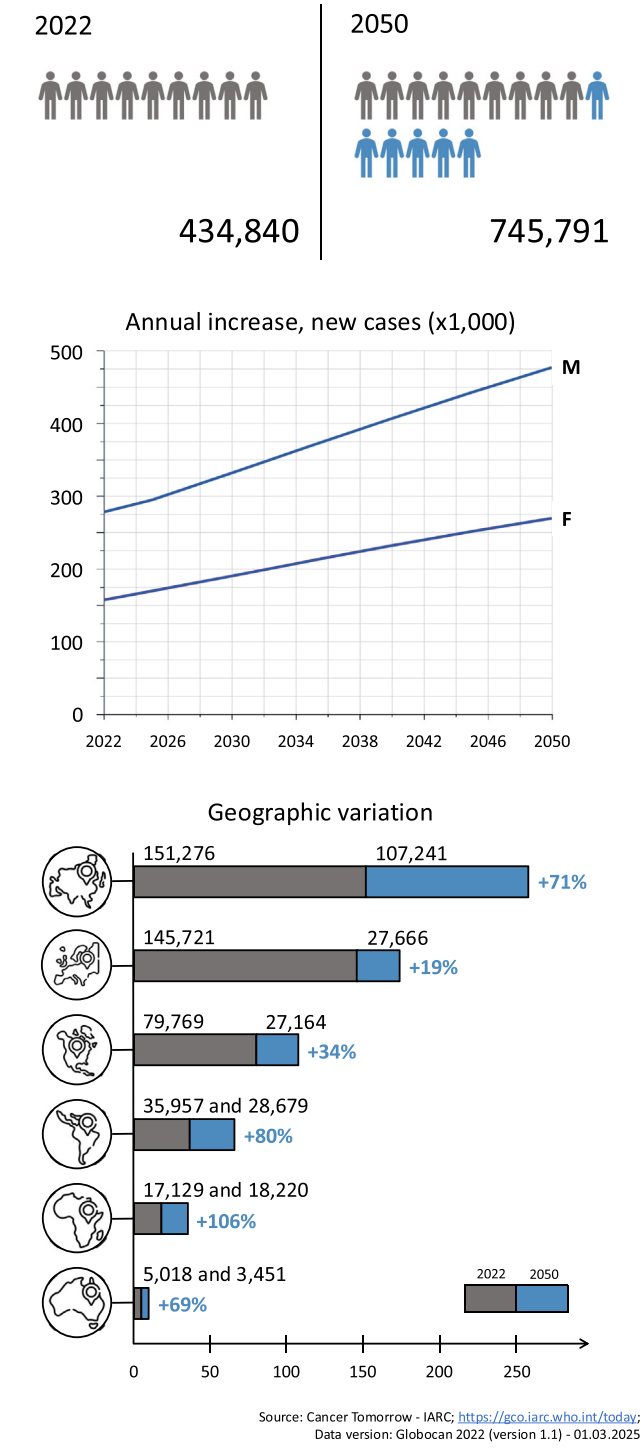


Fig. 6 – Projected renal cancer incidence through 2050. The figure illustrates the overall estimated new cases in 2050, detailing sex-specific trends over time and the variation according to geographic area.

hence, the term "obesity paradox" refers to the counterintuitive evidence that obesity facilitates RC development but is protective with respect to cancer-specific mortality. Mechanistically, body mass index–dependent fatty acid synthase activation might improve RC survival [87,88].

3.5.2.2. Insulin resistance or diabetes

Insulin resistance/diabetes increases the risk of RC independently [89–91]. The expression of IGF-1 resulted in an increase in RC cells in preclinical investigations via promotion of cell cycle progression and inhibition of apoptosis [92]. The RRs were 1.57 (1.36–1.82) in diabetic relative to nondiabetic individuals [93] in a meta-analysis and 1.44 (1.34–1.53) in a large population-based registry [94]. Secondary prevention through specific diet was found to be associated with risk reduction [95]. The effect of Glucagon-like peptide-1 receptor agonists on the risk of RC development is controversial [96,97].

3.5.2.3. Hypertension

Hypertension is a documented risk factor for RC [7,79]. The biological mechanism includes dysregulation of hypoxia inducible factor, lipid peroxidation, and formation of reactive oxygen species [98]. The association of hypertension and RC has been confirmed in a large meta-analysis reporting RRs ranging from 1.12 to 2.6 [89]. Diastolic blood pressure has more impact than systolic blood pressure on RC risk, and hypertension severity and lack of control were also found to be positively associated with RC [99]. Antihypertensive drugs may also be associated with RC [100]. However, these observations indirectly reflect hypertension severity and duration rather than a mechanistic effect of the medication. Taken together, obesity, insulin resistance/-diabetes, hypertension, and elevated low-density lipoproteins [101] collectively contribute to metabolic syndrome, which is in itself a risk factor for RC [4,6,102].

3.5.2.4. Chronic kidney disease and end-stage renal disease

Pathological changes in the renal parenchyma, such as chronic kidney disease and end-stage renal disease, increase RC incidence [87] and mortality [88] in patients treated with either dialysis or transplant. In the latter, RC is more frequently found in the native kidney relative to the transplanted kidney [103]. While acquired renal cystic disease raises the risk of both renal dysfunction and RC [104], and may act as a confounder; it is notable that reduced renal function is also linked to higher cancer-specific mortality in patients with RC who underwent surgical treatment [105].

3.5.2.5. Smoking

Smoking is an established risk factor for RC [79,106]. Preclinical evidence supports a relationship between tobacco smoke and stemness of RC cells, thus fueling carcinogenesis [107]. The estimated rate of RC cases attributable to cigarette smoking is 19% [78] and RRs ranges from 1.3 to 2.3 in individual reports [89] and pooled RR from a meta-analysis resulted 1.39 (1.28-1.51) for smokers relative to never-smokers and 1.20 (1.14-1.27) for former- relative to never-smokers [108]. This relationship is dependent on the dose and time, with a consistent increase according to the number of cigarettes per day and a consistent decrease according to the years since smoke cessation [108]. Follow-

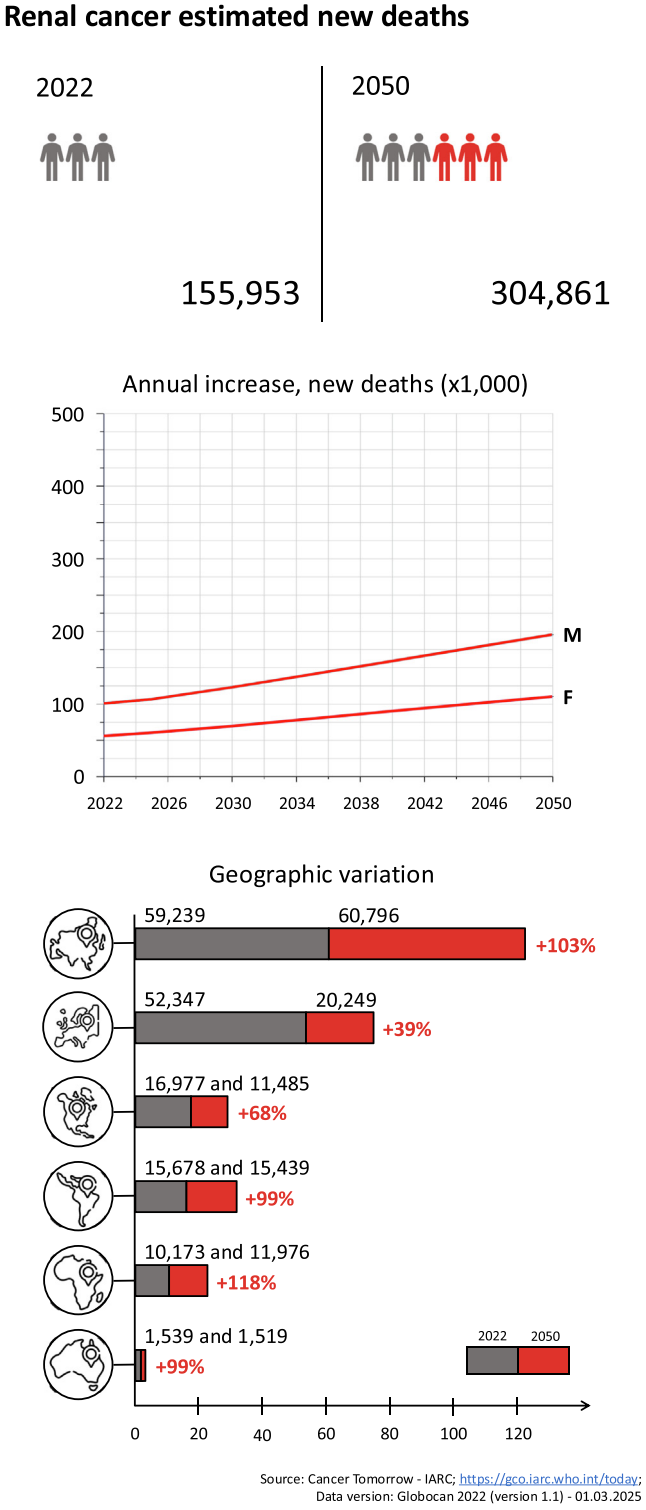


Fig. 7 – Projected renal cancer mortality through 2050. The figure illustrates the overall estimated new deaths in 2050, detailing sex-specific temporal trends and the variation according to geographic area.

ing smoking cessation, the risk of RC decreases for former smokers relative to current smokers, but remains higher relative to never smokers [108]. Consistently, current and former smokers have a higher risk of mortality due to RC than never smokers [109] even if smoking does not directly affect the risk of RC pulmonary metastasis [110,111]. Whether this risk is modified using electronic cigarettes or vaping devices is uncertain [112,113].

3.5.2.6. Other modifiable risk factors

Other possible modifiable risk factors include environmental exposure and lack of physical exercise [4,7]; however, the evidence supporting a causal relationship with RC is mixed. Despite increasing awareness of the contribution of environmental exposures to cancer development in general [114,115], adequate evidence is available for individual compounds only. Namely, perfluorinated chemicals and aristolochic acid [116], aristolochia-based herbal medicines [117], trichloroethylene and perchloroethylene [118], micro or nano plastic particles [119], and cadmium [120] increase RC incidence and mortality. No causal relationship between physical exercise and RC risk reduction has been demonstrated [7,121]. A higher level of physical activity during leisure time was associated with a lower RC incidence in a pooled analysis of 1.44 million participants with available details on sport and physical activity [122], even after adjustment for body mass index. In contrast, another investigation measuring sedentary lifestyle by time spent sitting did not find any association [123].

Dietary modification [95,124] and regular and prolonged use of nonsteroidal anti-inflammatory drugs [125,126] might have an impact on RC, but the available evidence is inconclusive [89]. Moderate alcohol consumption has a protective effect for unknown reasons [4,127]. The approximate RR ranges from 0.4 to 0.8 [89], however, it is noteworthy that alcohol is an established risk factor for other cancer types, such as oral cavity, pharynx, larynx, esophagus, colorectum, liver, and female breast cancer [78,128], and that this increased risk outweighs any benefit with respect to a reduction in the RC incidence [129]. Similarly, coffee consumption appears to have an inverse association with RC for reasons yet to be elucidated [130].

4. Discussion

This report summarizes contemporary RC epidemiology by assessing survival data and estimating potential future incidence. When applying these findings to clinical decision-making, guideline development, policymaking, or health care resources allocation, it is necessary to be aware of the intrinsic limitations of epidemiological studies.

Ideally, measurement of disease incidence captures the contribution of genetic predisposition and risk factors, testing those potentially at risk and diagnosing all individuals at risk. Similarly, measurement of disease-specific mortality aims to reflect the interplay between tumor biology and impact of contemporary medical care, assuming equal access to that care. However, in real-world datasets, it is noteworthy that differences in health care access, heterogeneity in screening programs, data collection methods, and disease indexing may introduce significant selection, reporting, or classification biases. In this regard, the relevant variations in incidence and mortality according to the human development index offer a pragmatic, albeit indirect, measure of these biases and care disparities.

Fig. 8 – Extrarenal clinical features in hereditary renal cancer syndromes. Extrarenal sites are categorized as central nervous system, eye, hear, mouth and oral cavity, thyroid and parathyroid, uterus and ovaries, testis, breast, blood cells, lung, stomach, pancreas, adrenal gland, bowel and skin. S.: Syndrome.

It is important to highlight that RC is not yet included among the primary cancers that are indexed in the SURVMARK-2 or SURVCAN, the two principal global cancer survival tools of the Global Cancer Observatory [10]. Given the current incidence and mortality statistics and the expected projections, its inclusion warrants serious consideration. In the absence of a global data source, we relied on individual registries. Such data sources were available for Europe, North America, and Oceania, while data for Asia, Africa, and South America were drawn from systematic reviews, meta-analyses, or original reports. Survival estimation is heavily influenced by the period considered, and tumor registry data may not fully capture the impact of evolving clinical advances—a phenomenon referred to as "treatment disconnect"—and, thus, must be interpreted within this context [131]. In the setting of RC, survival has improved significantly over time [132].

Moreover, projections through 2050 are based on the assumptions that the 2022 risk of developing or dying from kidney cancer remains constant, or in other words, that risk factors, cancer prevention, treatment, and survivorship care

Table 2 – Genes associated with renal cancer and hereditary renal cell carcinoma syndromes [a]

Gene or genetic background (gene location)	Frequency of PV or LPV in RCC patients (%)	Associated hereditary syndrome (Orphanet ID)	Prevalence	RCC risk (%)	Histology	RCC prognosis	Selected extrarenal clinical features
VHL (3p25.3) *ELOC* (8q21.11)	0.1–0.5 [b]	Von Hippel-Lindau disease (ORPHA:829)	1–9/100 000	30–40	Clear cell RCC (bilateral and multifocal)	Favorable	Retinal or central nervous system hemangioblastoma Endolymphatic sac tumor Pancreatic neuroendocrine tumors or serum cystadenoma Pheochromocytoma Epididymal/adnexal cystadenoma
TSC1 (9q34.13) *TSC2* (16p13.3)	0.1–0.3 [c]	Tuberous sclerosis complex (ORPHA:805)	1–9/100 000	<5	Clear cell RCC, papillary RCC, chromophobe RCC, renal angiomyolipoma, (bilateral and multifocal)	Intermediate	Angiofibroma and other skin lesions Brain cortical dysplasia Subependymal giant cell astrocytoma Lymphangioleiomyomatosis or pulmonary cyst/pneumothorax Seizures
MET (7q31.2)	0.2	Hereditary papillary RCC (ORPHA:47044)	1/100 000	100	Papillary (bilateral and multifocal)	Favorable	None
FLCN (17p11.2) *PRDM10 (11q24.3)*	0.1–1.8 [d]	Birt-Hogg-Dubé syndrome (ORPHA:122)	1–9/1 000 000	30	Chromophobe RCC, hybrid oncocytic RCC, oncocitoma, (bilateral and multifocal)	Favorable	Fibrofolliculomas and other skin lesions Pulmonary cysts/pneumothorax Parotid gland oncocytomas
SDHA (5p15.33) *SDHB* (1p36.13) *SDHC* (1q23.3) *SDHD* (11q23.1)	0.1–1.1 [c]	Hereditary pheochromocytoma/paraganglioma (ORPHA:29072)	1–9/1 000 000	<10	Clear cell RCC	Aggressive	Paraganglioma Pheochromocytoma Gastrointestinal stromal tumor
MiTF (3p13)	0.2–0.7	*MiTF*-related melanoma and RCC predisposition syndrome (ORPHA:293822)	<1/1 000 000	<10	*MiTF* family translocation RCC	Aggressive	Melanoma Pancreatic cancer Pheochromocytoma
CDC73 (1q31.2)	–	Hyperparathyroidism-jaw tumor syndrome (ORPHA:99880)	<1/1 000 000	<10	Wilms tumor, others, stromal tumors	Intermediate	Jaw fibroma Hyperparathyroidism Parathyroid cancer Uterine cancer
FH (1p42.1)	0.2–2.8	Fumarate hydratase-deficient RCC (ORPHA:523)	–	15–32	Fumarate hydratase-deficient RCC	Aggressive	Skin leiomyomas Uterine leiomyomas or leiomyosarcomas Adrenal nodules
PTEN (10q23.31)	0.1–0.3	Phosphatase and tensin homolog hamartoma syndrome (ORPHA:306498)	–	10–15	Clear cell RCC, papillary RCC, chromophobe RCC	Intermediate	Macrocephaly Facial trichilemmoma Breast cancer Thyroid cancer Endometrial cancer Prostate cancer Colorectal polyp
BAP1 (3p21.1)	0.1–0.5	*BAP1*-related tumor predisposition syndrome (ORPHA:289539)	–	<15	Clear cell RCC	Aggressive	Uveal and cutaneous melanoma Malignant pleural mesothelioma Lung cancer Breast cancer Pancreatic cancer Cholangiocarcinoma Ovary cancer Meningioma
SMARCB1 (22q11.23) and others	–	Renal medullary carcinoma (ORPHA:319319)	–	–	*SMARCB1*-deficient renal medullary carcinoma	Aggressive	Hereditary hemoglobinopathies
Translocations 3:6; 3:8; 3:11	–	Chromosome 3 translocation (Cr3T) syndrome	–	30	Clear cell RCC	Intermediate	None

LPV = likely pathogenic variant; PV = pathogenic variant; RCC = Renal Cell Carcinoma.

[a] For each syndrome, the prevalence in the overall population, the risk of renal cancer development, histology, prognosis, and selected extrarenal clinical manifestations are outlined.

[b] Frequencies for *VHL* only.

[c] Combined frequencies for all genes of interest.

[d] Frequencies for *FLC* only.

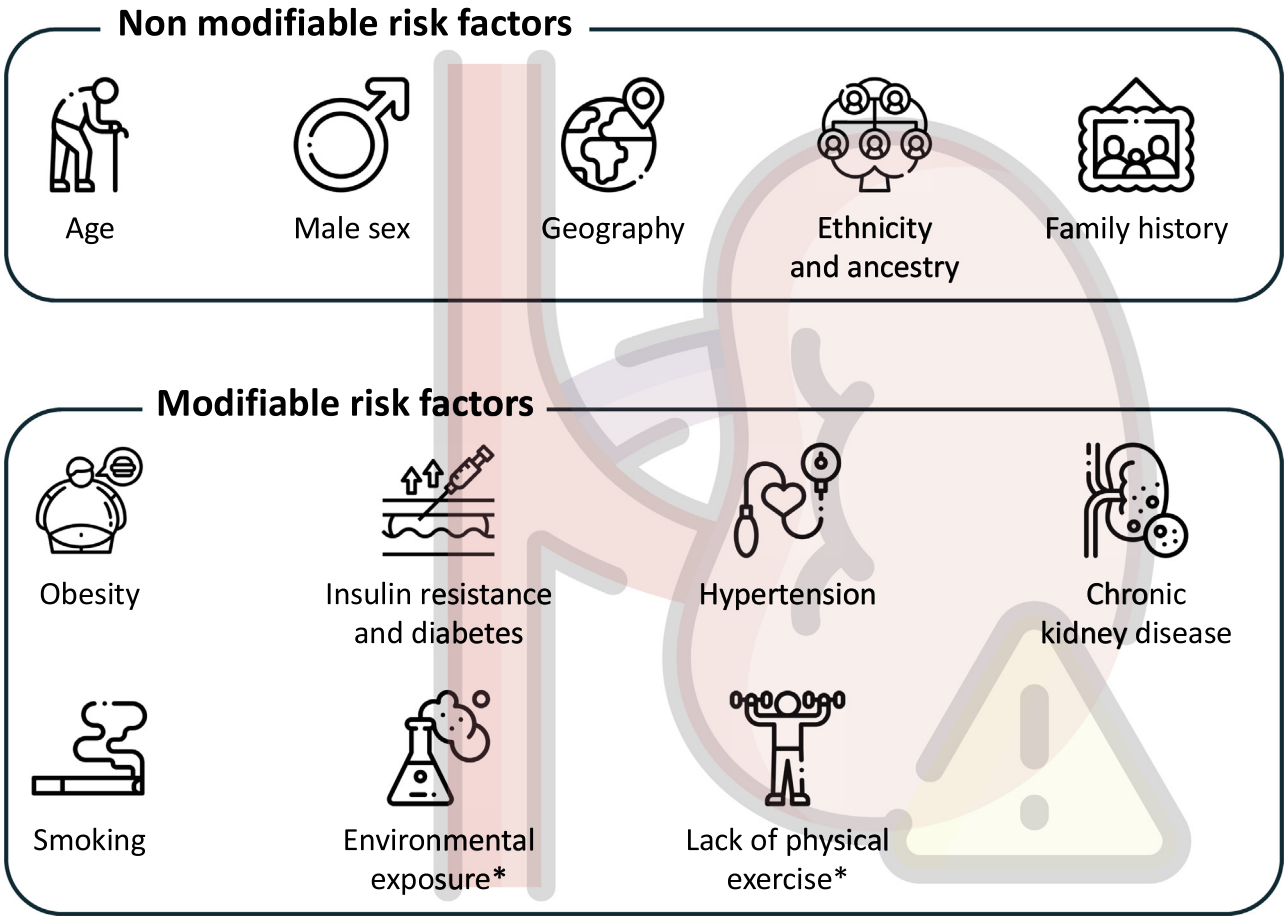


Fig. 9 – Non-modifiable and modifiable risk factors for renal cancer. *: Mixed evidence.

do not change over time. Accordingly, future estimation reflects only population growth and aging. Of course, deviation from these estimates is expected, owing to variability in risk factors over time. For instance, the prevalence of obesity has increased worldwide to pandemic levels [133–135]; tobacco use is increasing in some countries [136], while it is decreasing in others [137]. In addition, improvement in survival due to advances in diagnosis and treatment are likely.

A clear understanding of genetic predisposition is critical to guide testing strategies, especially given the tradeoffs between the low prevalence of hereditary RC and the costs and clinical implications of genetic testing [72,138]. Most data on RC genetic predisposition stem from unique settings of rare diseases, where fragmentation in patient care, knowledge acquisition, and research advancements may hinder the construction of robust evidence and practical guidelines [45]. Nonetheless, the relevance of genetic predisposition in RC extends beyond the setting of rare hereditary syndromes, since the same germline pathogenic variant responsible for hereditary RC may also play a role in sporadic oncogenesis through somatic genetic events [33]. For instance, 75–90% sporadic ccRCC cases exhibit a mutation in the *VHL* gene [40,139,140]. Another important limitation pertains to the lack of diversity in prevalence studies and genomic databases that are primarily based on individuals of European ancestry [141]. In this regard, an inclusive approach with a broader representation is the key to ensure generalizability of future research.

Finally, the evidence regarding RC risk factors remains inconclusive. Epidemiological studies are fraught with limitations due to measured and unmeasured confounders. For instance, patients who have arterial hypertension may undergo renal ultrasound more frequently, potentially introducing a detection bias into the estimates of RC incidence. Meanwhile, the molecular mechanisms that underpin RC oncogenesis, and thus its incidence and mortality, are not yet fully understood [79].

Notwithstanding these limitations, our report offers key insights into RC epidemiology and risk stratification. Specifically, potentially modifiable risk factors such as obesity, insulin resistance/diabetes, hypertension, chronic kidney disease, smoking, environmental exposure, and lack of physical exercise could be the focus of future efforts as targets for RC prevention and screening strategies [79]. Nevertheless, the optimal screening strategy for secondary prevention of RC is yet to be defined [142]. To date, there is no robust evidence to support nonselective screening for RC [143], while targeted screening has been tested in

the Yorkshire Kidney Screening Trial [144]. In this trial, among 4,019 ever smokers invited for lung cancer screening who agreed to undergo noncontrast abdominal computed tomography, ten (0.25%) had histologically proven RC, and the number needed to screen to eventually detect one case of histologically proven RCC was 402 [145]. Looking forward, a risk-adapted screening approach informed by the available evidence on RC risk factors could be a pragmatic and scalable approach to implement screening and early detection of RC [146].

5. Conclusions

RC incidence and mortality rates vary by geographic area and sex, and both are projected to rise in the coming decades alongside global population growth. The overall survival rate ranges from 40% to 75% at 5 yr after the diagnosis, depending on cancer and patient characteristics. Genetic testing is indicated for patients diagnosed with RC at young age, multifocal or bilateral tumors, a family history of at least another first- or second-degree relative diagnosed with RC, or histological or extrarenal features associated with hereditary RC syndromes. An expanding list of genes, which include *VHL*, *ELOC*, *TSC1/2*, *MET*, *FLCN*, PRDM10, *SDHA/B/C/D*, *MiTF*, *CDC73*, *FH*, *PTEN*, *BAP1*, *SMARCB1, CHEK2*, *MUTYH*, *BRCA2*, *ATM*, and *APC,* is linked to RC oncogenesis, underscoring genetic underpinnings that extend beyond hereditary syndromes. Nonmodifiable risk factors include sex, geography, ethnicity/ancestry, and family history. Modifiable risk factors include obesity, insulin resistance/diabetes, hypertension, chronic kidney disease, smoking, environmental exposure, and lack of physical exercise. Epidemiological insights are strategic tools for patients, clinicians, and policymakers, as these may hold the key to early detection, aid selective genetic testing, and guide risk-adapted prevention and screening strategies for RC.

***Author contributions*:** Alessandro Larcher had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Larcher, Campi, Kutikov.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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Supplementary data

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