available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Kidney Cancer – Editor's Choice

Editorial by Zachary Klaassen, Rashid K. Sayyid and Christopher J.D. Wallis on pp. 85–87 of this issue

Epidemiology of Renal Cell Carcinoma

Umberto Capitanio[a,b,*], *Karim Bensalah*[c], *Axel Bex*[d], *Stephen A. Boorjian*[e], *Freddie Bray*[f], *Jonathan Coleman*[g], *John L. Gore*[h], *Maxine Sun*[i,j], *Christopher Wood*[k], *Paul Russo*[l]

[a] *Department of Urology, San Raffaele Scientific Institute, Milan, Italy;* [b] *Division of Experimental Oncology/Unit of Urology, URI, IRCCS San Raffaele Hospital, Milan, Italy;* [c] *Department of Urology, University of Rennes, Rennes, France;* [d] *Department of Urology, The Netherlands Cancer Institute, Postbus, Amsterdam, The Netherlands;* [e] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [f] *Cancer Surveillance Section, International Agency for Research on Cancer, Lyon Cedex, France;* [g] *Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [h] *Department of Urology, University of Washington, Seattle Cancer Care Alliance, Seattle, WA, USA;* [i] *Lank Center for Genitourinary Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [j] *Department of Urology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [k] *M D Anderson Cancer Center, Houston, TX, USA;* [l] *Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Article info

Article history:
Accepted August 28, 2018

Associate Editor:
Giacomo Novara

Keywords:
Kidney cancer
Renal cancer
Epidemiology
Incidence
Prevalence
Mortality

EU ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Context: Despite the improvement in renal cell carcinoma (RCC) diagnosis and management observed during the last 2 decades, RCC remains one of the most lethal urological malignancies. With the expansion of routine imaging for many disorders, an increasing number of patients who harbour RCC are identified incidentally.
Objective: To summarise and compare RCC incidence and mortality rates, analyse the magnitude of risk factors, and interpret these epidemiological observations in the context of screening and disease management.
Evidence acquisition: The primary objective of the current review was to retrieve and describe worldwide RCC incidence/mortality rates. Secondly, a narrative literature review about the magnitude of the known risk factors was performed. Finally, data retrieved from the first two steps were elaborated to define the clinical implications for RCC screening.
Evidence synthesis: RCC incidence and mortality significantly differ among individual countries and world regions. Potential RCC risk factors include behavioural and environmental factors, comorbidities, and analgesics. Smoking, obesity, hypertension, and chronic kidney disease represent established risk factors. Other factors have been associated with an increased RCC risk, although selection biases may be present and controversial results have been reported.
Conclusions: Incidence of RCC varies worldwide. Within the several RCC risk factors identified, smoking, obesity, and hypertension are most strongly associated with RCC. In individuals at a higher risk of RCC, the cost effectiveness of a screening programme needs to be assessed on a country-specific level due to geographic heterogeneity in incidence and mortality rates, costs, and management implications. Owing to the low rates of RCC, implementation of accurate biomarkers appears to be mandatory.
Patient summary: The probability of harbouring kidney cancer is higher in developed countries and among smokers, obese individuals, and individuals with hypertension.

* Corresponding author. Department of Urology, San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy. Tel.: +39-02-2643-7286; Fax: +39-02-2643-7298.
E-mail address: umbertocapitanio@gmail.com (U. Capitanio).

https://doi.org/10.1016/j.eururo.2018.08.036
0302-2838/

Check for updates

1. Introduction

Worldwide, renal cell carcinoma (RCC) represents the sixth most frequently diagnosed cancer in men and the 10th in women, accounting for 5% and 3% of all oncological diagnoses, respectively [1]. RCC incidence rates have been increasing, and in higher-income settings, this may partially be due to an increase in the incidental detection of renal masses when abdominal imaging is performed for nonspecific musculoskeletal or gastrointestinal complaints. Although most detected lesions are small tumours, locally advanced disease continues to be diagnosed in a notable proportion of patients, with up to 17% of patients harbouring distant metastases at the time of diagnosis [2].

In Europe and North America, the lifetime risk for developing RCC ranges between 1.3% and 1.8%. According to the most updated data provided by the World Health Organization, there are more than 140 000 RCC-related deaths yearly, with RCC ranking as the 13th most common cause of cancer death worldwide [3].

The aim of this review is to summarise and compare the available evidence on RCC incidence and mortality rates, identify the most strongly associated risk factors, and interpret these epidemiological observations in the context of screening and disease management.

2. Evidence acquisition

The primary objective of the current review was to retrieve and describe worldwide RCC incidence/mortality rates. Secondly, a nonsystematic narrative literature review about the magnitude of the known risk factors was performed. Finally, data retrieved from the first two steps were elaborated to define the clinical implications for RCC screening.

The evidence acquired is presented and discussed according to three constructs.

2.1. Epidemiology

Descriptive analyses of worldwide RCC incidence and mortality rates were retrieved from the most recent version of GLOBOCAN database [3]. Geographic and temporal patterns were examined using age-standardised rates (ASRs) adjusted to the world standard population and expressed per 100 000 alongside cumulative risk—the probability of developing or dying from the disease in a lifetime (defined as over the age range 0–74 yr), in the absence of competing causes of death (see the Supplementary material) [3]. An alphanumeric scoring system describing the availability of incidence and mortality data has been established at the country level and is presented together with the estimates for each country, with the aim of providing a broad indication of the robustness of the estimation (see the Supplementary material) [3]. Acknowledged limitations of the epidemiological sources and a glossary of all terms used throughout the review are available in the Supplementary material.

2.2. Risk factors

RCC risk factors were derived from English-language original articles, previous systematic/narrative reviews, and meta-analyses published during the last 10 yr (January 2008–January 2018). Genetic and hereditary RCC cases were not the objective of the current review, and only sporadic RCC was considered and discussed.

Between January 2008 and January 2018, a literature Search of the following electronic resources was conducted: Medline (via PubMed) and Scopus. The search strategy included the following search terms: “Kidney Neoplasms” OR “Carcinoma Renal Cell” OR Kidney Neoplasm* OR Renal Neoplasm* OR Renal cell neoplasm* OR Kidney Cancer* OR Renal Cancer* OR Renal Cell Cancer* OR kidney tumor* OR renal tumor* OR renal cell tumor*; and “epidemiology” OR “incidence” OR “prevalence” OR “risk factor”. Only papers reporting duplication, case reports, comments, editorials, and congress abstracts were excluded. Additional relevant articles were selected from manuscript bibliographies. Given the descriptive, retrospective, noncomparative design of the studies identified, evidence synthesis was performed in a descriptive and narrative manner.

2.3. Clinical implications

Finally, data retrieved from the first two steps were elaborated to describe potential clinical implications of these epidemiological findings for RCC screening.

3. Evidence synthesis

3.1. Epidemiology of kidney cancer: demographic factors

The all-age incidence ASRs of RCC for both sexes is 4.4 per 100 000, with a cumulative risk (ages 0–74) of 0.51%. Incidence (Fig. 1), prevalence (Fig. 2) and mortality (Fig. 3) rates significantly vary worldwide, with Figure 4 depicting the cumulative risk of RCC incidence and mortality stratified according to world region and sex. Worldwide, North America had the highest ASR (11.7 per 100 000) followed by Western Europe (9.8) and Australia/New Zealand (9.2).

3.1.1. Europe

Incidence rates in both sexes were highest in Western Europe (9.8) but virtually equivalent in all the other European regions (Central and Eastern Europe: 8.7, Northern Europe: 8.3, and Southern Europe) [3]. Table 1 depicts the incidence and cumulative risk of RCC stratified for each country. In terms of survival, the highest estimated mortality rates were observed in Lithuania (4.9), Czech Republic (4.8), Latvia (4.7), and Estonia (4.6), with a cumulative risk of RCC mortality varying from 0.55% to 0.66% [4]. In 2015, 12 547 new cases of RCC were registered in UK, with an incidence ASR of 20.8 (95% confidence interval [CI] 20.5–21.2). Over the last decade in the UK, RCC incidence rates increased by 47% [5]. In terms of mortality, differences across the countries were recorded: although

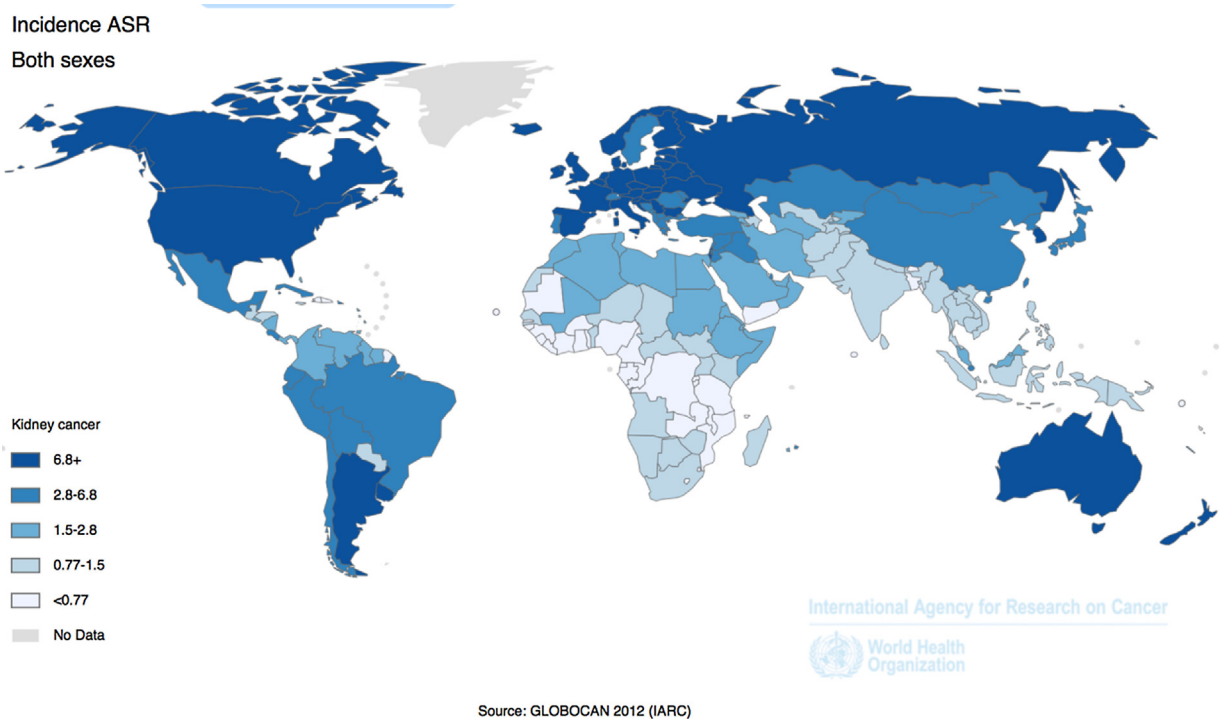

Fig. 1 – World incidence ASRs for both sexes. Numbers are expressed per 100 000 people. Reproduced with permission from the International Agency for Research on Cancer [3]. ASR = age-standardised rate.

mortality rates have declined in Scandinavian countries, France, Germany, Austria, the Netherlands, and Italy, in some European countries (ie, Ireland, Croatia, Greece, Estonia, and Slovakia), mortality rates are rising [6].

3.1.2. *North and South America*

Table 2 depicts the incidence and cumulative risk of RCC stratified for the USA and Canada. North America has the highest worldwide estimated incidence (ASR 12 per

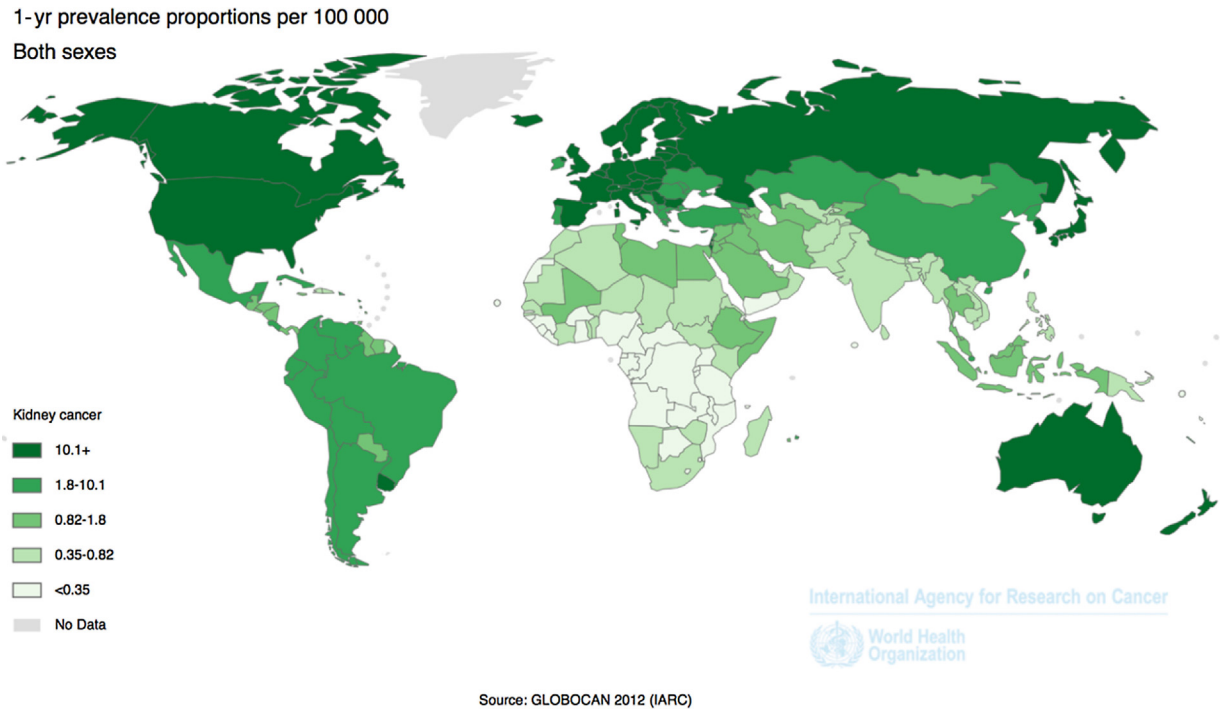

Fig. 2 – World prevalence proportions for both sexes. Numbers are expressed per 100 000 people. Reproduced with permission from the International Agency for Research on Cancer [3].

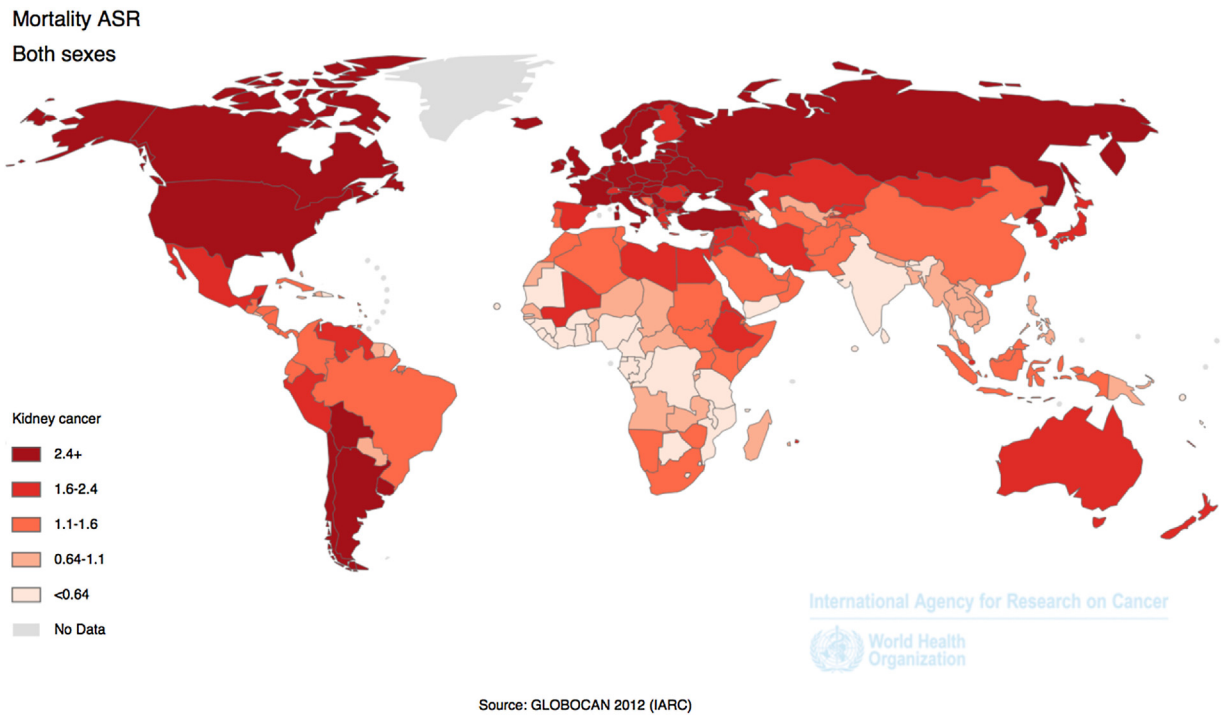

Fig. 3 – World mortality ASRs for both sexes. Numbers are expressed per 100 000 people. Reproduced with permission from the International Agency for Research on Cancer [3]. ASR = age-standardised rate.

100 000), with cumulative risks of 1.8% and 0.9% for males and females, respectively (Fig. 1). South and Central America have significantly lower RCC incidence (0.6% and 0.5%, respectively, for males and 0.3% for females). In specific countries (ie, Uruguay and Argentina), ASRs and cumulative risk were slightly lower compared with North American ASRs (Table 2).

The highest estimated mortality rates were seen in Uruguay (4.4 per 100 000), Argentina (3.6), Chile (3.1), and the USA (2.6), with a cumulative risk of mortality ranging from 0.3% to 0.52%. Data from the US demonstrate an increasing incidence [7]. Specifically, US incidence rate increased from 10.6/100 000 individuals in 2001 to 12.4/100 000 individuals in 2010 and increased with age.

3.1.3. *Asia*

Table 3 depicts the incidence and cumulative risk of RCC stratified for each Asian country. Cumulative risks of incidence were 0.6% and 0.3%, respectively, for males and females in both western and eastern Asia. Israel has the highest estimated incidence in Asia (ASR 10.0 per 100 000), with an overall cumulative risk of 1.2%. The highest estimated mortality rates were observed in Turkey (4.7), the State of Palestine (3.4), the Democratic Republic of Korea (3.4), and Singapore (3.3), with a cumulative risk of mortality between 0.36% and 0.54% per year of age.

3.1.4. *Africa*

Table 4 depicts the incidence and cumulative risk of RCC stratified for each African country. Overall, Africa has the lowest cumulative risk of incidence and mortality, below 0.2% for both sexes. Mauritius has the highest estimated incidence in Africa (4.2), with a cumulative risk of 0.37%. All other African countries showed significantly lower ASRs. The highest estimated mortality rates were seen in Egypt (2.4), Libya (2.3), Mali (1.8), and Tunisia (1.7), with a cumulative mortality risk between 0.17% and 0.27%.

3.1.5. *Oceania*

Table 5 depicts the incidence and cumulative risk of RCC stratified by country. Cumulative risks of incidence were 1.4% and 0.7% for males and females, respectively. Australia and New Zealand observed the highest estimated incidence (ASR 9.5 and 8.2 per 100 000, respectively), with an overall cumulative risk of 1%. The highest estimated mortality rates were observed in Australia (3.5 per 100 000) and New Zealand (3.0), with a cumulative risk of mortality between 0.31% and 0.41%.

3.2. *Risk factors*

Age and gender are strongly related with the risk of RCC: the estimated incidence increases in the older population. Indeed, the ASR per 10 000 is 0.5 below the age of 40 yr and progressively increases to 35.0 over 75 yr of age (40–44 yr: 2.9, 45–49 yr: 5.3, 50–54 yr: 8.8, 56–59 yr: 13.0, 60–64 yr: 17.9, 65–69 yr: 22.6, 70–74 yr: 26.9). Peak incidence is between 60 and 70 yr. In the UK in 2013–2015, more than a third (36%) of new cases occurred in people aged $\geq$75 yr. Incidence ASRs rise steadily from around age 40 to 44 yr and

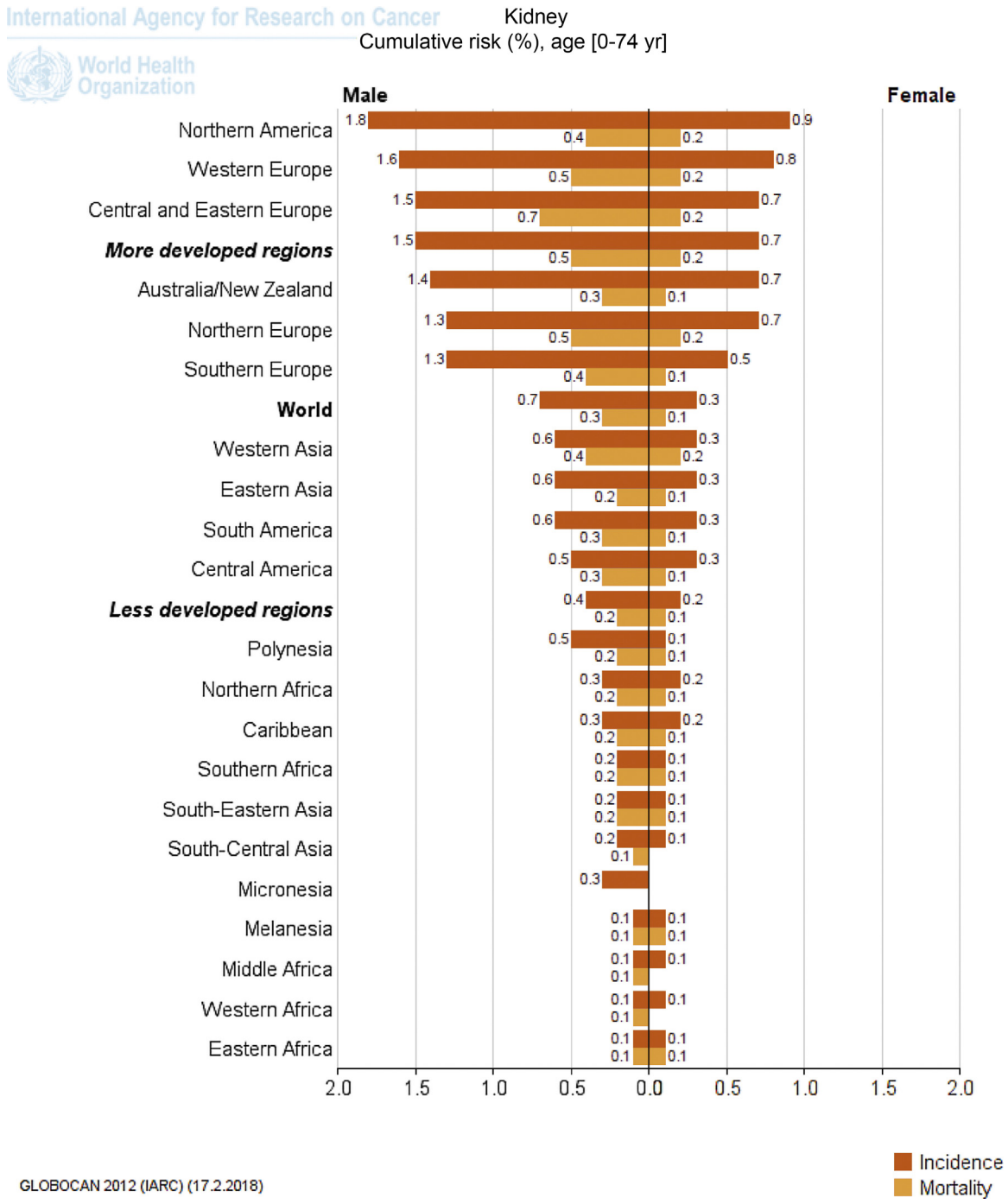

Fig. 4 – Cumulative risk of incidence and mortality of kidney cancer stratified for gender and world regions. Numbers are expressed per 100 000 people. Reproduced with permission from the International Agency for Research on Cancer [3].

more steeply from around age 65–69 yr [5]. The highest rates are in those over 85 yr old. There is a 1.5:1 male predominance, and incidence rates are significantly higher in males than in females across all age groups. The gap is widest in older patients [5].

The evaluation of RCC risk factors is biased by the fact that incidental cancer detection by ultrasounds and computed tomography (CT)/magnetic resonance imaging performed for other reasons might artificially have increased the association between RCC and specific cofactors [2]. Potential risk factors include lifestyle factors, comorbidities, drugs, and environmental causes.

3.2.1. *Lifestyle factors*

3.2.1.1. Body mass index. Obesity is commonly linked to several cancers, including RCC [8]. Translational studies demonstrated that RCC could be induced using prolonged intake of a high-fat diet, which are confirmed with pathological

Table 1 – Incidence and cumulative risk of kidney cancer in Europe

Population	Quality[a]	Numbers	Crude rate	ASR (W)	Cumulative risk
Czech Republic	A2	3313	31.4	16.7	2.01
Lithuania	A1	773	23.5	13.2	1.61
Slovakia	A1	1063	19.4	12.5	1.49
Estonia	A1	284	21.2	11.7	1.39
Belarus	A2	1575	16.5	11.1	1.29
Slovenia	A1	400	19.6	11.1	1.27
Latvia	A1	449	20.1	10.9	1.31
Germany	B2	18 615	22.7	10.6	1.27
Croatia	A2	821	18.7	10.0	1.16
France (metropolitan)	B2	11 023	17.4	9.7	1.14
Norway	A2	798	16.1	9.3	1.08
Hungary	G1	1554	15.6	9.1	1.03
Russian Federation	D2	19 313	13.5	8.9	1.05
Iceland	A1	45	13.7	8.8	1.17
The Netherlands	A2	2679	16.0	8.8	1.04
Italy	B2	11 300	18.5	8.7	1.01
Belgium	A2	1763	16.3	8.7	1.03
Ireland	A1	571	12.5	8.4	0.99
Luxembourg	D2	70	13.4	8.3	1.00
UK	A1	9714	15.5	8.2	0.93
Poland	C3	5244	13.7	8.1	0.95
Malta	A1	57	13.6	8.0	0.91
Austria	A2	1322	15.7	8.0	0.95
Finland	A1	882	16.3	7.9	0.90
Spain	B2	6474	13.8	7.9	0.89
Ukraine	A2	5240	11.7	7.5	0.87
Serbia	B2	1127	11.4	7.4	0.85
Denmark	A2	754	13.5	7.2	0.87
Bulgaria	A2	881	11.9	6.9	0.80
Montenegro	G6	59	9.3	6.6	0.75
Switzerland	B2	948	12.3	6.5	0.74
Sweden	A2	1125	11.8	6.4	0.75
Albania	G3	228	7.1	5.8	0.71
Romania	E1	1940	9.1	5.7	0.66
Bosnia Herzegovina	D5	292	7.8	5.2	0.57
Portugal	C3	1004	9.4	5.0	0.57
Republic of Moldova	G1	230	6.5	4.6	0.55
Greece	G3	1094	9.6	4.5	0.48
FYR Macedonia	G3	104	5.0	3.6	0.41
Cyprus	A3	46	4.1	3.0	0.35

ASR = age-standardised rate.
Data are sorted by ASRs. Numbers are expressed per 100 000 people.
Reproduced with permission from the International Agency for Research on Cancer [3].
[a] For Quality legend, please refer to the Supplementary material (Level of availability of incidence and mortality data).

Table 2 – Incidence and cumulative risk of kidney cancer in America

Population	Quality[a]	Numbers	Crude rate	ASR (W)	Cumulative risk
USA	A1	58 222	18.4	12.0	1.39
Uruguay	A2	465	13.7	9.4	1.12
Canada	A1	5579	16.1	9.3	1.06
Argentina	B3	4068	9.9	8.0	0.93
Chile	C2	1353	7.8	6.0	0.72
Puerto Rico	A2	272	7.3	4.9	0.56
Costa Rica	A2	179	3.7	3.7	0.42
Peru	E3	953	3.2	3.6	0.42
Mexico	E1	3851	3.3	3.5	0.40
Bolivia	G6	263	2.6	3.5	0.41
Belize	G2	8	2.5	3.2	0.27
Cuba	C1	517	4.6	3.1	0.34
Brazil	B2	6255	3.2	3.0	0.33
Ecuador	C3	403	2.7	2.9	0.31
Venezuela	G1	747	2.5	2.7	0.30
Colombia	C2	1048	2.2	2.4	0.26
Trinidad and Tobago	D2	32	2.4	2.3	0.23
Guyana	G2	14	1.8	2.2	0.21
France, Guadeloupe	G2	14	3.0	2.1	0.31
Panama	G2	68	1.9	2.0	0.26
Barbados	G2	8	2.9	1.9	0.20
Bahamas	G1	7	2.0	1.8	0.24
Suriname	G3	9	1.7	1.6	0.19
El Salvador	G2	93	1.5	1.5	0.17
Nicaragua	G3	63	1.1	1.5	0.16
Guatemala	G2	150	1.0	1.5	0.17
Honduras	G6	80	1.0	1.5	0.16
Paraguay	G3	78	1.2	1.5	0.16
France, Martinique	A2	11	2.7	1.4	0.15
Jamaica	C3	31	1.1	1.1	0.10
French Guiana	G2	2	0.8	0.7	0.06
Haiti	G3	58	0.6	0.7	0.08
Dominican Republic	G3	52	0.5	0.6	0.06

ASR = age-standardised rate.
Data are sorted by ASRs. Numbers are expressed per 100 000 people.
Reproduced with permission from the International Agency for Research on Cancer [3].
[a] For Quality legend, please refer to the Supplementary material (Level of availability of incidence and mortality data).

changes observed through histological sectioning [9]. Macleod et al. [10] relied on a prospective cohort of 77 260 residents of Washington, aged 50–76 yr, who completed a questionnaire on demographic, lifestyle, and health data to validate established and putative risk factors for incident RCC [10]. The study confirmed that obesity is significantly associated with RCC (body mass index $\geq$35 vs $<$25 kg/m^2: hazard ratio [HR] 1.71, 95% CI 1.06–2.79) [10]. The relative risk estimate corresponding to roughly 5 kg of body weight increases the risk of RCC by 25% in men and 35% in women [10–12]. The association between obesity and increased risk of RCC was confirmed in both the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the National Lung Screening Trial [13]. The biological mechanisms behind this association are unclear, although recent evidence suggests that the effects of circulating hormones such as insulin-like growth factors and adipokines might play a role [11]. Other possible biological mechanisms involved are sex steroids and chronic inflammation [12]. The use of statins among patients with RCC is associated with significantly improved cancer-specific and overall survival [14,15]. However, a recent meta-analysis demonstrated no association between the use of statins and risk of harbouring RCC [14].

3.2.1.2. Physical activity. Physical activity may decrease RCC risk by reducing obesity, blood pressure, insulin resistance, and lipid peroxidation. A recent meta-analysis reported an inverse association between physical activity and RCC risk (relative risk [RR] 0.88, 95% CI 0.79–0.97) [15]. Combining risk estimates from high-quality studies, this association was even stronger (RR 0.78, 95% CI 0.66–0.92) [15].

3.2.1.3. Fruit or vegetable intake. Fruit and vegetable consumption (in particular, cruciferous vegetables) has been associated with a reduction in the risk of RCC in some reports [16,17]. However, in the European Prospective

Table 3 – Incidence and cumulative risk of kidney cancer in Asia

Population	Quality[a]	Numbers	Crude rate	ASR (W)	Cumulative risk
Israel	A2	1002	13.0	10.0	1.17
Korea, Republic of	A2	5651	11.6	8.0	0.91
Turkey	C6	3992	5.4	5.6	0.62
Japan	B1	16 830	13.3	5.3	0.59
Singapore	A1	401	7.6	5.2	0.61
Korea, Democratic Republic of	G6	1318	5.4	4.3	0.53
China	C4	66 466	4.9	3.8	0.43
Qatar	A3	33	1.7	3.5	0.45
Jordan	D5	129	2.0	3.2	0.37
Lebanon	D6	142	3.3	3.2	0.35
Mongolia	D5	66	2.3	3.1	0.38
Syrian Arab Republic	G6	467	2.2	3.1	0.34
State of Palestine	F6	71	1.7	3.1	0.36
Kazakhstan	G2	491	3.0	2.9	0.33
Iraq	F6	581	1.7	2.9	0.32
Georgia	G2	167	3.9	2.7	0.29
Bahrain	A3	23	1.7	2.6	0.25
Iran, Islamic Republic of	C6	1641	2.2	2.6	0.28
Malaysia	C2	611	2.1	2.4	0.28
Saudi Arabia	D6	454	1.6	2.3	0.26
United Arab Emirates	D6	64	0.8	2.3	0.29
Kyrgyzstan	G2	91	1.7	2.2	0.26
Kuwait	A2	34	1.2	2.2	0.26
Timor-Leste	G6	14	1.2	2.1	0.26
Oman	A3	36	1.2	2.1	0.25
Armenia	G3	78	2.5	1.9	0.22
Turkmenistan	G2	75	1.5	1.8	0.21
Brunei	F5	6	1.5	1.8	0.16
Indonesia	F6	3225	1.3	1.5	0.17
Philippines	B2	1008	1.0	1.4	0.16
Tajikistan	G3	63	0.9	1.4	0.16
Afghanistan	G6	237	0.7	1.3	0.16
Azerbaijan	G2	135	1.4	1.3	0.15
Pakistan	E6	1646	0.9	1.3	0.14
Uzbekistan	G2	283	1.0	1.2	0.14
Thailand	B3	1017	1.5	1.2	0.13
Myanmar	G6	476	1.0	1.1	0.12
Lao PDR	G6	52	0.8	1.1	0.12
Nepal	G6	218	0.7	1.0	0.12
India	C5	9658	0.8	0.9	0.11
Cambodia	G6	101	0.7	0.9	0.10
Viet Nam	E4	810	0.9	0.9	0.09
Sri Lanka	D6	221	1.0	0.9	0.09
Bangladesh	F6	900	0.6	0.8	0.08
Yemen	E6	112	0.4	0.6	0.07
Bhutan	D6	3	0.4	0.6	0.06

ASR = age-standardised rate.
Data are sorted by ASRs. Numbers are expressed per 100 000 people.
Reproduced with permission from the International Agency for Research on Cancer [3].
[a] For Quality legend, please refer to the Supplementary material (Level of availability of incidence and mortality data).

Table 4 – Incidence and cumulative risk of kidney cancer in Africa

Population	Quality[a]	Numbers	Crude rate	ASR (W)	Cumulative risk
Mauritius	D2	53	4.0	4.2	0.37
Libya	C6	133	2.1	2.7	0.30
Egypt	C3	1740	2.1	2.4	0.26
Tunisia	C6	237	2.2	2.2	0.25
France, La Reunion	D2	21	2.4	2.1	0.19
Ethiopia	E6	1412	1.6	2.1	0.20
Mali	E6	307	1.9	1.9	0.15
Eritrea	G6	77	1.4	1.9	0.18
Somalia	G6	131	1.3	1.8	0.17
Algeria	C6	454	1.2	1.5	0.16
Sudan	F6	462	1.2	1.5	0.15
Morocco	E6	451	1.4	1.5	0.15
Djibouti	G6	11	1.2	1.5	0.14
South Sudan	G6	117	1.1	1.4	0.13
Kenya	E6	380	0.9	1.4	0.15
Zimbabwe	C6	137	1.1	1.3	0.11
Uganda	C6	305	0.9	1.2	0.09
Namibia	D6	19	0.8	1.2	0.14
South African Republic	D3	506	1.0	1.2	0.13
Senegal	G6	134	1.0	1.1	0.09
Niger	E6	92	0.6	1.0	0.12
Benin	F6	77	0.8	1.0	0.09
Chad	G6	89	0.8	0.9	0.09
Western Sahara	G6	5	0.9	0.9	0.06
Angola	G6	109	0.5	0.8	0.08
Central African Republic	G6	34	0.7	0.8	0.07
Madagascar	G6	139	0.6	0.8	0.07
Botswana	D6	12	0.6	0.8	0.10
Gabon	F6	12	0.8	0.8	0.05
Zambia	E6	80	0.6	0.7	0.07
Burundi	G6	44	0.5	0.7	0.05
Rwanda	F6	60	0.5	0.7	0.05
Malawi	C6	132	0.8	0.7	0.04
Ghana	F6	173	0.7	0.7	0.05
Mauritania	G6	23	0.6	0.7	0.05
Cote d'Ivoire	F6	127	0.6	0.7	0.06
Nigeria	E6	936	0.6	0.6	0.05
Togo	F6	36	0.6	0.6	0.06
Congo, Democratic Republic of	G6	337	0.5	0.6	0.04
Cameroon	E6	116	0.6	0.5	0.04
Burkina Faso	F6	70	0.4	0.5	0.05
Congo, Republic of	E6	21	0.5	0.5	0.03
Sierra Leone	G6	24	0.4	0.4	0.04
Lesotho	G6	6	0.3	0.4	0.03
Liberia	G6	14	0.3	0.3	0.03
Equatorial Guinea	G6	3	0.4	0.3	0.02
Guinea	E6	27	0.3	0.3	0.03
Guinea-Bissau	G6	5	0.3	0.3	0.02
Tanzania	E6	106	0.2	0.2	0.01
Swaziland	D6	2	0.2	0.2	0.02
Mozambique	E6	34	0.1	0.1	0.00
Comoros	G6	1	0.1	0.1	0.00
The Gambia	D6	0	0.0	0.0	0.00
Cape Verde	G6	0	0.0	0.0	0.00

ASR = age-standardised rate.
Data are sorted by ASRs. Numbers are expressed per 100 000 people.
Reproduced with permission from the International Agency for Research on Cancer [3].
[a] For Quality legend, please refer to the Supplementary material (Level of availability of incidence and mortality data).

Investigation into Cancer and Nutrition (EPIC) study, Weikert et al. [18] examined the association between fruits and vegetables and the risk of RCC. Dietary intake data and complete follow-up information on cancer incidence were available for 375 851 participants. During an average follow-up of 6 yr, 306 RCC cases were identified (0.1%). No significant associations between fruit and vegetable consumption and RCC risk were observed despite a wide range of intake (HR 0.97, 95% CI 0.85–1.11) [18]. Similarly, in the Vitamin and Lifestyle (VITAL) study, no association between fruit or vegetable intake and RCC was recorded [10]. When pooling the data from all available studies, a significantly decreased risk of RCC was observed in those eating cruciferous vegetables (RR 0.73, 95% CI 0.63–0.83) and in a subgroup of case-control studies (RR 0.69, 95% CI

Table 5 – Incidence and cumulative risk of kidney cancer in Australia

Population	Quality[a]	Numbers	Crude rate	ASR (W)	Cumulative risk
Australia	A1	3501	15.3	9.5	1.08
New Zealand	A1	586	13.1	8.2	0.97
New Caledonia	D5	15	5.8	4.9	0.57
French Polynesia	D5	12	4.3	4.3	0.53
Guam	D6	4	2.2	1.8	0.11
Papua New Guinea	G6	37	0.5	0.8	0.08
Fiji	D3	4	0.5	0.4	0.04
Samoa	D6	0	0.0	0.0	0.00
Solomon Islands	G6	0	0.0	0.0	0.00
Vanuatu	D6	0	0.0	0.0	0.00

ASR = age-standardised rate.
Data are sorted by ASRs. Numbers are expressed per 100 000 people.
Reproduced with permission from the International Agency for Research on Cancer [3].
[a] For Quality legend, please refer to the Supplementary material (Level of availability of incidence and mortality data).

0.60-0.78), but not in cohort studies (RR 0.96, 95% CI 0.71–1.21) [17].

3.2.1.4. Alcohol. Moderate alcohol intake showed a protective effect on RCC incidence relative to abstinence [19,20]. Lew et al. [20] analysed the participants included in the NIH-AARP Diet and Health Study (n = 492 187 and 1814 RCC cases), and found an inverse association between alcohol intake and the risk of RCC. When the association was examined after excluding RCC cases diagnosed within the first 2 yr of follow-up, the results did not change appreciably. In male patients, the inverse effect was observed with beer consumption; in women, the inverse effect was observed with wine and liquor consumption, but not beer. The multivariate RR for an increment of one drink per day of alcohol drinks among drinkers was 0.96 (95% CI 0.94–0.99) in men and 0.73 (95% CI 0.60–0.88) in women [20]. Similarly, Pelucchi et al. [21] evaluated data from two Italian multicentre case-control studies, including 1115 incidental, histologically confirmed RCC cases and 2582 controls hospitalised with acute, non-neoplastic conditions. Compared with nondrinkers, the multivariate odds ratios of RCC were 0.87 (95% CI 0.73–1.04) for four or fewer drinks per day, 0.76 (95% CI 0.59–0.99) for more than four to eight or fewer drinks per day, and 0.70 (95% CI 0.50–0.97) for more than eight alcoholic drinks per day, with a significant inverse trend in risk (p = 0.01) [21]. Within the PLCO Trial, increasing alcohol consumption was associated with a reduced RCC risk compared with nondrinkers (>9.75 g/d: HR 0.67, 95% CI 0.50–0.89) [22]. Conversely, in the VITAL study, no association between alcohol intake and RCC was recorded [10]. A recent meta-analysis confirmed that alcohol intake from wine, beer, and liquor is associated with a reduced risk of RCC [23]. However, when these associations were examined separately by sex, statistically significant inverse associations were restricted to wine among females (RR 0.82, 95% CI 0.73–0.91) and to beer and liquor among males (RR 0.87, 95% CI 0.83–0.91 and RR 0.95, 95% CI 0.92–0.99, respectively) [23].

3.2.1.5. Smoking. Smoking has been linked to a number of common cancers, including RCC. Tobacco smoke includes a mix of carcinogens implicated in the aetiology of renal cell cancer. In the VITAL study, smoking was independently associated with RCC (>37.5 pack-years vs never: HR 1.58, 95% CI 1.09–2.29) [10]. Similarly, in the PLCO trial, the intensity of smoking was confirmed to be significantly associated with a higher risk of developing RCC and with a higher risk of high-grade RCC [13]. Moreover, relative risk is directly associated with smoking duration and decreases over time after cessation. A recent meta-analysis of >24 papers demonstrated a pooled RR of RCC incidence of 1.31 (1.22–1.40) for all smokers, 1.36 (1.19–1.56) for current smokers, and 1.16 (1.08–1.25) for former smokers. The corresponding RCC cancer-specific mortality risks were 1.23 (1.08–1.40), 1.37 (1.19–1.59), and 1.02 (0.90–1.15) [24].

3.2.2. Comorbidities

3.2.2.1. Hypertension. There is evidence that hypertension is an independent risk factor for RCC [10,25,26]. A number of prospective studies investigated the association between blood pressure and the risk of RCC, using either recorded BP levels or reported hypertension as the principal exposure variable [10,27]. In the VITAL study, hypertension was independently associated with RCC risk (HR 1.70, 95% CI 1.30–2.22) [10]. A recent meta-analysis of 18 prospective studies further supports a positive association between hypertension and RCC risk. A history of hypertension was associated with 67% increased risk of RCC, and each 10-mmHg increase in blood pressure was associated with 10–22% increased risk of RCC, after accounting for heterogeneity and publication bias [27]. The biological mechanisms behind this relationship remain unclear, but some authors have hypothesised the involvement of chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species. Hypertensive individuals may suffer chronic renal hypoxia caused by the transcription of hypoxia-inducible factors that promote tumour cell proliferation and angiogenesis [28,29]. Importantly, hypertensive patients may also be more likely to get cross-sectional renal imaging and therefore identify incidental renal tumours.

3.2.2.2. Urinary stones. A recent meta-analysis evaluated the association between a history of kidney stones and RCC [30]. The pooled RR of RCC in patients with kidney stones was 1.76 (95% CI 1.24–2.49). Subgroup analysis demonstrated that the history of kidney stones was significantly associated with increased RCC risk only in males (RR 1.41, 95% CI 1.11–1.80), but not in females (RR 1.13 [95% CI 0.86–1.49]) [30].

3.2.2.3. Diabetes. Type 2 diabetes is associated with an increased risk of several types of cancer [31,32]. However, its relationship with RCC remains unclear. In the VITAL study, there was no observed relationship between diabetes and RCC after accounting for multiple confounders [10]. Conversely, in the Nurses' Health study [33], relying on 330 cases of pathologically confirmed incident RCC among roughly 120 000 women, type 2 diabetes was significantly associated with an increased risk of RCC (HR

1.60 [95% CI 1.19–2.17]). These associations were consistent across different strata of BMI, smoking, and hypertension. Moreover, RCC risk increased with an increasing number of comorbidities, including obesity, hypertension, and type 2 diabetes. Specifically, women who had all these three conditions had four-fold higher probability of RCC development compared with women without comorbidities [33].

3.2.2.4. Liver and chronic kidney diseases. Cystic degenerative changes (acquired cystic kidney disease) and a higher incidence of RCC are typical features of end-stage kidney disease. RCC of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCC is at least 10 times higher than in the general population [34,35].

In the VITAL study, the presence of a kidney disease (HR 2.58, 95% CI 1.21–5.50) or viral hepatitis (HR 1.80, 95% CI 1.03–3.14) was independently associated with RCC [10]. Hepatitis C virus (HCV) infection causes cirrhosis and hepatocellular carcinoma, but is also aetiologically linked to several extrahepatic medical conditions including renal disorders and malignancies. In RCC patients, the rate of HCAB positivity has been reported to be higher (8%) than that in colon cancer patients (1%; $p < 0.01$), and RCC patients with HCV RNA positivity were significantly younger than RCC patients who were HCV RNA negative ($p = 0.01$) [36].

3.2.3. Reproductive and hormonal factors

An increased risk of RCC has been associated with parity among women in several cohort studies, although the association is not conclusive [37–40]. Associations with other reproductive factors, including the use of oral contraceptives and hormone replacement therapy, are not consistently observed [41].

3.2.4. Analgesics

Analgesics are the most commonly used over-the-counter drugs worldwide, with epidemiological data suggesting that analgesic use increases the risk of RCC. Cho and colleagues [42] examined the relationship between analgesic use and RCC risk in the Nurses' Health Study and the Health Professionals Follow-up Study. Aspirin and acetaminophen use were not associated with RCC risk. However, regular use of nonaspirin nonsteriodal anti-inflammatory drugs (NSAIDs) was associated with an increased risk of RCC (pooled multivariate relative risk 1.51 [95% CI 1.12–2.04)]. A meta-analysis by Choueiri et al. [43] evaluated the association between analgesic use and RCC risk. Study-specific effect estimates were pooled to compute the overall relative risk using a random-effects model for each analgesic category. The use of acetaminophen and nonaspirin NSAIDs was associated with an increased risk of RCC (pooled RR 1.28, 95% CI 1.15–1.44, and 1.25, 95% CI 1.06–1.46, respectively). For aspirin use, no association was found except for non-US studies (five studies, pooled RR 1.17, 95% CI 1.04–1.33). Similar increases in risks were seen with higher analgesic intake [43].

3.2.5. Environmental factors

In terms of occupational exposure, RCC generally is not considered an occupational disease; but elevated risk has been linked to specific occupations and specific industrial agents. Trichloroethylene is by far the most extensively examined chemical in relation to RCC risk [37,38]. Despite the evidence being limited, exposure to x radiation and gamma-radiation industrial agents, including arsenic, inorganic arsenic compounds, cadmium, perfluorooctanoic acid, welding fumes, nitrate, and radon in drinking water, are not regarded as potential RCC risk factors [44–47]. However, more robust studies are needed to confirm these findings.

3.3. Epidemiology in kidney cancer: what are the clinical implications for screening?

Screening is a strategy used to detect disease within an asymptomatic population. The rationale for screening is that the detection of asymptomatic disease might lead to an earlier staged disease (stage migration) [48] and better outcomes from treatment [49,50]. However, the cost effectiveness of a screening programme depends on many other aspects: (1) incidence and prevalence of the disease, (2) sensitivity and specificity of the detection method, (3) impact of an early diagnosis on the natural history of the disease, (4) impact of overtreatment, and (5) healthcare expenditures. The increased use of CT in the past—especially in the USA and Europe—resulted in a simulated form of screening, which led to potential overtreatment [51]. Moreover, exaggerate cross-sectional imaging (as has been suggested for the USA [51]) may introduce "contamination" of screening studies. In other words, introducing cross-sectional imaging theoretically in countries without this opportunity may result in a higher yield of screen-detected tumours than, for example, in the USA where a proportion of the population is being imaged for various reasons anyway.

Focusing on RCC, the highest incidence of RCC reaches 10–15 per 100 000 with an estimated cumulative risk of incident cases of roughly 0.5% per year of age. Important variations exist according to the geographic area. Obesity, hypertension, and smoking independently double the adjusted RR of developing RCC.

Different screening modalities have been analysed in the setting of sporadic RCC. Some authors proposed the use of urine dipstick, but the low diagnostic yield and the low accuracy in detecting RCC preclude any role for this option [52]. Several serum and urine biomarkers have been suggested (eg, aquaporin 1, perilipin 2, KIM1, and others [53]), although none have achieved clinical importance. Screening computed tomography was demonstrated to be non–cost effective, with a high proportion of false-positive cases. Conversely, abdominal ultrasound arises as a potential tool due to its characteristics (noninvasive, well-established, and widely utilised), although no robust data are available to determine whether ultrasound-based screening may be able to affect the natural history of the diseases due to high intervariability and low sensitivity for the detection of small renal masses. Finally, several authors have proposed targeted screening programmes for RCC in patients at a higher risk according to their clinical characteristics and comorbidities [52].

Assessing the epidemiological and risk factor data in the setting of RCC, some considerations regarding the role of screening are worth mentioning. Firstly, the cost effectiveness of a screening programme needs to be assessed on a country-specific level since key differences in RCC incidence, risk factor prevalence, and healthcare context exist among the different countries. Secondly, if risk factors are not present, RCC incidence is very low and–unless new biomarkers will become available—a screening programme relying on the available imaging technology is difficult to be cost effective. Thirdly, given the RCC incidence data we demonstrate, a screening programme would subject participants to a significant risk of overdiagnosis, overtreatment, and emotional impact-related consequences..

4. Conclusions

RCC incidence and mortality rates vary significantly around the globe. Potential risk factors include behavioural and environmental factors, comorbidities, and analgesics. To date, the consistent risk factors for RCC are smoking, obesity, hypertension, and chronic kidney disease. Many other factors have been associated with an increased RCC risk, although these associations may be confounded by selection biases and inconsistent results in the available studies. In individuals at a higher risk of RCC, the cost effectiveness of a screening programme needs to be assessed on a country-specific level. Owing to the low incidence of RCC, there is an unmet need for accurate biomarkers.

Author contributions: Umberto Capitanio 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: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Acquisition of data: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Analysis and interpretation of data: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Drafting of the manuscript: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Critical revision of the manuscript for important intellectual content: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Capitanio, Bensalah, Bex, Boorjian, Bray, Coleman, Gore, Sun, Wood, Russo.
Other: None.

Financial disclosures: Umberto Capitanio certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.08.036.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Capitanio U, Montorsi F. Renal cancer. Lancet 2016;387:894–906.
[3] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr.
[4] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.
[5] http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence-heading-Zero.
[6] Levi F, Ferlay J, Galeone C, et al. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int 2008;101:949–58.
[7] King SC, Pollack LA, Li J, King JB, Master VA. Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. J Urol 2014;191:1665–70.
[8] Bergström A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and renal cell cancer—a quantitative review. Br J Cancer 2001;85:984–90.
[9] Yang X-F, Ma G, Feng N-H, Yu D-S, Wu Y, Li C. Twist2 and CD24 expression alters renal microenvironment in obesity associated kidney cancer. Eur Rev Med Pharmacol Sci 2018;22:358–64.
[10] Macleod LC, Hotaling JM, Wright JL, et al. Risk factors for renal cell carcinoma in the VITAL study. J Urol 2013;190:1657–61.
[11] Liao LM, Hofmann JN, Cho E, Pollak MN, Chow W-H, Purdue MP. Circulating levels of obesity-related markers and risk of renal cell carcinoma in the PLCO cancer screening trial. Cancer Causes Control 2017;28:801–7.
[12] Gild P, Ehdaie B, Kluth LA. Effect of obesity on bladder cancer and renal cell carcinoma incidence and survival. Curr Opin Urol 2017;27:409–14.
[13] Lotan Y, Karam JA, Shariat SF, et al. Renal-cell carcinoma risk estimates based on participants in the prostate, lung, colorectal, and ovarian cancer screening trial and national lung screening trial. Urol Oncol 2016;34, 167.e9–16.
[14] Zhang X-L, Liu M, Qian J, et al. Statin use and risk of kidney cancer: a meta-analysis of observational studies and randomized trials. Br J Clin Pharmacol 2014;77:458–65.
[15] Behrens G, Leitzmann MF. The association between physical activity and renal cancer: systematic review and meta-analysis. Br J Cancer 2013;108:798–811.
[16] Zhao J, Zhao L. Cruciferous vegetables intake is associated with lower risk of renal cell carcinoma: evidence from a meta-analysis of observational studies. PLoS One 2013;8:e75732.
[17] Liu B, Mao Q, Wang X, et al. Cruciferous vegetables consumption and risk of renal cell carcinoma: a meta-analysis. Nutr Cancer 2013;65:668–76.
[18] Weikert S, Boeing H, Pischon T, et al. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 2006;118:3133–9.
[19] Jay R, Brennan P, Brenner DR, et al. Alcohol consumption and the risk of renal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). Wozniak MB, Brennan P, Brenner DR,

Overvad K, Olsen A, Tjønneland A, Boutron-Ruault MC, Clavel-Chapelon F, Fagherazzi G, Katzke V, Kühn T, Boeing H, Bergmann MM, Steffen A, Naska A, Trichopoulou A, Trichopoulos D, Saieva C, Grioni S, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Hjartåker A, Weiderpass E, Arriola L, Molina-Montes E, Duell EJ, Santiuste C, Alonso de la Torre R, Barricarte Gurrea A, Stocks T, Johansson M, Ljungberg B, Wareham N, Khaw KT, Travis RC, Cross AJ, Murphy N, Riboli E, Scelo G. Int J Cancer. 2015 Oct 15;137 (8):1953-66. [Epub 2015 Apr 28]. d oi: 10.1 002/ijc.29559. Urol Oncol 2017;35(3):117.

[20] Lew JQ, Chow W-H, Hollenbeck AR, Schatzkin A, Park Y. Alcohol consumption and risk of renal cell cancer: the NIH-AARP diet and health study. Br J Cancer 2011;104:537–41. http://dx.doi.org/10.1038/sj.bjc.6606089.

[21] Pelucchi C, Galeone C, Montella M, et al. Alcohol consumption and renal cell cancer risk in two Italian case-control studies. Ann Oncol 2008;19:1003–8.

[22] Karami S, Daugherty SE, Purdue MP. A prospective study of alcohol consumption and renal cell carcinoma risk. Int J Cancer 2015;137:238–42.

[23] Xu X, Zhu Y, Zheng X, Xie L. Does beer, wine or liquor consumption correlate with the risk of renal cell carcinoma? A dose-response meta-analysis of prospective cohort studies. Oncotarget 2015;6:13347–58.

[24] Cumberbatch MG, Rota M, Catto JWF, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol 2016;70:458–66.

[25] Chien C-C, Han M-M, Chiu Y-H, et al. Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. J Cancer 2017;8:9–18.

[26] Mazzucotelli V, Piselli P, Verdirosi D, et al. De novo cancer in patients on dialysis and after renal transplantation: north-western Italy, 1997–2012. J Nephrol 2017;30:851–7.

[27] Hidayat K, Du X, Zou S-Y, Shi B-M. Blood pressure and kidney cancer risk. J Hypertens 2017;35:1333–44.

[28] Sharifi N, Farrar WL. Perturbations in hypoxia detection: a shared link between hereditary and sporadic tumor formation? Med Hypotheses 2006;66:732–5. http://dx.doi.org/10.1016/j.mehy.11.2005.003.

[29] Gago-Dominguez M, Castelao JE, Yuan J-M, Ross RK, Yu MC. Lipid peroxidation: a novel and unifying concept of the etiology of renal cell carcinoma (United States). Cancer Causes Control 2002;13:287–93.

[30] Cheungpasitporn W, Thongprayoon C, O'Corragain OA, et al. The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. QJM 2015;108:205–12.

[31] Hendriks SH, Schrijnders D, van Hateren KJ, et al. Association between body mass index and obesity-related cancer risk in men and women with type 2 diabetes in primary care in the Netherlands: a cohort study (ZODIAC-56). BMJ Open 2018;8:e018859.

[32] Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol 2018;6:e6–15.

[33] Joh H-K, Willett WC, Cho E. Type 2 diabetes and the risk of renal cell cancer in women. Diabetes Care 2011;34:1552–6.

[34] Christensson A, Savage C, Sjoberg DD, et al. Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years. Int J Cancer 2013;133:1452–8.

[35] Lowrance WT, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the risk of incident cancer. J Am Soc Nephrol 2014;25:2327–34.

[36] Gonzalez HC, Lamerato L, Rogers CG, Gordon SC. Chronic hepatitis C infection as a risk factor for renal cell carcinoma. Dig Dis Sci 2015;60:1820–4. http://dx.doi.org/10.1007/s10620-015-3521-3.

[37] Lambe M, Lindblad P, Wuu J, Remler R, Hsieh CC. Pregnancy and risk of renal cell cancer: a population-based study in Sweden. Br J Cancer 2002;86:1425–9.

[38] Kabat GC, Silvera SAN, Miller AB, Rohan TE. A cohort study of reproductive and hormonal factors and renal cell cancer risk in women. Br J Cancer 2007;96:845–9.

[39] Molokwu JC, Prizment AE, Folsom AR. Reproductive characteristics and risk of kidney cancer: Iowa Women's Health Study. Maturitas 2007;58:156–63.

[40] Lee JE, Hankinson SE, Cho E. Reproductive factors and risk of renal cell cancer: the Nurses' Health Study. Am J Epidemiol 2009;169:1243–50.

[41] Chow W-H, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010;7:245–57.

[42] Cho E, Curhan G, Hankinson SE, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. Arch Intern Med 2011;171:1487–93.

[43] Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies. Int J Cancer 2014;134:384–96.

[44] Desimone MC, Rathmell WK, Threadgill DW. Pleiotropic effects of the trichloroethylene-associated P81S VHL mutation on metabolism, apoptosis, and ATM-mediated DNA damage response. J Natl Cancer Inst 2013;105:1355–64.

[45] Moore LE, Boffetta P, Karami S, et al. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res 2010;70:6527–36.

[46] Abdul KSM, Jayasinghe SS, Chandana EPS, Jayasumana C, De Silva PMCS. Arsenic and human health effects: a review. Environ Toxicol Pharmacol 2015;40:828–46.

[47] Song JK, Luo H, Yin XH, et al. Association between cadmium exposure and renal cancer risk: a meta-analysis of observational studies. Sci Rep 2015;5:17976.

[48] Di Trapani E, Dell'Oglio P, Larcher A, et al. Pathological high-risk renal cell carcinoma: trends in clinical characteristics over 25 years. Anticancer Res 2018;38:4123–30.

[49] Rouprêt M. Smoking status is not sufficient to accurately target patients who would benefit from screening for bladder and kidney cancer. Eur Urol Focus 2015;1:52–3.

[50] Pinsky PF, Dunn B, Gierada D, et al. Incidental renal tumours on low-dose CT lung cancer screening exams. J Med Screen 2017;24:104–9.

[51] Welch HG, Skinner JS, Schroeck FR, Zhou W, Black WC. Regional variation of computed tomographic imaging in the United States and the risk of nephrectomy. JAMA Intern Med 2018;178:221–7.

[52] Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. World J Urol 2018;36:1341–53.

[53] Morrissey JJ, Mobley J, Figenshau RS, Vetter J, Bhayani S, Kharasch ED. Urine aquaporin 1 and perilipin 2 differentiate renal carcinomas from other imaged renal masses and bladder and prostate cancer. Mayo Clin Proc 2015;90:35–42.