



# Incidence of childhood renal tumours: An international population-based study

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## Abstract

Malignant renal tumours represent 5% of childhood cancers and include types with likely different aetiology: Wilms tumour (WT), rhabdoid renal tumour, kidney sarcomas and renal carcinomas. WT is the most common renal tumour in children, previously shown to vary internationally and with ethnicity. Using the comprehensive database of the International Incidence of Childhood Cancer study (IICC), we analysed global variations and time trends in incidence of renal tumour types in children (age 0-14 years) and adolescents (age 15-19 years). The results were presented by 14 world regions, and five ethnic groups in the US. We included 15 320 renal tumours in children and 800 in adolescents reported to the 163 contributing registries during 2001-2010. In children, age-standardised incidence rate (ASR) of renal tumours was 8.3 per million (95% confidence interval, CI = 8.1, 8.4); it was the highest in North America and Europe (9-10 per million) and the lowest in most Asian regions (4-5 per million). In the US, Blacks had the highest ASR (10.9 per million, 95% CI = 10.2, 11.6) and Asian and Pacific Islanders the lowest (4.4 per million, 95% CI = 3.6, 5.1). In adolescents, age-specific incidence rate of renal tumours was 1.4 per million (95% CI = 1.3, 1.5). WT accounted for over 90% of all renal tumours in each age from 1 to 7 years and the proportion of renal carcinomas increased gradually with age. From 1996 to 2010, incidence remained mostly stable for WT (average annual

**Abbreviations:** AAPC, average annual percent change; ASR, age-standardised incidence rate; CCSK, clear cell sarcoma of kidney; CI, confidence interval; DCO, registrations from death certificate only; IARC, International Agency for Research on Cancer; ICC, International Classification of Childhood Cancer; ICD-O-3, third edition of the International Classification of Diseases for Oncology; IGF-2 LOI, loss of imprinting of IGF-2; IGF-2, insulin-like growth factor 2 gene locus; IICC, International Incidence of Childhood Cancer; IRR, incidence rate ratio; ITD, internal tandem duplication; M/F, male to female incidence rate ratio; MV, microscopic verification; NOS, not otherwise specified; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator; SWI/SNF, Switch/sucrose nonfermentable; WT, Wilms tumour.

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[Correction added on 3 September 2020, after first online publication: There is a change in copyright and 'United States' has been changed to 'US' throughout the article.]

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percent change, AAPC = 0.1) and increased for renal carcinomas in children (AAPC = 3.7) and adolescents (AAPC = 3.2). Our findings warrant further monitoring.

#### KEYWORDS

cancer epidemiology, childhood renal tumour, paediatric kidney cancer, population-based cancer registry study, Wilms tumour

## 1 | INTRODUCTION

Malignant renal tumours represent 5% of all cancers occurring before the age of 15 years.<sup>1</sup> The major specific types are nephroblastoma (Wilms tumour, WT), rhabdoid renal tumour, kidney sarcomas, and renal carcinomas. Incidence of WT, the most common renal tumour in children, was shown to vary internationally and with ethnicity in previous reports.<sup>1-5</sup> In the 1970s, the incidence of WT in Black populations was three times that in East Asian populations.<sup>2</sup> Age distribution at diagnosis also differed between populations; the peak incidence ranged between 1 and 3 years of age in White populations, while in East Asia it peaked in infants (children younger than 1 year).<sup>2,4</sup> WT is one of the few childhood cancers that is reported to be approximately 10% more common in females than in males<sup>1</sup> although a female excess was not seen in the East Asian populations in the 1970s.<sup>2</sup> Incidence rates were increasing in Europe by 0.7% per year in the period 1978 to 1997<sup>4</sup> whereas they were stable in the US during 2001 to 2009.<sup>5</sup>

WT often presents as a solitary lesion, but approximately 7% were reported to be multicentric and 5% to 8% bilateral.<sup>4,6-8</sup> Unilateral tumours occur at a slightly older age than bilateral ones, in accordance with Knudson's two hit hypothesis.<sup>9</sup> Approximately 10% of WT occur as part of several distinct congenital malformation syndromes.<sup>7</sup> Overgrowth syndromes, in particular, Beckwith-Wiedemann syndrome carry an approximately 5% risk of developing WT.<sup>10</sup> Syndromes involving genitourinary anomalies combined with aniridia and variable mental retardation, or with nephrotic syndrome are associated with mutations of the WT1 gene on chromosome 11p13 and carry a greatly increased risk of developing WT.<sup>11-13</sup>

Rhabdoid renal tumour is a rare aggressive cancer occurring in infancy and early childhood. It was recognised as a distinct tumour type in 1978, although initially it was classified as a possible rhabdomyosarcomatoid variant of WT.<sup>14</sup> It is associated with mutation of the INI1 gene on chromosome 22q in both renal and nonrenal rhabdoid tumours.<sup>15</sup>

Kidney sarcomas include clear cell sarcoma of kidney (CCSK), also a rare childhood renal tumour. The clinical course is characterised by a propensity for metastases to bone, brain and lungs, by a longer period at risk of relapse and by poorer outcome than WT.<sup>16</sup> Although clinical or genetic studies revealed the characteristics of these very rare tumours, epidemiological data have never been reported.

Renal carcinomas, the most common renal tumour type in adults, are rare in childhood. Children are at risk of renal carcinomas when affected by Von Hippel-Lindau disease or tuberous sclerosis, and a specific translocation at chromosome Xp11.2 or 6p21 has been reported in younger children with renal carcinomas.<sup>17,18</sup> Renal

### What's new?

Based on more than 16,000 incident cases in the period 2001-2010, this study offers the most complete overview to date of the worldwide patterns of renal tumours in children and adolescents. Using the comprehensive International Incidence of Childhood Cancer database, the authors also describe the distribution of rare entities such as rhabdoid renal tumour or kidney sarcomas. The results indicate the stable incidence of Wilms tumour, the most common renal tumour in children, consistently with a likely genetic origin. The rising incidence of renal carcinomas with age and over time is likely caused by environmental risk factors, warranting further monitoring.

medullary carcinoma is reported to occur in young individuals with sickle cell trait.<sup>19</sup> All-age incidence of renal carcinomas were shown to be increasing,<sup>20</sup> however, the trend in incidence of renal carcinomas in children and adolescents has not been reported.

Geographical and temporal variations in incidence reveal potential roles of genetic predisposition or external risk factors and provide a basis for public health policy and aetiological research. The International Agency for Research on Cancer (IARC) has coordinated a global study series, the International Incidence of Childhood Cancer (IICC).<sup>21-23</sup> However, the latest comprehensive comparison of international patterns of incidence of renal tumours is based on the first volume of IICC (IICC-1) and refers to the 1970s and early 1980s.<sup>2</sup>

In our study, we used the most up-to-date information collected for the third volume of IICC (IICC-3) to analyse in detail global variations in incidence of renal tumours in children aged 0 to 14 years and adolescents aged 15 to 19 years in the period 2001 to 2010. We also examined the temporal changes in incidence over the 15-year period 1996 to 2010, and long term time trends using information from all three volumes of IICC.<sup>21-23</sup> The results are interpreted in terms of their impact on cancer control in the childhood and adolescent population.

## 2 | METHODS

### 2.1 | Study design and data sources

The principal data source was the IICC-3 database, which was constructed using data from 308 population-based cancer registries

operating in 82 countries, departments and territories on five continents.<sup>1,23</sup> The quality and comparability of the data included in the IICC-3 database were assessed and improved during a thorough peer-review process<sup>1,24</sup> and only approved datasets were considered for the analyses.

All cases of malignant renal tumours as defined by the 2017 update of the third edition of the International Classification of Childhood Cancer (ICCC-3-2017)<sup>25</sup> were extracted from the IICC-3 database. Malignant renal tumours constitute diagnostic group VI of ICC-3-2017 and are categorised into three subgroups (VIa–WT and other non-epithelial renal tumours, VIb–renal carcinomas and VIc–unspecified malignant renal tumours; Table S1). The subgroup VIa is further split into three divisions, separating nephroblastoma (WT, VIa1), rhabdoid renal tumour (VIa2) and kidney sarcomas (VIa3), as shown in Table S1.

The individual cancer records included coded information on the registry, sex, age, date of birth, date of incidence and tumour sequence (ie, the numerical order of occurrence of the neoplasm), site, morphology, behaviour, laterality and most valid basis of diagnosis. The tumour site, morphology, behaviour and basis of diagnosis were coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).<sup>26,27</sup>

Person-years at risk, also extracted from the IICC-3 database, were mostly provided by the registries by calendar year, single year of age and sex. Any missing data were estimated at IARC by linear interpolation or extrapolation, as described in the IICC-3 publication.<sup>24</sup>

## 2.2 | Constitution of datasets

The large number of cancer registries contributing their data to the IICC-3 database resulted in a considerable variation in the size, period of coverage, target age range and other aspects. Therefore, different datasets were used for various statistical analyses; each of them maximising study size as well as geographical representation. Some populations were covered by both paediatric (the paediatric dataset) and general cancer registries (the general dataset). While a majority of the paediatric cancer registries target cancers occurring before the age of 15 years, the general cancer registries record cancers occurring in all years of age. Where the same population was covered by two registries, only one of them was included in any analysis giving a preference for a paediatric cancer registry in the analyses targeting the age range 0 to 14 years. The contribution of the individual registries to each dataset is shown in Table S2.

All eligible registries providing data for each calendar year of the 10-year period 2001 to 2010 were included in the analyses of geographical variations. With the aim of smoothing excessive variations produced by small numbers of cases in some individual cancer registries, we have pooled the available data into UN-defined regions or an aggregate of UN-defined regions (<https://unstats.un.org/unsd/methodology/m49/>), as shown in Table S2. Most results are presented for 14 world regions or populations and a combined total. In addition, it was possible to present the USA results by five ethnic

groups. Within the region of South Asia, eligible data were only available from India. The described region definition was also driven by data availability and the sizes of the resulting respective regional datasets, as in the earlier study.<sup>1</sup> Age-specific incidence rates by laterality of WT were computed in a dataset limited to the registries providing information on laterality for at least 95% of WT cases.

Incidence time trends were studied in two separate analyses. In the first analysis, we included all registries contributing data of consistently high quality to each year of the 15-year study period 1996 to 2010 within IICC-3 (Table S2). In the second analysis, we compared the incidence rates across several decades, based on the published numbers of cases and the associated populations at risk from the registries covering similarly defined populations in all three IICC volumes<sup>21–23</sup> and reporting 15 or more renal tumours in each volume. As the subgroup VIa was not split into divisions and the target age-range was 0 to 14 years in the IICC-1<sup>21</sup> and IICC-2,<sup>22</sup> the comparison of rates between the three volumes was limited to three categories, namely WT and other non-epithelial renal tumours (VIa), renal carcinomas (VIb) and unspecified malignant renal tumours (VIc) and their combination.

## 2.3 | Statistical analysis

All incidence rates are expressed per million person-years of the relevant population at risk. Age-specific incidence rates were calculated for 5-year age groups (0–4, 5–9, 10–14 and 15–19) or for single years of age. Incidence rates for the age-range 0 to 14 or 0 to 19 were adjusted using direct standardisation method and the weights 12, 10, 9 and 9 for the four respective age groups,<sup>28</sup> as in the previous publication.<sup>1</sup> The resulting age-standardised incidence rates (ASRs) allowed making comparisons between populations with differing age structure. We calculated male to female incidence rate ratios (M/F) over the 0 to 14 years as the quotient of the age-standardised incidence rate for males divided by that for females and in the age group 15 to 19 years M/F was calculated as the quotient of the age-specific incidence rates. The 95% confidence intervals (CI) were calculated by standard methods.<sup>29,30</sup>

Change in incidence rates over the period 1996 to 2010 was assessed from Poisson regression modelling of the log rate for the individual calendar years, coded from 1996 to 2010, and expressed as an average annual percent change (AAPC) with its 95%CI.

We also compared the incidence level derived from the paediatric dataset for IICC-3 with those published in IICC-1 and IICC-2 and calculated the incidence rate ratio (IRR) comparing the ASR for the age 0 to 14 years reported in IICC-3 to the ASR in IICC-1, the latter serving as a reference. Their ratio was assessed using the 95% CI.<sup>29</sup>

Statistical analyses were conducted using Stata/IC (version 12.1)<sup>31</sup> for rates and Joinpoint software<sup>32</sup> for changes in rates.

## 3 | RESULTS

In total, 15 320 renal tumours in children aged 0 to 14 years occurring in 2.1 billion person-years and 800 renal tumours in adolescents aged

**TABLE 1** Overview of the data included in the analyses of incidence of renal tumours for the period 2001 to 2010

	Age 0-14 years					Age 15-19 years						
	Person-years <sup>a</sup> (thousands)	Renal tumour cases	Proportion of renal tumours in all cancer cases (%)			Person-years <sup>a</sup> (thousands)	Renal tumour cases	Proportion of renal tumours in all cancer cases (%)				
			DCO (%)	MV (%)	NOS (%)			DCO (%)	MV (%)	NOS (%)		
All world regions	2 100 273	15 320	5.2	0.4	96.6	1.2	582 537	800	0.7	2.1	91.8	5.5
<i>World region</i>												
North Africa	18 606	104	5.2	2.9	92.3	5.8	6 980	7	0.7	14.3	85.7	28.6
Sub-Saharan Africa	167 696	1030	11.1	1.3	91.7	0.6	6 780	16	1.6	0.0	75.0	12.5
Central America and Caribbean	50 637	295	4.7	3.4	94.9	2.7	16 333	22	0.9	22.7	77.3	4.5
South America	140 549	844	4.6	0.6	97.3	2.3	14 737	13	0.5	15.4	76.9	23.1
North America	661 232	5563	5.2	0.3	98.3	0.6	235 385	380	0.7	0.5	95.5	1.6
East Asia	133 678	541	3.2	0.6	94.1	2.6	53 486	52	0.7	0.0	90.4	7.7
South Asia	65 713	229	4.0	0.9	98.3	1.7	25 901	17	0.7	11.8	88.2	5.9
Southeast Asia	76 729	376	4.2	2.2	81.1	6.1	28 944	28	0.9	11.5	67.9	17.9
West Asia	78 603	494	4.9	0.8	96.2	1.0	23 316	24	0.6	0.0	95.8	0.0
Eastern Europe	134 174	1093	6.0	0.8	95.3	4.1	50 525	85	1.0	0.0	85.9	16.5
Northern Europe	151 598	1226	5.5	0.2	98.2	0.6	54 498	63	0.6	0.0	95.2	1.6
Southern Europe	85 322	699	4.9	0.0	92.7	1.1	21 679	35	0.7	0.0	94.3	5.7
Western Europe	285 149	2445	5.6	0.0	98.6	0.1	26 482	36	0.6	6.7	97.2	2.8
Oceania	50 585	381	5.1	0.0	97.6	0.5	17 492	22	0.5	4.5	95.5	9.1
<i>Ethnic group in the USA</i>												
Asian and Pacific Islander	30 560	122	3.3	0.0	99.2	0.8	10 437	9	0.6	11.1	88.9	0.0
Black	99 659	970	7.7	0.2	98.5	0.4	35 134	86	1.5	0.0	97.7	0.0
Hispanic White	114 987	811	4.2	0.1	98.8	0.4	35 053	38	0.5	0.0	94.7	2.6
Native American	9863	49	5.9	0.0	100	0.0	3533	6	1.4	0.0	83.3	0.0
White non-Hispanic	351 453	3027	5.0	0.4	98.9	0.5	130 310	196	0.6	0.5	95.9	1.5

Abbreviations: DCO, registrations from death certificate only (the percentages were calculated after exclusion of the registries that do not have access to death certificates); MV, microscopic verification; NOS, not otherwise specified (unspecified tumours classified to Vic of International Classification of Childhood Cancer,<sup>25</sup> see Table S1).

<sup>a</sup>Person-years have been rounded to the nearest thousand, so they do not add up exactly. The registries' contribution to the analyses is shown in Table S2.

Source: International Incidence of Childhood Cancer, volume 3.<sup>23</sup>

**TABLE 2** Incidence of renal tumours by world region and ethnicity, 2001 to 2010

	(A) Children (age 0-14 years)																													
	WT and other non-epithelial renal tumours (VIa)				Wilms tumour (VIa1)				Rhabdoid renal tumour (VIa2)				Kidney sarcomas (VIa3)				Renal carcinomas (VIb)				Unspecified (VIc)									
	Cases	ASR	95%CI	M/F	Cases	ASR	95%CI	M/F	Cases	ASR	95%CI	M/F	Cases	ASR	95%CI	M/F	Cases	ASR	95%CI	M/F	Cases	ASR	95%CI							
All world regions	15 320	8.3	[8.1,8.4]	14 596	7.9	[7.8,8.1]	13 838	7.5	[7.4,7.7]	0.9	[0.8,0.9]	327	0.2	[0.2,0.2]	1.1	[0.9,1.3]	431	0.2	[0.2,0.3]	1.8	[1.5,2.2]	543	0.2	[0.2,0.3]	1.1	[0.9,1.3]	181	0.1	[0.1,0.1]	
<i>World region</i>																														
North Africa	104	6.4	[5.2,7.6]	96	5.9	[4.7,7.1]	95	5.9	[4.7,7.0]	1.1	[0.7,1.6]	1	0.1	[0.0,0.4]	—	—	0	0.0	—	—	—	—	2	0.1	[0.0,0.4]	1.0	[0.1,15.3]	6	0.4	[0.1,0.8]
Sub-Saharan Africa	1030	6.7	[6.2,7.1]	1013	6.6	[6.1,7.0]	978	6.3	[5.9,6.7]	0.9	[0.8,1.0]	12	0.1	[0.0,0.1]	1.4	[0.4,4.4]	23	0.1	[0.1,0.2]	2.4	[1.0,5.8]	11	0.1	[0.0,0.1]	0.6	[0.2,2.0]	6	0.0	[0.0,0.1]	
Central America and Caribbean	295	6.7	[5.9,7.4]	280	6.3	[5.6,7.1]	264	6.0	[5.3,6.7]	0.8	[0.6,1.0]	8	0.2	[0.1,0.4]	0.6	[0.2,2.7]	8	0.2	[0.1,0.3]	1.3	[0.3,5.4]	7	0.1	[0.1,0.3]	1.2	[0.3,5.6]	8	0.2	[0.1,0.4]	
South America	844	6.7	[6.3,7.2]	802	6.4	[6.0,6.9]	762	6.1	[5.7,6.6]	1.0	[0.9,1.1]	14	0.1	[0.1,0.2]	1.0	[0.3,2.8]	26	0.2	[0.1,0.3]	1.7	[0.8,3.8]	23	0.2	[0.1,0.2]	0.8	[0.4,1.9]	19	0.1	[0.1,0.2]	
North America	5563	9.5	[9.2,9.7]	5301	9.1	[8.9,9.4]	4972	8.5	[8.3,8.8]	0.9	[0.8,0.9]	143	0.3	[0.2,0.3]	1.0	[0.7,1.4]	186	0.3	[0.3,0.4]	1.7	[1.3,2.3]	230	0.3	[0.3,0.4]	1.2	[0.9,1.5]	32	0.1	[0.0,0.1]	
East Asia	541	5.1	[4.7,5.6]	498	4.8	[4.4,5.2]	446	4.3	[3.9,4.7]	1.0	[0.8,1.2]	24	0.2	[0.1,0.3]	0.9	[0.4,2.0]	28	0.3	[0.2,0.4]	1.1	[0.5,2.4]	29	0.2	[0.1,0.3]	1.4	[0.7,3.0]	14	0.1	[0.1,0.2]	
South Asia	229	4.1	[3.5,4.6]	206	3.7	[3.2,4.2]	201	3.6	[3.1,4.1]	1.1	[0.8,1.5]	2	0.0	[0.0,0.1]	0.9	[0.1,15.0]	3	0.0	[0.0,0.1]	—	—	19	0.3	[0.2,0.5]	1.2	[0.5,3.1]	4	0.1	[0.0,0.2]	
Southeast Asia	376	5.4	[4.9,6.0]	335	4.9	[4.3,5.4]	323	4.7	[4.2,5.2]	1.2	[1.0,1.5]	1	0.0	[0.0,0.1]	0.0	—	11	0.2	[0.1,0.3]	2.5	[0.7,9.4]	18	0.2	[0.1,0.4]	0.3	[0.1,1.0]	23	0.3	[0.2,0.5]	
West Asia	494	6.7	[6.1,7.3]	467	6.4	[5.8,7.0]	448	6.1	[5.6,6.7]	0.9	[0.7,1.0]	4	0.1	[0.0,0.1]	1.0	[0.1,6.8]	15	0.2	[0.1,0.3]	3.7	[1.1,13.2]	22	0.3	[0.2,0.4]	1.5	[0.6,3.5]	5	0.1	[0.0,0.2]	
Eastern Europe	1093	9.7	[9.1,10.3]	1010	9.0	[8.5,9.6]	980	8.8	[8.2,9.3]	0.8	[0.7,0.9]	11	0.1	[0.0,0.2]	1.5	[0.4,5.2]	19	0.2	[0.1,0.3]	3.5	[1.2,10.7]	38	0.3	[0.2,0.3]	0.6	[0.3,1.2]	45	0.4	[0.3,0.5]	
Northern Europe	1226	9.2	[8.7,9.7]	1184	8.9	[8.4,9.4]	1109	8.4	[7.9,8.8]	0.8	[0.7,0.9]	35	0.3	[0.2,0.4]	0.9	[0.5,1.7]	40	0.3	[0.2,0.4]	2.5	[1.2,5.0]	35	0.2	[0.1,0.3]	1.7	[0.9,3.5]	7	0.1	[0.0,0.1]	
Southern Europe	699	9.1	[8.4,9.7]	671	8.7	[8.1,9.4]	643	8.4	[7.7,9.0]	1.1	[0.9,1.2]	19	0.3	[0.2,0.4]	1.1	[0.4,2.6]	9	0.1	[0.1,0.2]	0.5	[0.1,1.9]	20	0.2	[0.1,0.3]	0.8	[0.3,2.0]	8	0.1	[0.0,0.2]	
Western Europe	2445	9.8	[9.4,10.2]	2375	9.6	[9.2,10.0]	2276	9.2	[8.8,9.6]	0.9	[0.8,1.0]	46	0.2	[0.1,0.2]	1.4	[0.8,2.6]	53	0.2	[0.2,0.3]	1.4	[0.8,2.5]	68	0.2	[0.2,0.3]	1.0	[0.6,1.6]	2	0.0	[0.0,0.0]	
Oceania	381	8.4	[7.6,9.3]	358	8.0	[7.2,8.8]	341	7.6	[6.8,8.4]	0.7	[0.6,0.9]	7	0.2	[0.1,0.3]	2.4	[0.5,12.2]	10	0.2	[0.1,0.4]	1.6	[0.4,5.7]	21	0.4	[0.2,0.6]	1.2	[0.5,2.8]	2	0.0	[0.0,0.2]	
<i>Ethnic group in the USA</i>																														
Asian and Pacific Islander	122	4.4	[3.6,5.1]	119	4.3	[3.5,5.0]	104	3.7	[3.0,4.4]	1.0	[0.7,1.4]	6	0.2	[0.1,0.5]	1.0	[0.2,4.8]	9	0.3	[0.1,0.6]	0.8	[0.2,2.8]	2	0.1	[0.0,0.2]	0.0	—	1	0.0	[0.0,0.2]	
Black	970	10.9	[10.2,11.6]	889	10.2	[9.5,10.8]	848	9.7	[9.0,10.3]	0.9	[0.8,1.0]	15	0.2	[0.1,0.3]	1.8	[0.6,5.4]	26	0.3	[0.2,0.4]	4.2	[1.6,11.3]	77	0.7	[0.5,0.9]	1.7	[1.0,2.7]	4	0.0	[0.0,0.1]	
Hispanic White	811	7.4	[6.9,7.9]	786	7.2	[6.7,7.7]	725	6.6	[6.2,7.1]	0.8	[0.7,0.9]	31	0.3	[0.2,0.4]	0.6	[0.3,1.2]	30	0.3	[0.2,0.4]	1.4	[0.7,3.0]	22	0.2	[0.1,0.3]	1.1	[0.5,2.6]	3	0.0	[0.0,0.1]	
Native American	49	5.7	[4.1,7.3]	45	5.3	[3.7,6.8]	43	5.0	[3.5,6.5]	0.7	[0.4,1.3]	2	0.2	[0.0,0.9]	1.0	[0.1,15.6]	0	0.0	—	—	—	4	0.4	[0.1,1.1]	0.3	[0.0,3.1]	0	0.0	—	
White non-Hispanic	3027	9.9	[9.6,10.3]	2911	9.6	[9.3,10.0]	2745	9.1	[8.7,9.4]	0.9	[0.8,0.9]	71	0.2	[0.2,0.3]	1.2	[0.8,1.9]	95	0.3	[0.3,0.4]	1.6	[1.0,2.4]	101	0.3	[0.2,0.3]	1.0	[0.6,1.4]	15	0.0	[0.0,0.1]	

(Continues)

(B) Adolescents (age 15-19 years)																								
	Renal tumours (VI)			WT and other non-epithelial renal tumours (VIIa)			Wilms tumour (VIIa1)			Rhabdoid renal tumour (VIIa2)			Kidney sarcomas (VIIa3)			Renal carcinomas (VIIb)			Unspecified (VIIc)					
	Cases	Rate	95% CI	Cases	Rate	95% CI	Cases	Rate	95% CI	Cases	Rate	95% CI	Cases	Rate	95% CI	M/F	Rate	95% CI	Cases	Rate	95% CI			
All world regions	800	1.4	[1.3,1.5]	192	0.3	[0.3,0.4]	181	0.3	[0.3,0.4]	4	0.0	[0.0,0.0]	7	0.0	[0.0,0.0]	564	1.0	[0.9,1.0]	0.7	0.1	[0.6,0.9]	44	0.1	[0.1,0.1]
<i>World region</i>																								
North Africa	7	1.0	[0.4,2.1]	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-	5	0.7	[0.2,1.7]	1.4	0.3	[0.2,8.6]	2	0.3	[0.0,1.0]
Sub-Saharan Africa	16	2.4	[1.3,3.8]	5	0.7	[0.2,1.7]	5	0.7	[0.2,1.7]	0	0.0	-	0	0.0	-	9	1.3	[0.6,2.5]	1.0	0.3	[0.3,3.5]	2	0.3	[0.0,1.1]
Central America and Caribbean	22	1.3	[0.8,2.0]	13	0.8	[0.4,1.4]	13	0.8	[0.4,1.4]	0	0.0	-	0	0.0	-	8	0.5	[0.2,1.0]	0.6	0.1	[0.1,2.4]	1	0.1	[0.0,0.3]
South America	13	0.9	[0.5,1.5]	1	0.1	[0.0,0.4]	1	0.1	[0.0,0.4]	0	0.0	-	0	0.0	-	9	0.6	[0.3,1.2]	0.8	0.2	[0.2,3.0]	3	0.2	[0.0,0.6]
North America	380	1.6	[1.5,1.8]	76	0.3	[0.3,0.4]	70	0.3	[0.2,0.4]	2	0.0	[0.0,0.0]	4	0.0	[0.0,0.0]	298	1.3	[1.1,1.4]	0.7	0.0	[0.6,0.9]	6	0.0	[0.0,0.1]
East Asia	52	1.0	[0.7,1.2]	9	0.2	[0.1,0.3]	9	0.2	[0.1,0.3]	0	0.0	-	0	0.0	-	39	0.7	[0.5,1.0]	0.9	0.1	[0.5,1.6]	4	0.1	[0.0,0.2]
South Asia	17	0.7	[0.4,1.1]	3	0.1	[0.0,0.3]	3	0.1	[0.0,0.3]	0	0.0	-	0	0.0	-	13	0.5	[0.3,0.9]	1.0	0.0	[0.3,2.9]	1	0.0	[0.0,0.2]
Southeast Asia	28	1.0	[0.6,1.4]	6	0.2	[0.1,0.5]	4	0.1	[0.0,0.4]	1	0.0	[0.0,0.2]	1	0.0	[0.0,0.2]	17	0.6	[0.3,0.9]	0.6	0.2	[0.2,1.6]	5	0.2	[0.1,0.4]
West Asia	24	1.0	[0.7,1.5]	11	0.5	[0.2,0.8]	11	0.5	[0.2,0.8]	0	0.0	-	0	0.0	-	13	0.6	[0.3,1.0]	0.3	0.0	[0.1,0.9]	0	0.0	-
Eastern Europe	85	1.7	[1.3,2.0]	32	0.6	[0.4,0.9]	32	0.6	[0.4,0.9]	0	0.0	-	0	0.0	-	39	0.8	[0.5,1.0]	0.6	0.3	[0.3,1.1]	14	0.3	[0.2,0.5]
Northern Europe	63	1.2	[0.9,1.4]	12	0.2	[0.1,0.4]	12	0.2	[0.1,0.4]	0	0.0	-	0	0.0	-	50	0.9	[0.7,1.2]	0.5	0.0	[0.3,1.0]	1	0.0	[0.0,0.1]
Southern Europe	35	1.6	[1.1,2.1]	5	0.2	[0.1,0.5]	4	0.2	[0.1,0.5]	0	0.0	-	1	0.0	[0.0,0.3]	28	1.3	[0.9,1.9]	1.1	0.1	[0.5,2.3]	2	0.1	[0.0,0.3]
Western Europe	36	1.4	[0.9,1.8]	11	0.4	[0.2,0.7]	9	0.3	[0.2,0.6]	1	0.0	[0.0,0.2]	1	0.0	[0.0,0.2]	24	0.9	[0.6,1.3]	0.8	0.0	[0.4,1.8]	1	0.0	[0.0,0.2]
Oceania	22	1.3	[0.8,1.9]	8	0.5	[0.2,0.9]	8	0.5	[0.2,0.9]	0	0.0	-	0	0.0	-	12	0.7	[0.4,1.2]	0.7	0.1	[0.2,2.2]	2	0.1	[0.0,0.4]
<i>Ethnic group in the USA</i>																								
Asian and Pacific Islander	9	0.9	[0.4,1.6]	2	0.2	[0.0,0.7]	2	0.2	[0.0,0.7]	0	0.0	-	0	0.0	-	7	0.7	[0.3,1.4]	5.7	0.0	[0.7,47.4]	0	0.0	-
Black	86	2.4	[1.9,3.0]	14	0.4	[0.2,0.7]	13	0.4	[0.2,0.6]	0	0.0	-	1	0.0	[0.0,0.2]	72	2.0	[1.6,2.5]	1.0	0.0	[0.6,1.6]	0	0.0	-
Hispanic White	38	1.1	[0.7,1.4]	4	0.1	[0.0,0.3]	2	0.1	[0.0,0.2]	1	0.0	[0.0,0.2]	1	0.0	[0.0,0.2]	33	0.9	[0.6,1.3]	1.0	0.0	[0.5,1.9]	1	0.0	[0.0,0.2]
Native American	6	1.7	[0.6,3.7]	1	0.3	[0.0,1.6]	1	0.3	[0.0,1.6]	0	0.0	-	0	0.0	-	5	1.4	[0.5,3.3]	0.2	0.0	[0.0,2.1]	0	0.0	-
White non-Hispanic	196	1.5	[1.3,1.7]	47	0.4	[0.3,0.5]	44	0.3	[0.2,0.4]	1	0.0	[0.0,0.0]	2	0.0	[0.0,0.1]	146	1.1	[0.9,1.3]	0.6	0.0	[0.4,0.8]	3	0.0	[0.0,0.1]

Note: Tumour groups are defined in Table S1. The registries' contribution to the analyses is shown in Table S2. Abbreviations: ASR, age-standardised incidence rate per million person-years; CI, confidence interval; M/F, male to female incidence rate ratio; Rate, age-specific incidence rate; Unspecified, unspecified malignant renal tumours; WT, Wilms tumour; -, not calculated due to insufficient number. Source: International Incidence of Childhood Cancer, volume 3.<sup>2,3</sup>

15 to 19 occurring in 583 million person-years were included in the analyses for the decade 2001 to 2010 (Table 1). On average, renal tumours constituted 5.2% of all childhood cancers reported in the included cancer registries; this percentage ranged from 3.2% in East Asia to 11.1% in Sub-Saharan Africa (Table 1). Among adolescents, renal tumours accounted for 0.7% of cancers across all world regions, ranging from 0.5% in South America and Oceania to 1.6% in Sub-Saharan Africa. The proportion of registrations from death certificate only (DCO) was 0.4% among children and 2.1% among adolescents. The unspecified category of renal tumours (ICCC-3 VIc) constituted a smaller proportion of cases in children compared to adolescents, with up to 28.6% in North Africa (Table 1).

### 3.1 | Variation in incidence by world region and ethnicity

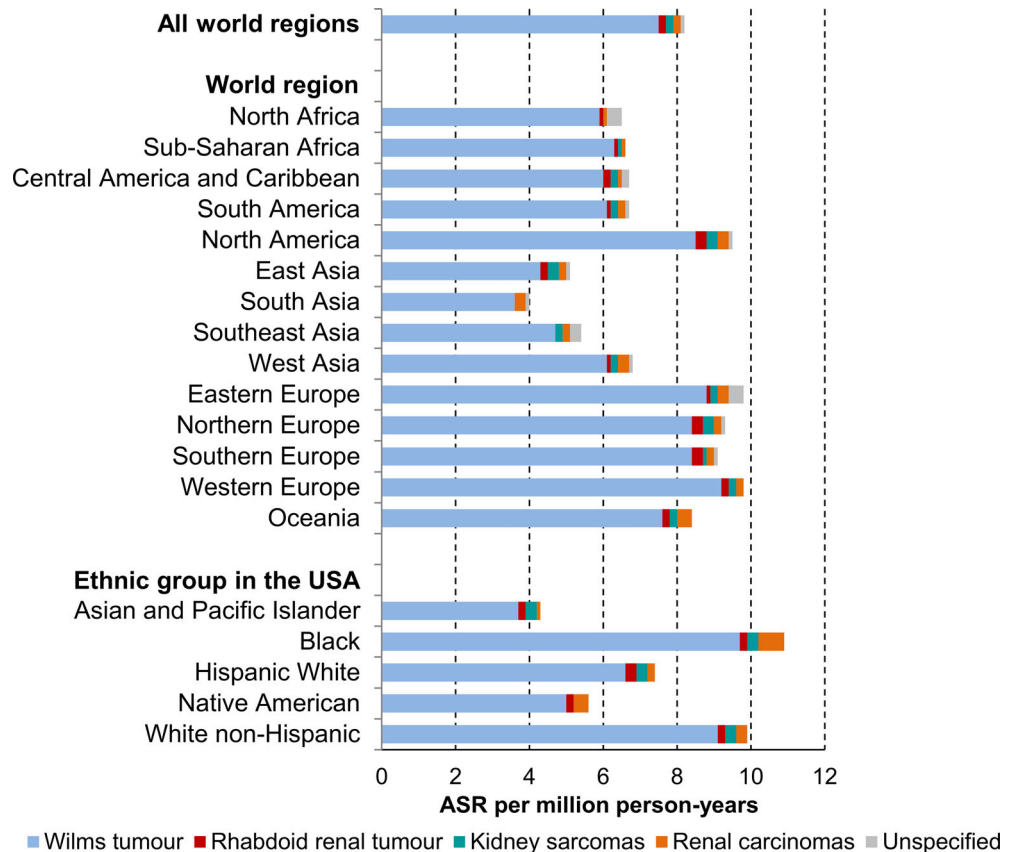
Table 2 shows number of cases, age-standardised incidence rate (ASR) for children (age 0-14 years) and age-specific incidence rate (Rate) for adolescents (age 15-19 years), and male to female incidence rate ratio (M/F) by world region and by ethnic group in the USA, during 2001 to 2010, by renal tumour type. In all world regions combined, ASR of renal tumours was 8.3 per million (95% CI = 8.1, 8.4) in children (Table 2A) and Rate was 1.4 per million (95% CI = 1.3, 1.5) in adolescents (Table 2B). In children, ASRs of renal tumours were highest in

North America and European regions, ranging between 9.1 (95% CI = 8.4, 9.7) and 9.8 per million (95% CI = 9.4, 10.2), while they were lowest, between 4.1 (95% CI = 3.5, 4.6) and 5.4 per million (95% CI = 4.9, 6.0), in most Asian regions except in West Asia (ASR = 6.7 per million, 95% CI = 6.1, 7.3). In the USA, the highest rate was seen for Blacks (ASR = 10.9 per million, 95% CI = 10.2, 11.6), while the rate in the Asian and Pacific Islanders (ASR = 4.4 per million, 95% CI = 3.6, 5.1) was comparable to those of most Asian regions.

### 3.2 | Variation in incidence by tumour type and sex

WT (defined as VIa1 in Table S1) was the most common renal tumour in children aged 0 to 14 in all the world regions and the ethnic groups in the USA (Figure 1). The overall rates of renal tumours were thus strongly influenced by the rate of WT (Figure 1). The M/F of WT was 0.9 (95% CI = 0.8, 0.9) overall in children. The largest predominance of females was observed in Oceania (M/F = 0.7, 95% CI = 0.6, 0.9), while males predominated only in Southeast Asia (M/F = 1.2, 95% CI = 1.0, 1.5), as shown in Figure S1 and Table 2A.

During 2001 to 2010, 431 cases of kidney sarcomas (ASR = 0.2 per million, 95% CI = 0.2, 0.3) and 327 cases of rhabdoid renal tumour (ASR = 0.2 per million, 95% CI = 0.2, 0.2) were reported overall in children aged 0 to 14 years, representing 3% and 2% of renal tumours



**FIGURE 1** Age-standardised incidence rates (ASRs) of renal tumours in children aged 0 to 14 years by world region and ethnicity, 2001 to 2010 (n = 15 320). Source: International Incidence of Childhood Cancer, volume 3.<sup>23</sup> Tumour groups are defined in Table S1. The registries' contribution to the analyses is shown in Table S2. ASR, age-standardised incidence rate; Unspecified, unspecified malignant renal tumours

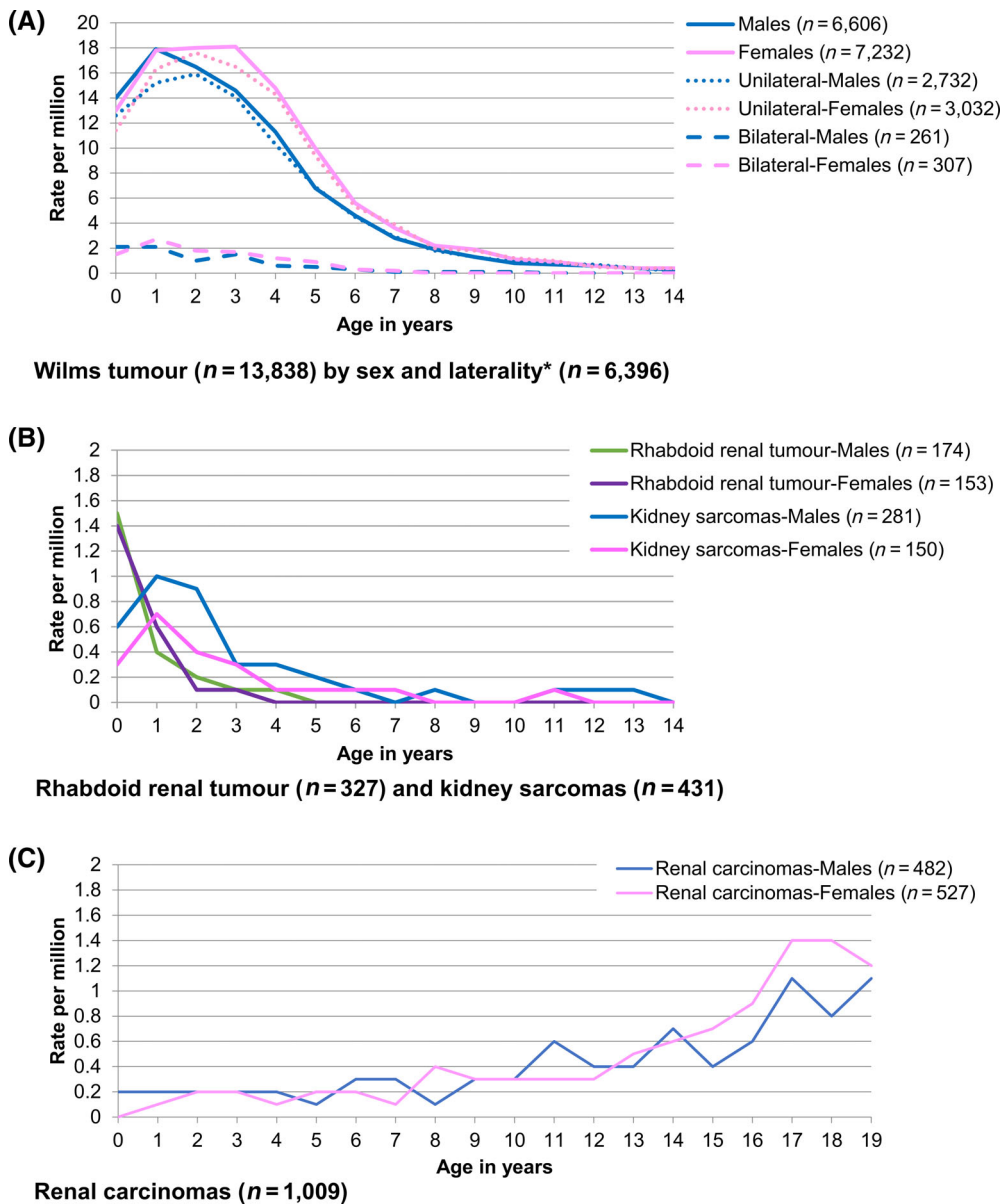
respectively. Clear cell sarcoma of kidney (CCSK) constituted wholly the division of kidney sarcomas (Vla3). Incidence of rhabdoid renal tumour (Vla2) was virtually the same between the two sexes among children (M/F = 1.1, 95% CI = 0.9, 1.3). Marked male excess was seen among the kidney sarcoma cases (Vla3) in children (M/F = 1.8, 95% CI = 1.5, 2.2).

Incidence of renal carcinomas was highest among Blacks in the USA in both children and adolescents. While no difference in incidence was seen between the two sexes before the age of 15 years (M/F = 1.1, 95% CI = 0.9, 1.3; Table 2A), adolescent females were affected more than males (M/F = 0.7, 95% CI = 0.6, 0.9; Table 2B). We observed 39 medullary carcinoma cases in the whole series in the USA; 85% of them occurred in the Black population (19 in children and 14 in adolescents).

Case numbers of renal tumour types other than WT were too small for clear geographical or ethnic pattern of incidence to emerge among children and adolescents.

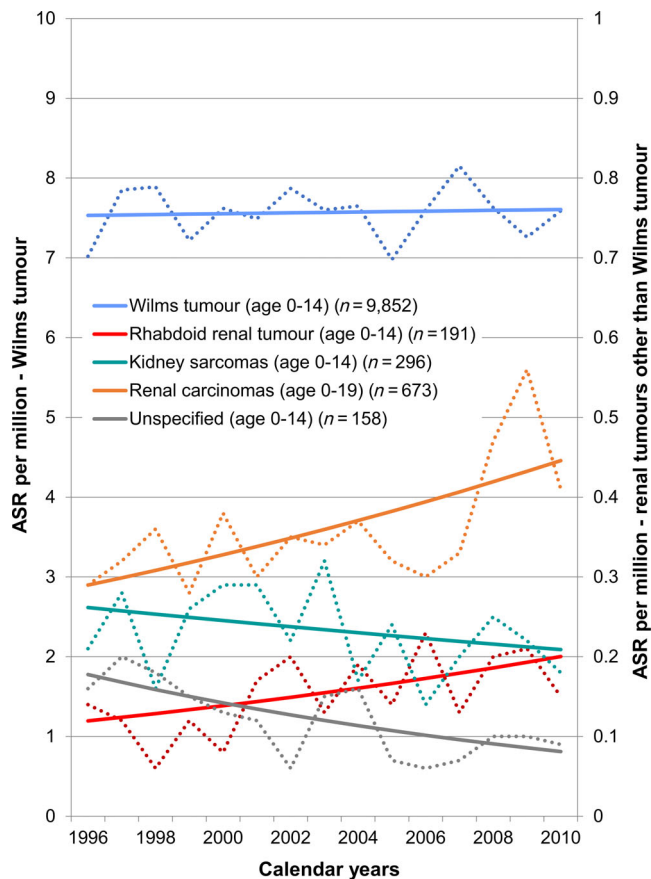
### 3.3 | Age-specific incidence patterns

Based on all world regions combined data, WT accounted for over 90% of all renal tumours in each age from 1 to 7 years, but distribution slightly varied by region or ethnicity (Figure S2 and Table S3). The proportion of renal carcinomas increased gradually with age and became the predominant renal tumour from the age of 14 years onward. Figure 2 shows the age-specific incidence rates of renal tumours by tumour type, using data of all world regions combined for



**FIGURE 2** Age-specific incidence of renal tumours, all world regions combined, 2001 to 2010. Source: International Incidence of Childhood Cancer, volume 3.<sup>23</sup> Tumour groups are defined in Table S1. The registries' contribution to the analyses is shown in Table S2. A, Wilms tumour (n = 13 838) by sex and laterality\* (n = 6396). B, Rhabdoid renal tumour (n = 327) and kidney sarcomas (n = 431). C, Renal carcinomas (n = 1009). \*Only the registries providing information on the laterality for at least 95% Wilms tumour cases are included. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]





**FIGURE 3** Time trends in incidence of renal tumours, all world regions combined, 1996 to 2010 ( $n = 11\,170$ ). Source: International Incidence of Childhood Cancer, volume 3.<sup>23</sup> Tumour groups are defined in Table S1. The registries' contribution to the analyses is shown in Table S2. ASR, age-standardised incidence rate; *Unspecified*, Unspecified malignant renal tumours; *Solid line*: predicted ASR; *Dotted line*: observed ASR. Scale on the left axis: ASR for Wilms tumour; Scale on the right axis: ASR for renal tumours other than Wilms tumour

the period 2001 to 2010. The age-specific incidence of WT peaked at the age of 1 year in males at 17.9 per million-person years, while in females, a similar peak remained almost constant at the age of 1, 2 and 3 years, with the respective rates of 17.8, 18.0 and 18.1 per million (Figure 2A). A similar pattern was observed in all world regions, except in East Asia where the highest incidence was seen in infancy (Figure S3).

Out of 6396 WT cases from registries with reliable data on laterality, 5764 (90.1%) were unilateral (ASR = 7.1 per million, 95% CI = 6.9, 7.2), 568 (8.9%) bilateral (ASR = 0.7 per million, 95% CI = 0.7, 0.8) and 64 (1.0%) with unknown laterality (ASR = 0.1 per million, 95% CI = 0.1, 0.1). The age-specific incidence peaked at 2 years of age in unilateral WT in both sexes, while bilateral WT peaked at the age of 1 year in females and before the age of 1 year in males (Figure 2A). The age-specific incidence peaked at age 0 in rhabdoid renal tumour (Rate = 1.5 per million) and at age 1 in kidney sarcomas, with no sex differences in the age-incidence pattern (Figure 2B). Using the general dataset, 1009 renal carcinomas were reported in age 0 to 19 years

(ASR = 0.4 per million, 95% CI = 0.4, 0.4). Incidence rate increased with age, reaching the highest rate of 1.3 per million at the age of 17 years (Figure 2c).

### 3.4 | Time trends in incidence during 1996 to 2010

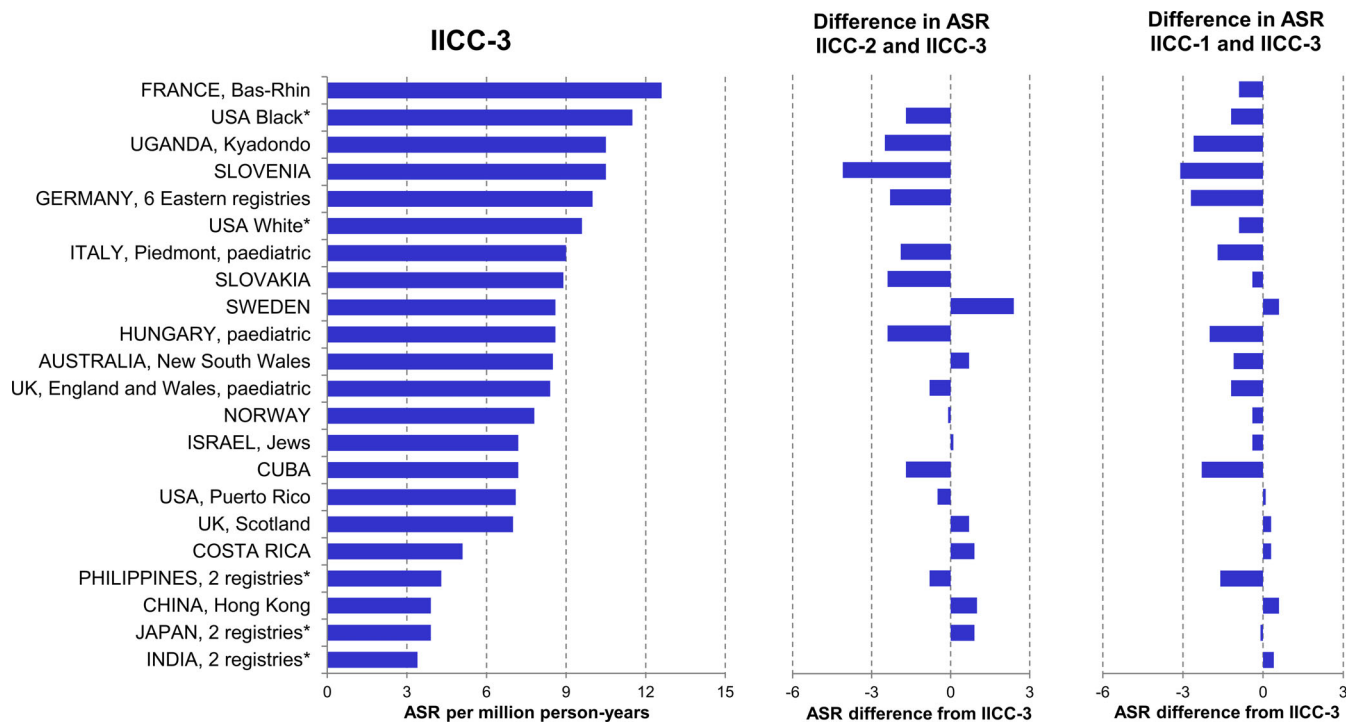
Incidence time trends in the period 1996 to 2010 are shown in Figure 3 and Table S4. The incidence rates were stable for the entire group of renal tumours (VI) in children aged 0 to 14 years (AAPC = 0.1, 95% CI = -0.4, 0.6), due to the stable incidence of WT (AAPC = 0.1, 95% CI = -0.5, 0.6; Table S4). However, we noted a strong increase of 4.1% (95% CI = 1.0, 7.3) per year in the incidence of all renal tumours in Southeast Asia. This was driven by the increase in WT incidence (VIa1) in males (AAPC = 6.8, 95% CI = 3.4, 10.2), which influenced the combined rate for both sexes (AAPC = 5.2, 95% CI = 1.6, 8.9), while no increase was observed in females (AAPC = 3.5, 95% CI = -0.9, 8.2) in this region. The combined data for all world regions in children aged 0 to 14 years have shown an increase in incidence of rhabdoid renal tumour (VIa2; AAPC = 3.7, 95% CI = 0.2, 7.5) and renal carcinomas (Figure 3 and Table S4). The marked increase in the incidence of renal carcinomas in females (AAPC = 4.2, 95% CI = 0.9, 7.6) affected the combined rate for both sexes (AAPC = 3.7, 95% CI = 1.4, 6.0), while no change was observed in males (AAPC = 2.9, 95% CI = -0.3, 6.3).

The results for the age 15 to 19 years are not tabulated; we observed an increase in incidence of renal carcinomas in males (AAPC = 3.7, 95% CI = 0.3, 7.1), which greatly contributed to the significant increase in the combined rate for both sexes (AAPC = 3.2, 95% CI = 0.5, 5.9), while no increase was seen in adolescent females (AAPC = 2.8, 95% CI = -0.2, 5.8).

Of note is the marked decrease of the overall incidence of unspecified malignant renal tumours by 5.4% (95% CI = -8.7, -2.1) per year in age 0 to 14 years (Table S4).

### 3.5 | Incidence trends and geographical variations in children aged 0 to 14 years over four decades

We identified 21 countries contributing data for 22 similarly defined populations to all three IICC volumes with 15 or more renal tumour cases in children (age 0-14 years) in each volume after pooling data from two or more registries in India, Japan, Philippines and the USA. (Figure 4 and Table S5). Among them, incidence rates of WT and other non-epithelial renal tumours (VIa) in IICC-3 were highest in France (Bas-Rhin, ASR = 12.6 per million, 95% CI = 8.8, 16.5), USA Black (ASR = 11.5 per million, 95% CI = 10.2, 12.7), Uganda (Kyadondo, ASR = 10.5 per million, 95% CI = 8.7, 12.3), and Slovenia (ASR = 10.5 per million, 95% CI = 7.9, 13.2), while they were lowest in India (ASR = 3.4 per million, 95% CI = 3.0, 3.8), Japan (ASR = 3.9 per million, 95% CI = 3.2, 4.6), China (ASR = 3.9 per million, 95% CI = 3.0, 4.8) and Philippines (ASR = 4.3 per million, 95% CI = 3.8, 4.8). Between the 1970s and the 2000s, the incidence of renal carcinomas (VIb) doubled



**FIGURE 4** Age-standardised incidence rates (ASRs) of Wilms tumour and other non-epithelial renal tumours in children aged 0 to 14 years in the selected registries in IICC-1,<sup>21</sup> IICC-2<sup>22</sup> and IICC-3.<sup>23</sup> The selected registries are those that contributed data for similarly defined populations to all three International Incidence of Childhood Cancer (IICC) volumes<sup>21-23</sup> and reported 15 or more renal tumour cases in each volume. ASR, age-standardised incidence rate. \*Data from regional registries were pooled (India: Bangalore and Mumbai, Japan: Miyagi and Osaka, Philippines: Manila and Rizal, USA: SEER9, Los Angeles and New York State). The selected cases were those classified to the International Classification of Childhood Cancer (ICCC) subgroup VIa in each IICC volume, although the definition of this subgroup differed slightly between the three sources<sup>21-23</sup> [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

from 0.1 to 0.2 per million (IRR = 2.0, 95% CI = 1.5, 2.7), while the incidence for WT (VIa) slightly increased from 6.9 to 7.7 per million (IRR = 1.1, 95% CI = 1.0, 1.2) and the incidence of unspecified malignant renal tumours (VIc) halved from 0.2 to 0.1 per million (IRR = 0.5, 95% CI = 0.3, 0.8; Table S6).

## 4 | DISCUSSION

In our study, we assessed the geographical and temporal distribution of renal tumours by type in children (age 0-14 years) and adolescents (age 15-19 years), using comparable quality data provided by all population-based cancer registries worldwide over the study period. Our analyses were based on diverse populations, both geographically and ethnically, and included over 16 000 cases incident in the period 2001 to 2010.

### 4.1 | Wilms tumour

The high incidence of WT in the Black population of the USA and in the predominantly White populations of North America and Europe and the comparably lower rates in Asian populations in our study are

consistent with previous reports.<sup>2,3</sup> A relatively small study from 2004 comparing somatic genetics of WT showed a far lower proportion of WT with abnormalities of the insulin-like growth factor 2 gene locus (IGF-2) in the sample of 21 tumours from Japan than for the 41 tumours from White children in New Zealand.<sup>33</sup> A larger study of 114 WT in Japanese children also showed a lower proportion of loss of imprinting of IGF-2 (IGF-2 LOI) than in Caucasian population.<sup>34</sup> IGF-2 driven WT are associated with overgrowth syndromes and with perilobar nephrogenic rests; both these features are more common in White children with an older age at diagnosis.<sup>33,35</sup> Although larger samples, including from other countries or ethnic groups would be needed to validate these associations, the observation of the incidence peak in infancy and the lower total incidence in East Asian population in our study is consistent with the genetic origin of WT aetiology. Genetic nature of WT is further confirmed by the earlier age at diagnosis of bilateral than unilateral tumours, as observed previously in Europe<sup>4</sup> and the USA<sup>36,37</sup>, in consistency with the two-hit hypothesis.<sup>9</sup> The proportion of bilateral WT (8.9%) we found was slightly higher than in previous reports (5-8%).<sup>7,8</sup> This might indicate improved diagnostic imaging procedure, improved reporting, or improved identification of bilateral tumours.

Our finding of a 90% majority of WT in the group of all renal tumours from the age of 1 to 7 years, observed in large populations,

may be used in making therapeutic recommendations about the applicable age range for omitting biopsy before preoperative chemotherapy, which has been discussed in European clinical study groups.<sup>38,39</sup>

We did not observe temporal trends in the incidence of WT within the period 1996 to 2010, suggesting that environmental factors play a marginal role in the aetiology of this tumour, although the modifiable risk factors for WT are not well understood. Folic acid diet fortification in the USA was suggested as a possible driver of a reduction of the WT incidence.<sup>40</sup> However, the absence of temporal trend in the USA seen in our study suggests that a careful interpretation and a more specific study are required to confirm this association and elucidate mechanisms. The reasons for the increase in Southeast Asia are unclear but might include better diagnosis or registration, whereby more renal tumours may be now classified as WT rather than unspecified. The relatively high proportions of DCO cases, NOS histology and a low MV in this region indicate that there remains a scope for data quality improvement.

#### 4.2 | Rhabdoid renal tumour

Our data show the rare and early life occurrence of rhabdoid renal tumour. Switch/sucrose nonfermentable (SWI/SNF) related, matrix associated, actin dependent regulator (SMARCB1), a core subunit of the SWI/SNF chromatin-remodelling complex, is inactivated in the large majority of rhabdoid tumours, and germline heterozygous SMARCB1 mutations form the basis for rhabdoid predisposition syndrome.<sup>41</sup> Based on these findings, diagnostic accuracy has improved recently.<sup>42</sup> The present study, in which incidence of rhabdoid renal tumour was increasing while the total incidence of the combined category VI was stable, may suggest an improved recognition of this entity by pathologists. Possibly, some of these cases could have been previously also classified as unspecified malignant renal tumours (VIc); which we have shown has decreased. Rhabdoid tumour of the kidney is the most aggressive childhood renal tumour.<sup>14,43</sup> The survival of this type of tumour is under 50% in clinical trials; a young age at diagnosis is a poor prognostic factor.<sup>14</sup>

#### 4.3 | Kidney sarcomas

In our study, we estimated, to the best of our knowledge for the first time, the international patterns of incidence of clear cell sarcoma of kidney (CCSK), using the large number of these cases. The incidence in males was nearly twofold of that in females under 15 years of age, similar to that seen in clinical trial setting.<sup>16</sup> Recent studies demonstrated that the majority of CCSK have somatic internal tandem duplication (ITD) in X-linked BCOR affecting the 3' part of the exon 16 coding sequence.<sup>16,44-46</sup> A minority of cases have a somatic translocation t(10:17)(q22;p13) resulting in a fusion of *YWHAE* with either *NUTM2B* or *NUTM2E*. After the introduction of more intensive treatment schedules, the outcome of patients diagnosed with CCSK has improved substantially.<sup>16</sup> However, considering the minority of

patients who do not have a favourable prognostic clinical signature (especially patients with stage IV disease, young patients and patients with relapsed disease), and the risk of long term side effects from more intensive therapy, novel approaches to their treatment strategy are still needed.<sup>16</sup> International collaboration is essential to collect epidemiological and clinical data and biological samples as well as to implement clinical trials for these very rare renal tumours.

#### 4.4 | Renal carcinomas

We have shown that renal carcinomas became progressively more common with age, so that by the age of 14 years they represented 50% of renal tumours. Especially high incidence was observed in the Black population of the USA, in which all-age incidence is also high.<sup>20</sup> The high proportion of the medullary carcinoma seen in the Black children and adolescents in the USA indicates a link with sickle cell disease<sup>19</sup>; sickle cell trait affecting 7.3% of Black newborns.<sup>47</sup> We observed increase in incidence in males before the age of 15 years and in females in the age 15 to 19 years over time. The increase may reflect a wider use of imaging diagnostic techniques<sup>48</sup> and growing exposure to dietary risk factors,<sup>49</sup> obesity<sup>50</sup> or medications, even in the young population. All-age incidence was shown to be increasing in both sexes, most notably in Latin America<sup>20</sup> where the purported reasons for this increase include better diagnosis as well as increasing prevalence of obesity among other factors.<sup>20</sup> Although renal carcinomas may arise as a second cancer in survivors of childhood cancer,<sup>51</sup> only 34 cases of 1009 cases (3%) in the age group 0-19 years were registered as subsequent cancers during 2001-2010 in our study and these cannot explain the marked incidence rise. Further investigation is required to clarify the reason for the increase in incidence of renal carcinomas in children and adolescents.

#### 4.5 | Unspecified malignant renal tumours

The observed decrease in the incidence of unspecified malignant renal tumours (VIc) is encouraging, as it is likely to reflect more precise diagnosis and the ensuing more precise coding of renal tumours. A lack of imaging and diagnostic tests available in Sub-Saharan Africa influences also the diagnosis of other childhood malignancies, especially leukaemia and central nervous system tumours, and may explain the high proportion of renal tumours among all malignancies in this region.

#### 4.6 | Strengths and limitations

The foremost strength of our study is its large size allowing detection of population patterns even for very rare entities. While the largest previous study of international patterns in the incidence of renal tumours included 163 cases in the Black population of the USA,<sup>2</sup> our study included over 900 such cases. The ethnic and geographical diversity of the covered populations allows conclusions to be drawn on patterns of distributions of the larger diagnostic entities, notably WT and renal

carcinomas by geography, ethnicity, sex, age and laterality. Some of the data used spanned over more than 40 years of observations, which allowed assessment of long-term time trends. Our study thus provides the most complete overview of incidence patterns and trends of renal tumours in children to date and, for the first time, describes the incidence patterns of rhabdoid renal tumour, kidney sarcomas and renal tumours in adolescents aged 15 to 19 years.

On the other hand, the proportion of cases from low and middle-income countries available for our study was low and an even smaller proportion could be included in the time trends analyses. Our comparison with the results from IICC-1<sup>21</sup> and IICC-2<sup>22</sup> is indicative of the direction of the change, as the covered periods and areas might have differed somewhat between the three studies. Although the target periods of the two previous volumes were the 1970s and 1980s respectively, the time periods of the contributing registries differed both in length and starting years. Classification of renal tumours has also evolved over time and the categories of rhabdoid renal tumour and kidney sarcomas, which were not reported separately in the data of IICC-1 and IICC-2, might have been grouped with WT or possibly with the unspecified tumours.

Although the quality indicators (microscopic verification [MV], registrations from death certificate only [DCO], not otherwise specified [NOS]) were considered satisfactory in the IICC-3 data, they were less favourable in adolescents and in some world regions. In some subgroups, the proportion of MV was as low as two-thirds of all cases, however, microscopic verification is not required for establishing the diagnosis of WT.<sup>52</sup> The proportion of unspecified tumours was decreasing over the study period and was satisfactorily low in children in virtually all registries.

Variables requested from the population-based cancer registries were limited to essential information on a patient and a tumour and collection of further data items would be an asset, in addition to further improvement of data quality. In particular, it would be useful to collect complete information on laterality of WT from more registries, as well as additional information on associated congenital malformations, stage or extent of disease at diagnosis, types of treatment and follow-up of patients for vital status.

## 5 | CONCLUSIONS

In our study, we provide the most complete global overview of geographical patterns and time trends of incidence of renal tumours, combined and by type, for the most recent 15-year period in children aged 0 to 14 years and, for the first time, in adolescents aged 15 to 19 years. The observed incidence patterns of WT, the most common renal tumour in children, are consistent with a likely genetic origin. The increase in renal carcinomas with age and over time, which differs by sex, is likely caused by environmental risk factors possibly including lifestyle or improving diagnostic procedure. The strengths and weaknesses of the presented data indicate the need to secure further expansion and improvement in quality of cancer registration on local, national, and international levels.

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## CONFLICT OF INTEREST

All authors declare to have no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data used in our study were extracted from the databases of the referred studies<sup>21-23</sup>; much of this information is in the public domain. Datasets used for statistical analyses will be made available upon reasonable request and permissions granted by the data contributors.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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*Oceania*—Australia: H. Phung (Australian Capital Territory Cancer Registry); S. Rushton (New South Wales Central Australia Cancer Registry); S. Q. Li (Northern Territory Cancer Registry); E. Walpole (Queensland Cancer Registry); K. D'Onise (South Australian Cancer Registry); A. Venn (Tasmanian Cancer Registry); V. Thursfield (Victorian Cancer Registry); R. Trevithick (Western Australian Cancer Registry); France, French Polynesia: Laure Yen Kai Sun (French Polynesia Cancer Registry); France, New Caledonia: S. Laumond (New Caledonia Cancer Registry); New Zealand: C. Fowler (New Zealand Cancer Registry); K. Ballantine (New Zealand Children's Cancer Registry).