Incidence of childhood renal tumours: an international population-based study

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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; ICCC: International Classification of Childhood Cancer; ICD-O-3: 3rd edition of the International Classification of Diseases for Oncology; IGF-2: insulin-like growth factor 2 gene locus; IGF-2 LOI: loss of imprinting of IGF-2; 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 non-fermentable; WT: Wilms tumour

Novelty and Impact

In this study, including more than 16,000 cases, we observe and interpret worldwide patterns of malignant renal tumours in children and adolescents. Using the large database of the International Incidence of Childhood Cancer, we also describe the distribution of rare entities such as rhabdoid renal tumour or kidney sarcomas. This collaboration of 163 registries also generates definitive data on the stable incidence of Wilms tumour and the rising incidence of renal carcinomas, which warrant further monitoring.

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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 USA. 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 USA, 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. During 1996-2010, incidence remained mostly stable for WT (average annual 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.

Introduction

Malignant renal tumours represent 5% of all cancers occurring before the age of 15 years[1]. 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[1-5]. In the 1970s, the incidence of WT in Black populations was three times that in East Asian populations[2]. Age distribution at diagnosis also differed between populations; the peak incidence ranged between one and three years of age in White populations, while in East Asia it peaked in infants (children younger than 1 year)[2, 4]. WT is one of the few childhood cancers that is reported to be approximately 10% more common in females than in males[1] although a female excess was not seen in the East Asian populations in the 1970s[2]. Incidence rates were increasing in Europe by 0.7% per year in the period 1978-1997[4] whereas they were stable in the USA during 2001-2009[5].

WT often presents as a solitary lesion, but approximately 7% were reported to be multicentric and 5-8% bilateral[4, 6-8]. Unilateral tumours occur at a slightly older age than bilateral ones, in accordance with Knudson's two hit hypothesis[9]. Approximately 10% of WT occur as part of several distinct congenital malformation syndromes[7]. Overgrowth syndromes, in particular Beckwith–Wiedemann syndrome carry an approximately 5% risk of developing WT[10]. 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[11-13].

Rhabdoid renal tumour is a rare aggressive cancer occurring in infancy and early childhood. It was recognized as a distinct tumour type in 1978, although initially it

was classified as a possible rhabdomyosarcomatoid variant of WT[14]. It is associated with mutation of the INI1 gene on chromosome 22q in both renal and non-renal rhabdoid tumours[15].

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[16]. 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 [17, 18]. Renal medullary carcinoma is reported to occur in young individuals with sickle cell trait[19]. All-age incidence of renal carcinomas were shown to be increasing[20], 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)[21-23]. 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[2].

In this 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 0-14 years and adolescents aged 15-19 years in the period 2001-2010. We also examined the temporal changes in incidence over the 15-year period 1996-2010, and long term time trends using information from all three volumes of IICC[21-23]. The results are interpreted in terms of their impact on cancer control in the childhood and adolescent population.

Methods

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[1, 23]. The quality and comparability of the data included in the IICC-3 database were assessed and improved during a thorough peer-review process[1, 24] 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)[25] were extracted from the IICC-3 database. Malignant renal tumours constitute diagnostic group VI of ICCC-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 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3)[26, 27].

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[24].

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 0-14 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 2001-2010 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 racial or 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[1]. 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 1996-2010 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[21-23] 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 0-14 years in the IICC-1[21] and IICC-2[22], 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.

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 0-14 or 0-19 were adjusted using direct standardisation method and the weights 12, 10, 9 and 9 for the four respective age groups[28], as in the previous publication[1]. 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 0-14 years as the quotient of the age-standardised incidence rate for males divided by that for females and in the age group 15-19 years M/F was calculated as the quotient of the age-specific incidence rates. The 95% confidence intervals (CI) were calculated by standard methods[29, 30]. Change in incidence rates over the period 1996-2010 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 0-14 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[29].

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

Results

In total, 15,320 renal tumours in children aged 0-14 years occurring in 2.1 billion person-years and 800 renal tumours in adolescents aged 15-19 occurring in 583 million person-years were included in the analyses for the decade 2001-2010 (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).

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 2001-2010, 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.

Variation in incidence by tumour type and sex

WT (defined as VIa1 in Table S1) was the most common renal tumour in children aged 0-14 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=0.9, 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 2001-2010, 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 0-14 years, representing 3% and 2% of renal tumours respectively. Clear cell sarcoma of kidney (CCSK) constituted wholly the division of kidney sarcomas (VIa3). Incidence of rhabdoid renal tumour (VIa2) 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 (VIa3) 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.

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 the period 2001-2010. 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 6,396 WT cases from registries with reliable data on laterality, 5,764 (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 two 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, 1,009 renal carcinomas were reported in age 0-19 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).

Time trends in incidence during 1996-2010

Incidence time trends in the period 1996-2010 are shown in Figure 3 and Table S4. The incidence rates were stable for the entire group of renal tumours (VI) in children aged 0-14 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). 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 0-14 years have shown an increase in incidence of rhabdoid renal tumour (VIa2), (AAPC=3.7, 95%CI= 0.2, 7.5) and renal carcinomas. 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 15-19 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 0-14 years (Table S4).

Incidence trends and geographical variations in children aged 0-14 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, 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 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).

Discussion

In this 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 2001-2010.

Wilms Tumour (WT)

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[2, 3]. 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[33]. 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[34]. 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[33, 35]. 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[4] and the USA[36, 37] , in consistency with the two-hit hypothesis[9]. The proportion of bilateral WT (8.9%) we found was slightly higher than in previous reports (5-8%)[7, 8]. 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[38, 39].

We did not observe temporal trends in the incidence of WT within the period 1996-2010, 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[40]. However, the absence of temporal trend in the USA seen in this 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 is still a scope for data quality improvement.

Rhabdoid renal tumour

Our data show the rare and early life occurrence of rhabdoid renal tumour. Switch/sucrose non-fermentable (SWI/SNF) related, matrix associated, actin dependent regulator (SMARCB1), a core subunit of the SWI/SNF chromatin-remodeling complex, is inactivated in the large majority of rhabdoid tumours, and germline heterozygous SMARCB1 mutations form the basis for rhabdoid predisposition syndrome[41]. Based on these findings, diagnostic accuracy has improved recently[42]. 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[14, 43]. The survival of this type of tumour is under 50% in clinical trials; a young age at diagnosis is a poor prognostic factor[14].

Kidney sarcomas

In this study, we estimated, to 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 two-fold of that in females under

15 years of age, similar to that seen in clinical trial setting[44]. 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[44-47]. 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[44]. 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[44]. 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.

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[20]. The high proportion of the medullary carcinoma seen in the Black children and adolescents in the USA indicates a link with sickle cell disease[19]; sickle cell trait affects 7.3% of Black newborns[48]. We observed increase in incidence in males before the age of 15 years and in females in the age 15-19 years over time. The increase may reflect a wider use of imaging diagnostic techniques[49] and growing exposure to dietary risk factors[50], obesity[51] or medications, even in the young population. All-age incidence was shown to be increasing in both sexes, most notably in Latin America[20] where the purported reasons for this increase include

better diagnosis as well as increasing prevalence of obesity among other factors[20]. Although renal carcinomas may arise as a second cancer in survivors of childhood cancer[52], only 34 cases of 1,009 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.

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 CNS tumours, and may explain the high proportion of renal tumours among all malignancies in this region.

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[2], 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. This 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 15-19 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[21] and IICC-2[22] 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[53]. 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.

Conclusions

In this 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 0-14 years and, for the first time, in adolescents aged 15-19 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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Disclaimer

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Conflict of interest

All authors declare to have no conflict of interest.

Declarations

Selected preliminary results were displayed in a poster of the 51th congress of the International Society of Paediatric Oncology and the abstract of this communication was published in Pediatric Blood and Cancer, Volume66, IssueS4 (https://doi.org/10.1002/pbc.27989).

Data accessibility

The data used in this study were extracted from the databases of the referred studies[21-23]; 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.

References

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesseling P, Shin HY, Stiller CA, IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. The Lancet Oncology 2017;18: 719-731.

2. Stiller CA, Parkin DM. International variations in the incidence of childhood renal tumours. Br J Cancer 1990;62: 1026-1030.

3. Nakata K, Ito Y, Magadi W, Bonaventure A, Stiller CA, Katanoda K, Matsuda T, Miyashiro I, Pritchard-Jones K, Rachet B. Childhood cancer incidence and survival in Japan and England: A population-based study (1993-2010). Cancer Sci 2018;109: 422-434.

4. Pastore G, Znaor A, Spreafico F, Graf N, Pritchard-Jones K, Steliarova-Foucher E. Malignant renal tumours incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42: 2103-2114.

5. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. Pediatrics 2014;134: e945-955.

6. Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Fourth edition. Lyon: International Agency for Research on Cancer, 2016.

7. Perlman EJ, Grosfeld JL, Togashi K, Boccon-Gibod L. Nephroblastoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press, 2004.

8. Charlton J, Irtan S, Bergeron C, Pritchard-Jones K. Bilateral Wilms tumour: a review of clinical and molecular features. Expert Rev Mol Med 2017;19: e8.

9. Knudson AG, Jr., Strong LC. Mutation and cancer: a model for Wilms' tumor of the kidney. JNCI Journal of the National Cancer Institute 1972;48: 313-324.

10. Little J, eds. Epidemiology of childhood cancer. IARC scientific publication N149. Lyon, France: International Agency for Research on Cancer, 1999. 386p.

11. Breslow NE, Norris R, Norkool PA, Kang T, Beckwith JB, Perlman EJ, Ritchey ML, Green DM, Nichols KE, National Wilms Tumor Study Group. Characteristics and outcomes of children with the Wilms tumor-Aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol 2003;21: 4579-4585.

12. Brok J, Treger TD, Gooskens SL, van den Heuvel-Eibrink MM, Pritchard-Jones K. Biology and treatment of renal tumours in childhood. Eur J Cancer 2016;68: 179-195.

13. Treger TD, Chowdhury T, Pritchard-Jones K, Behjati S. The genetic changes of Wilms tumour. Nature reviews Nephrology 2019;15: 240-251.

14. Tomlinson GE, Breslow NE, Dome J, Guthrie KA, Norkool P, Li S, Thomas PR, Perlman E, Beckwith JB, D'Angio GJ, Green DM. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. J Clin Oncol 2005;23: 7641-7645.

15. Biegel JA, Tan L, Zhang F, Wainwright L, Russo P, Rorke LB. Alterations of the *hSNF5/INI1* Gene in Central Nervous System Atypical Teratoid/Rhabdoid Tumors and Renal and Extrarenal Rhabdoid Tumors. Clinical Cancer Research 2002;8: 3461-3467.

16. Gooskens SL, Graf N, Furtwangler R, Spreafico F, Bergeron C, Ramirez-Villar GL, Godzinski J, Rube C, Janssens GO, Vujanic GM, Leuschner I, Coulomb-L'Hermine A, et al. Position paper: Rationale for the treatment of children with CCSK in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol 2018;15: 309-319.

17. Argani P, Antonescu CR, Illei PB, Lui MY, Timmons CF, Newbury R, Reuter VE, Garvin AJ, Perez-Atayde AR, Fletcher JA, Beckwith JB, Bridge JA, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol 2001;159: 179-192.

18. Young EE, Brown CT, Merguerian PA, Akhavan A. Pediatric and adolescent renal cell carcinoma. Urol Oncol 2016;34: 42-49.

19. Alvarez O, Rodriguez MM, Jordan L, Sarnaik S. Renal medullary carcinoma and sickle cell trait: A systematic review. Pediatr Blood Cancer 2015;62: 1694-1699.

20. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International Variations and Trends in Renal Cell Carcinoma Incidence and Mortality. European Urology 2015;67: 519-530.

21. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. International Incidence of Childhood Cancer. Lyon, France: International Agency for Research on Cancer, 1988.

22. Parkin DM, Kramarova E, Draper GJ, Masuyer E, Michaelis J, Neglia J, Qureshi S, Stiller CA, eds. International Incidence of Childhood Cancer, Volume II. Lyon, France: International Agency for Research on Cancer, 1998.

23. Steliarova-Foucher E, Colombet M, Ries LAG, Hesseling P, Moreno F, Shin HY, Stiller CA. International Incidence of Childhood Cancer, Volume III (electronic version) Lyon: International Agency for Research on Cancer, 2017.

24. Steliarova-Foucher E, Stiller C, Colombet M, Dolya A, Moreno F, Ries LAG. Data quality and comparability. In: Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Shin HY, Hesseling P, Stiller C. International Incidence of Childhood Cancer, volume III: International Agency for Research on Cancer, In press.

25. Steliarova-Foucher E, Colombet M, Ries LAG, Rous B, Stiller CA. Classification of tumours. In: Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Shin HY, Hesseling P, Stiller CA. International Incidence of Childhood Cancer, Volume III. Lyon: International Agency for Research on Cancer, In press.

26. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, eds. International Classification of Diseases for Oncology, Third Edition. Geneva: World Health Organization, 2000.

27. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, eds. International Classification of Diseases for Oncology, Third Edition, First Revision. Geneva: World Health Organization, 2013.

28. Segi M, Cancer mortality for selected sites in 24 countries (1950-1957). Department of Public Health, Tohoku University School of Medicine, 1960.

29. Rothman KJ. Modern Epidemiology. Boston: Little, Brown, 1986.

30. Long JS, Freese J. Regression Models for Categorical Dependent Variables Using Stata, 3rd ed. College Station, TX: Stata Press, 2001.

31. StataCorp. Stata Statistical Software: Release 12 College Station. TX: StataCorp LP, 2011.

32. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19: 335-351.

33. Fukuzawa R, Breslow NE, Morison IM, Dwyer P, Kusafuka T, Kobayashi Y, Becroft DM, Beckwith JB, Perlman EJ, Reeve AE. Epigenetic differences between Wilms' tumours in white and east-Asian children. Lancet 2004;363: 446-451.

34. Haruta M, Arai Y, Watanabe N, Fujiwara Y, Honda S, Ohshima J, Kasai F, Nakadate H, Horie H, Okita H, Hata J, Fukuzawa M, et al. Different incidences of epigenetic but not genetic abnormalities between Wilms tumors in Japanese and Caucasian children. Cancer Sci 2012;103: 1129-1135.

35. Breslow NE, Beckwith JB, Perlman EJ, Reeve AE. Age distributions, birth weights, nephrogenic rests, and heterogeneity in the pathogenesis of Wilms tumor. Pediatr Blood Cancer 2006;47: 260-267.

36. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. Medical and pediatric oncology 1993;21: 172-181.

37. Breslow N, Beckwith J, Ciol M, Sharples K. Age distribution of Wilms' tumor: report from the National Wilms' Tumor Study. Cancer Res 1988;48: 1653-1657.

38. de la Monneraye Y, Michon J, Pacquement H, Aerts I, Orbach D, Doz F, Bourdeaut F, Sarnacki S, Philippe-Chomette P, Audry G, Coulomb A, Freneaux P, et al. Indications and results of

diagnostic biopsy in pediatric renal tumors: A retrospective analysis of 317 patients with critical review of SIOP guidelines. Pediatr Blood Cancer 2019;66: e27641.

39. Jackson TJ, Williams RD, Brok J, Chowdhury T, Ronghe M, Powis M, Pritchard-Jones K, Vujanic GM, Children's Cancer Leukaemia Group Renal Tumours Group. The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy: Report of the UK experience in the SIOP UK WT 2001 trial. Pediatr Blood Cancer 2019;66: e27627.

40. Linabery AM, Johnson KJ, Ross JA. Childhood cancer incidence trends in association with US folic acid fortification (1986-2008). Pediatrics 2012;129: 1125-1133.

41. Kim KH, Roberts CW. Mechanisms by which SMARCB1 loss drives rhabdoid tumor growth. Cancer Genet 2014;207: 365-372.

42. Kinoshita Y, Tamiya S, Oda Y, Mimori K, Inoue H, Ohta S, Tajiri T, Suita S, Tsuneyoshi M. Establishment and characterization of malignant rhabdoid tumor of the kidney. Oncology reports 2001;8: 43-48.

43. Furtwangler R, Kager L, Melchior P, Rube C, Ebinger M, Nourkami-Tutdibi N, Niggli F, Warmann S, Hubertus J, Amman G, Leuschner I, Vokuhl C, et al. High-dose treatment for malignant rhabdoid tumor of the kidney: No evidence for improved survival-The Gesellschaft fur Padiatrische Onkologie und Hamatologie (GPOH) experience. Pediatric blood & cancer 2018;65.

44. Gooskens SL, Graf N, Furtwangler R, Spreafico F, Bergeron C, Ramirez-Villar GL, Godzinski J, Rube C, Janssens GO, Vujanic GM, Leuschner I, Coulomb-L'Hermine A, et al. Position paper: Rationale for the treatment of children with CCSK in the UMBRELLA SIOP-RTSG 2016 protocol. Nature reviews Urology 2018;15: 309-319.

45. Astolfi A, Melchionda F, Perotti D, Fois M, Indio V, Urbini M, Genovese CG, Collini P, Salfi N, Nantron M, D'Angelo P, Spreafico F, et al. Whole transcriptome sequencing identifies BCOR internal tandem duplication as a common feature of clear cell sarcoma of the kidney. Oncotarget 2015;6: 40934-40939.

46. Roy A, Kumar V, Zorman B, Fang E, Haines KM, Doddapaneni H, Hampton OA, White S, Bavle AA, Patel NR, Eldin KW, John Hicks M, et al. Recurrent internal tandem duplications of BCOR in clear cell sarcoma of the kidney. Nature communications 2015;6: 8891.

47. Ueno-Yokohata H, Okita H, Nakasato K, Akimoto S, Hata J, Koshinaga T, Fukuzawa M, Kiyokawa N. Consistent in-frame internal tandem duplications of BCOR characterize clear cell sarcoma of the kidney. Nat Genet 2015;47: 861-863.

48. Ojodu J, Hulihan MM, Pope SN, Grant AM, Centers for Disease Control and Prevention. Incidence of sickle cell trait--United States, 2010. MMWR Morbidity and mortality weekly report 2014;63: 1155-1158.

49. Leao RR, Ahmad AE, Richard PO. Should Small Renal Masses Be Biopsied? Current urology reports 2017;18: 7.

50. Melkonian SC, Daniel CR, Ye Y, Tannir NM, Karam JA, Matin SF, Wood CG, Wu X. Gene-environment interaction of genome-wide association study-identified susceptibility loci and meat-cooking mutagens in the etiology of renal cell carcinoma. Cancer 2016;122: 108-115.

51. Landberg A, Falt A, Montgomery S, Sundqvist P, Fall K. Overweight and obesity during adolescence increases the risk of renal cell carcinoma. Int J Cancer 2019;145: 1232-1237.

52. Wilson CL, Ness KK, Neglia JP, Hammond S, Shnorhavorian M, Leisenring WL, Stovall M, Robison LL, Armstrong GT. Renal carcinoma after childhood cancer: a report from the childhood cancer survivor study. Journal of the National Cancer Institute 2013;105: 504-508.

53. Ferlay J, Burkhard C, Whelan S, Parkin DM, eds. Check and conversion programs for cancer registries (IARC/IACR Tools for Cancer Registries). Lyon: International Agency for Research on Cancer, 2005.

Figure legends

Figure 1. Age-standardised incidence rates (ASRs) of renal tumours in children aged 0-14 years by world region and ethnicity, 2001-2010 (N=15,320). Source: International Incidence of Childhood Cancer, volume 3[23]. 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.

Figure 2. Age-specific incidence of renal tumours, all world regions combined, 2001-2010. Source: International Incidence of Childhood Cancer, volume 3[23]. 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=6,396). b) Rhabdoid renal tumour (N=327) and kidney sarcomas (N=431). c) Renal carcinomas (N=1,009). *Only the registries providing information on the laterality for at least 95% Wilms tumour cases are included.

Figure 3. Time trends in incidence of renal tumours, all world regions combined, 1996-2010 (N=11,170) . Source: International Incidence of Childhood Cancer, volume 3[23]. 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.

Figure 4. Age-standardised incidence rates (ASRs) of Wilms tumour and other non-epithelial renal tumours in children aged 0-14 years in the selected registries in IICC-

1[21], IICC-2[22] and IICC-3[23]. The selected registries are those that contributed data for similarly defined populations to all three International Incidence of Childhood Cancer (IICC) volumes[21-23] 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[21-23].