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Childhood nephroblastoma in Southern and Eastern Europe and the US: Incidence variations and temporal trends by human development index

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ABSTRACT

Background: Despite advances in the management of nephroblastoma (Wilms' tumor, WT), the etiology of the tumor remains obscure. We aimed to compare nephroblastoma incidence rates and time trends among children (0–14 years) in 12 Southern and Eastern European (SEE) countries and the Surveillance, Epidemiology, and End Results Program (SEER), USA, in relation to the human development index (HDI).

Methods: In total 1776 WT cases were recorded in 13 SEE collaborating registries (circa 1990–2016), whereas data on 2260 cases (1990–2012) were extracted from the SEER database. Age-standardized incidence rates (AIRs) were calculated and correlated with HDI, whereas temporal trends were evaluated using Poisson regression and Joinpoint analyses.

Results: The overall SEE AIR ($9.2/10^6$) was marginally higher than that of the SEER ($8.3/10^6$), whereas significant differences were noted among the 13 SEE registries which comprised mainly Caucasian populations. A statistically significant temporal increase in incidence was noted only in Belarus. Most cases (~75%) were diagnosed before the fifth year of life, with rates steadily declining thereafter; median age at diagnosis was similar in SEE countries and SEER. A slight male preponderance in the first year of life (male:female = 1.1) was

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followed by a female preponderance in the older age groups (male:female = 0.7). Lastly, a statistically significant positive association between higher HDI and increasing nephroblastoma incidence was noted (regression coefficient: +3.25, 95%CI: +1.35, +5.15).

Conclusions: Variations in incidence and time trends across the examined registries, changing male-to-female patterns with advancement in age, and positive associations with the HDI imply a plausible role for environmental and genetic factors in disease etiology, and these need to be explored further.

1. Introduction

Renal tumors account for around 6% of all pediatric cancers. Wilms' tumor (WT), also known as nephroblastoma, is the most common renal tumor (~90%) in children, with an annual incidence of six to nine per million children in White Caucasian populations [1–4]. Several studies have reported collectively on the incidence of renal tumors, which can be considered as a proxy for the WT incidence. An annual increase of < 1% in WT incidence in Europe during the 1978–1997 period was reported by the Automated Childhood Cancer Information System project (ACCIS) and was attributed mainly to increases identified in southern and eastern regions, especially among infants and young children [3]. In the same report the highest age-standardized incidence rate (AIR) for renal tumors, essentially reflecting that of WT, was found in the West. A recent publication on the 'International incidence of childhood cancer, 2001–10′ reported equally high AIRs of the disease in the western and eastern (9.8) regions, followed by the northern (9.3) and southern (9.1) regions of Europe [5].

Wilms' tumor is an embryonal type of cancer, and in 5–10% of cases may occur as part of a genetic predisposition syndrome, such as WAGR (Wilms' tumor–aniridia–genitourinary abnormalities–mental retardation), Denys–Drash, Beckwith–Wiedemann, Simpson–Golabi–Behmel, Perlman, and Li-Fraumeni syndromes [6]. On the other hand, several non-syndromic malformations are also associated with WT, including asymmetric overgrowth (hemihypertrophy) and genitourinary abnormalities. Genetic alterations – including mutations of the WT1 gene on chromosome 11p13, of the β-catenin gene (CTNNB1), deletions of the PAX6 gene, loss of heterozygocity at 11p15, as well as chromosomal copy number gains (1q) and losses (1p/16q) – are reported to be related to an increased risk of WT [7]. Approximately 2% of the patients have a family history of WT, but even sporadic cases are thought to have a strong genetic component in their etiology [8].

The median age at diagnosis is 3.5 years, and > 80% of all WT cases are diagnosed before the age of 5 years [9]. Age differences in relation to gender and race/ethnicity have been also identified [1]. The distribution of nephrogenic rests, which are thought to be the precursor lesions of Wilms' tumors, varies by race. Nephrogenic rests are present in 40% of WT patients and in 90% of bilateral (stage V) cases [10]. Moreover, previous studies have shown that ethnicity affects the incidence rates more than the geographical region of residence [11].

Overall, there is a paucity of data regarding risk factors other than age, race/ethnicity, genetic and familial features. The human development index (HDI) [12], representing a composite score of the level of development of each country, seems also to be implicated in the etiology of the disease as it positively correlates with increasing WT incidence [13]. Since 2009, the Nationwide Registry of Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST; narechem.gr) in Greece has expanded to include the most common renal tumor, namely WT. We aimed to calculate, for the first time, incidence rates and trends and to compare our data with those from Southern and Eastern Europe (SEE), as derived from an informal network of 13 regional or national cancer registries operating in 12 countries, and the Surveillance, Epidemiology, and End Results Program (SEER), USA. Additional comparisons of temporal trends and examination of socioeconomic differentials, using the HDI as a proxy, were undertaken in the hope of generating tentative etiological hypotheses.

2. Methods

2.1. Participating registries and variables of interest

A network of 13 registries operating in 12 SEE countries (Belarus, Croatia, Cyprus, Greece, Malta, Poland, Portugal, Romania, Serbia, Slovenia, Turkey, and Ukraine), initiated in the context of the EUROCOURSE project [14–16], provided data on childhood (0–14 years) WT cases diagnosed during registration periods circa 1990–2016. Respective data were also extracted from the SEER (US) database over the period 1990–2012 (last available year) [17–19].

Disease classification followed the International Classification of Diseases for Oncology – 3rd Edition (ICD-O-3) coded morphology and behavior [20] and the European Network for Cancer Registries recommendations [21]. Regarding morphological classification, only nephroblastoma cases based on the ICD-O-3 code 8960 were included in the analyses [22].

Other study variables included demographic data (age at diagnosis, gender) and HDI. The latter has been developed by the United Nations Development Program (UNDP) and is a summary measure of average achievement in three key dimensions of human development: life expectancy, education, and per-capita income indicators. In line with previous reports [23], we explored the potential association between HDI and incidence of WT in the participating cancer registries. The annual HDI values for each country during the respective available registration periods were extracted from the UNDP website [24]. The two Portuguese registries were merged for the common registration periods, for the purpose of obtaining single incidence rates for every country, whereas for the regional registry of Izmir the HDI value was obtained from another reference [25]. Based on the association of the Izmir HDI with the overall Turkey HDI in the period 1993–2007, we estimated the Izmir HDI for the last registration years, based on changes observed in the overall HDI for Turkey. Regarding the SEER, we used the overall USA HDI, which is considered to reflect the HDI of the SEER population that shares the same demographic characteristics with the overall US population. We also ran the HDI analyses after excluding the SEER data.

The underlying population characteristics for the corresponding registration years – stratified by age group, gender and calendar year – were also derived by the participating registries or were available online for the SEER database.

2.2. Statistical analysis

AIRs adjusted to the world (Segi) population and crude incidence rates (CIRs) were calculated in four age groups (< 1, 1–4, 5–9, 10–14 year s) for each cancer registry and overall, and were eventually expressed as cases per million children per year [26]. For the comparison of the medians, the median test for two samples was used. Annual percentage changes (APCs) of the incidence rates were estimated using Poisson regression analysis, whereas the presence of potential breaks in temporal trends was evaluated with joinpoint regression analysis.

The association between annual HDI values per country and the respective number of WT cases was evaluated using random effects Poisson regression to take into account the within-country variability. The underlying population was used as the offset variable, and year at