Epidemiology

2

Manish Pathak and Dattatray Bhusare

2.1 Introduction

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of the health problems. Epidemiology plays an important role in identifying the etiology and pathogenesis of various diseases including malignancies.

2.2 Incidence and Geographical Variation

Wilms' tumor (WT) is the most common renal tumor of childhood, affecting seven to eight per million person years in children. It accounts for 95% of all pediatric renal cancers and 6% of all cancers below 15 years of age [1–3]. More than 77% of children are diagnosed before 5 years of age [4]. Most of the tumors are unilateral with the incidence of bilateral WT ranges from 5 to 7% [1, 4, 5].

The gender-specific incidence is almost similar with slight female preponderance in most of the regions except in Eastern Asia [3, 6]. Initially the WT was thought to be an "index tumor" of childhood with little variation in tumor incidence between the different countries and ethnic groups [7]. However, the recent data has revealed the difference in incidence between different geographic regions and ethnic groups within that geographic region [8]. Cunningham et al. analyzed World Health Organization (WHO) International Incidence of Childhood Cancer (IICC) Volume III dataset and found that the median global incidence of WT was 7.7 (IQR 5.5–9.1) age-specified rate per million (ASR/million) [8].

Though the low-income countries (LIC) had the highest median incidence of WT at 9.8 (6.2–16.4) ASR/million, but the difference was not found to be statistically significant. The limited data from the LIC was one of the limitations of that analysis [8].

Steliarova-Foucher et al. did the study of the population-based registry of childhood cancer of the decade 2001–2010 [9]. World standard age-standardized rate (WSR) of 4.1 per million person years for the renal tumors was found to be lowest for India. The incidence varied in various geographic regions. The Eastern and Western Europe had WSR of 9.8, while Sub-Saharan Africa had the WSR of 6.7. The WSR in Native Americans in the USA was 9.3 in comparison to the highest WSR of 10.9 in American Blacks. Interestingly, the Asians and pacific islanders residing in the USA had the low WSR of 4.2, similar to that in Eastern and Southern Asia. This

M. Pathak (✉)
Department of Pediatric Surgery, All India Institute of Medical Sciences, Jodhpur, India

D. Bhusare
Department of Pediatric Surgery, Mahatma Gandhi Mission Medical College, Navi Mumbai, India

Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_2

indicates that ethnicity plays a major role on incidence of WT than the geographic residence [9].

2.3 Age and Sex Predisposition

There is slight female preponderance of the tumor with male-to-female ratio of 0.92:1.00 for those with unilateral disease and 0.68:1.00 for bilateral disease in the USA [10]. The mean age at diagnosis is about 6 months earlier in boys than girls. The mean age of diagnosis is 41.6 months in boys and 46.9 months in girls for unilateral disease [10]. It has been noted that patients of either gender with bilateral disease present approximately 1 year before those with unilateral disease. The unilateral multifocal tumor was found to be intermediate between unilateral and bilateral disease. The mean age at diagnosis for those who present with bilateral disease is 29.5 months for boys and 32.6 months for girls [10].

Pastore et al. extracted the data from the datasets of the Automated Childhood Cancer Information System (ACCIS) during the period 1988–1997 and analyzed the malignant renal tumors incidence and survival in European children. In their report male-to-female ratio was 0.9. There were bimodal peaks at age 1 and 3 years. The median age at diagnosis was 2 years for males and 3 years for females [4].

The median age at diagnosis of WT in South Africa has been reported to be 39 months, while the French African Pediatric Oncology Group found it to be 36 months [11, 12].

The NWTS data shows that WT occurs earlier in persons with Asian descent. The age at diagnosis was late in Blacks than Whites [10]. Similar trend was seen in international data and in Britain [6, 13]. All WT associated with congenital malformations except hemihypertrophy have younger age at diagnosis [10].

2.4 Causative Hypothesis and Role of Environmental Factors

The normal kidney develops from mesenchymal stem cells, under the inductive influence of ureteric bud on metanephric blastema. These metanephric blastemal cells completely disappear 4–6 weeks prior to birth. The abnormal persistence of these cells is labelled nephrogenic rest (NR), and multiple rests are called nephroblastomatosis [14, 15].

Most of these nephrogenic rests remain either dormant or regress, but some undergo hyperplastic or neoplastic proliferation. The neoplastic proliferation can either be benign (adenomatous rests) or malignant (WT) [14]. It has been hypothesized that mutational events in utero may be responsible for this abnormal presence of NR [15]. Higher incidence of WT in association with some congenital malformations and syndromes also suggest the role of mutation in its causation. The genetics and molecular biology of the WT has been discussed in detail separately, so we will not elaborate it further in this chapter.

The molecular and genetic studies may explain the inherited abnormalities and demonstrate the type and exact site of mutations. To identify the cause of new mutations and other acquired changes in the genome is still a challenge. The epidemiologic studies try to fill this gap by trying to identify the environmental causes of these acquired changes and determine the interaction between carcinogen and the genome [15]. WT being a rare disease, the case control studies are the most feasible studies to determine the causative factors leading to WT. The difficulty of conducting etiologic epidemiologic studies due to the rarity of WT has been circumvented by coupling the etiologic studies to the studies of the results of the Wilms tumor [15]. Various case control studies have been conducted to study the role of paternal occupational exposure and maternal occupational and hormonal exposure during pregnancy [16–22]. The various maternal exposure studies included radiation exposure, oral contraceptives, pesticides, tea, coffee, alcohol, hair dye, vaginal infection, etc. The paternal occupational exposure studies included exposure to hydrocarbon, lead, boron, paper mills, and farming with pesticides use before birth.

There have been inconsistencies in the pattern of exposure, and most of the studies had small number of cases. Based on this it seems unlikely that environmental exposure has any significant role to play in the pathogenesis of WT [15].

2.5 Syndromic and Non-syndromic Associations

WT is known to be associated with some predisposition syndromes, genetic abnormalities, and clinical malformations. Several overgrowth syndromes such as Beckwith-Weidman syndrome (BWS), Perlman syndrome, and Simpson-Golabi-Behmel syndrome have been associated with WT [23, 24]. BWS is the most common overgrowth syndrome with estimated prevalence of 1 in 14,000 [24]. It is linked with genetic or epigenetic abnormalities in WT2 gene at 11p15 region. Mutations of WT1 gene at 11p 13 is associated with other predisposition syndromes like Denys-Drash Syndrome (DDS), Frasier syndrome, WAGR syndrome, and bilateral WT [25]. Approximately 90% of the patients with DDS, 30% with WAGR syndrome, and 20–30% with BWS develop WT [24, 26, 27].

The non-syndromic malformations associated with WT include hemihypertrophy and genitourinary malformations. Hemihypertrophy may be isolated or can be associated with other predisposition syndrome like BWS. The risk of WT in patients with hemihypertrophy is 3–5% [24, 25]. Similarly, genitourinary malformations can be associated with other syndromes like DDS or WAGR. Isolated genitourinary malformations associated with WT include undescended testis, hypospadias, or kidney abnormalities. About 5% of the patients with WT have been found to have associated genitourinary malformations [24, 25].

2.6 WT in Low-Income Countries

The cooperative group clinical trials have demonstrated excellent results with more than 90% 5-year overall survival (OS) rate in WT [28, 29]. However, the OS of WT is still poor in developing countries and countries with lower socioeconomic development [30–35]. Several studies have been conducted to find out the causes of the sub-optimal results in LIC. It has been noted that Sub-Saharan African region has the high incidence of WT, delayed presentation, advanced stage at the time of diagnosis, and dismal outcome [35]. Rabeh et al. retrospectively reviewed the clinical records of 35 children with WT at a cancer institute in Lebanon. Half of their patients presented with advanced stage disease (III and IV), and a similar trend has been noted in most of the low- and middle-income countries (LMIC) [36]. The rate of bilateral tumors was also higher in their series (11%) than that observed in high-income countries.

This inferior outcome in developing countries may be due to socioeconomic factors like malnutrition, delayed and advanced stage of presentation, limited healthcare facilities, abandonment of the treatment, etc. However, there are some pointers like high incidence, higher proportion of bilateral tumors, and advanced stage at presentation suggesting that these tumors are biological different leading to the poor outcome. Murphy et al. did the molecular characterization of the WT patients of Kenyan origin (Sub-Saharan Africa) [35]. Based on the clinical features, DNA sequencing, immunohistochemistry, and imaging mass spectrometry (IMS), they suggested that these tumors have molecular features of aggressive phenotype. Thus, this unique tumor phenotype may be responsible for the disease aggressiveness and resistance to chemotherapy in this ethnic group [35].

2.7 Role of Tumor Registries

Tumor registries receive and collect data about cancer patients. These registries provide an important epidemiological data to the health professionals, researchers, administrators, and health policy makers. Tumor registries can be either population-based or hospital-based. The population-based registries collect data about the cancer from the general population. In comparison, the hospital-based registries maintain and collect the data about all the cancer patients managed in that hospital. There are special cancer registries also that maintain and collect data about a particular cancer type. International Association of Cancer Registries has members from most of the countries in the world. The percentage of population covered in these registries

varies widely among different countries. The countries with higher socioeconomic level of development and better treatment facilities have advanced tumor registration system and better reporting than those with LIC with poor socioeconomic system [9].

Benefits and role of the tumor registries include the following:

1. To know the current status of the disease in the population and determining the trends over time
2. To determine the cancer pattern among various populations and subpopulations
3. To identify the etiology and risk factors
4. To help in health policy decision-making by guiding the health resource allocation and determining the impact of various health interventions and cancer control efforts done at population level
5. To help in clinical and epidemiological research

References

1. Little J. Epidemiology of childhood cancer. Lyon: International Agency for Research on Cancer; 1999.
2. Bernstein L, Linet M, Smith MA, Olshan AF. Renal tumors. In: Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995.
3. Chu A, Heck JE, Ribeiro KB, Brennan P, Boffetta P, Buffler P, et al. Wilms' tumour: a systematic review of risk factors and meta-analysis. Paediatr Perinat Epidemiol. 2010;24:449–69. https://doi.org/10.1111/j.1365-3016.2010.01133.x.
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;42:2103–14. https://doi.org/10.1016/j.ejca.2006.05.010.
5. Green DM. Wilms' tumour. Eur J Cancer. 1997;33:409–18.
6. Stiller CA, Parkin DM. International variations in the incidence of childhood renal tumours. Br J Cancer. 1990;62:1026–30. https://doi.org/10.1038/bjc.1990.432.
7. Innis MD. Nephroblastoma: possible index cancer of childhood. Med J Aust. 1972;1:18–20. https://doi.org/10.5694/j.1326-5377.1972.tb46675.x.
8. Cunningham ME, Klug TD, Nuchtern JG, Chintagumpala MM, Venkatramani R, et al. Global disparities in Wilms tumor. J Surg Res. 2020;247:34–51. https://doi.org/10.1016/j.jss.2019.10.044.
9. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 2017;18:719–31. https://doi.org/10.1016/S1470-2045(17)30186-9.
10. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. Med Pediatr Oncol. 1993;21:172–81. https://doi.org/10.1002/mpo.2950210305.
11. Davidson A, Hartley P, Desai F, Daubenton J, Rode H, Millar A. Wilms tumour experience in a South African centre. Pediatr Blood Cancer. 2006;46:465–71. https://doi.org/10.1002/pbc.20388.
12. Moreira C, Nachef MN, Ziamati S, Ladjaj Y, Barsaoui S, Mallon B, et al. Treatment of nephroblastoma in Africa: results of the first French African pediatric oncology group (GFAOP) study. Pediatr Blood Cancer. 2012;58:37–42. https://doi.org/10.1002/pbc.23284.
13. Stiller CA, McKinney PA, Bunch KJ, Bailey CC, Lewis IJ. Childhood cancer and ethnic group in Britain: a United Kingdom children's Cancer Study Group (UKCCSG) study. Br J Cancer. 1991;64:543–8. https://doi.org/10.1038/bjc.1991.347.
14. Beckwith JB, Kiviat NB, Bonadio JF. Nephrogenic rests, nephroblastomatosis, and the pathogenesis of Wilms' tumor. Pediatr Pathol. 1990;10:1–36. https://doi.org/10.3109/15513819009067094.
15. Sharpe CR, Franco EL. Etiology of Wilms' tumor. Epidemiol Rev. 1995;17:415–32. https://doi.org/10.1093/oxfordjournals.epirev.a036201.
16. Bithell JF, Stewart AM. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br J Cancer. 1975;31:271–87. https://doi.org/10.1038/bjc.1975.62.
17. Bunin GR, Kramer S, Marrero O, Meadows AT. Gestational risk factors for Wilms' tumor: results of a case-control study. Cancer Res. 1987;47:2972–7.
18. Lindblad P, Zack M, Adami HO, Ericson A. Maternal and perinatal risk factors for Wilms' tumor: a nationwide nested case-control study in Sweden. Int J Cancer. 1992;51:38–41. https://doi.org/10.1002/ijc.2910510108.
19. Bunin GR, Nass CC, Kramer S, Meadows AT. Parental occupation and Wilms' tumor: results of a case-control study. Cancer Res. 1989;49:725–9.
20. Sharpe CR, Franco EL, de Camargo B, Lopes LF, Barreto JH, Johnsson RR, et al. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. Am J Epidemiol. 1995;141:210–7. https://doi.org/10.1093/oxfordjournals.aje.a117422.
21. Wilkins JR, Sinks TH Jr. Occupational exposures among fathers of children with Wilms' tumor. J Occup Med. 1984;26:427–35. https://doi.org/10.1097/00043764-198406000-00015.

22. Olshan AF, Breslow NE, Daling JR, Falletta JM, Grufferman S, Robison LL, et al. Wilms' tumor and paternal occupation. Cancer Res. 1990;50:3212–7.
23. Ng A, Griffiths A, Cole T, Davison V, Griffiths M, Larkin S, et al. Congenital abnormalities and clinical features associated with Wilms' tumour: a comprehensive study from a centre serving a large population. Eur J Cancer. 2007;43:1422–9. https://doi.org/10.1016/j.ejca.2007.03.020.
24. Scott RH, Stiller CA, Walker L, Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet. 2006;43:705–15. https://doi.org/10.1136/jmg.2006.041723.
25. Dumoucel S, Gauthier-Villars M, Stoppa-Lyonnet D, Parisot P, Brisse H, Philippe-Chomette P, et al. Malformations, genetic abnormalities, and Wilms tumor. Pediatr Blood Cancer. 2014;61:140–4. https://doi.org/10.1002/pbc.24709.
26. Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JE, et al. Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell. 1991;67:437–47. https://doi.org/10.1016/0092-8674(91)90194-4.
27. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. J Pediatr. 1998;132:398–400. https://doi.org/10.1016/s0022-3476(98)70008-3.
28. Tournade MF, Com-Nougue C, de Kraker J, Ludwig R, Rey A, Burgers JM, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. J Clin Oncol. 2001;19:488–500.
29. O'Leary M, Krailo M, Anderson JR, Reaman GH, Children's Oncology Group. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. Semin Oncol. 2008;35:484–93. https://doi.org/10.1053/j.seminoncol.2008.07.008.
30. Sanpakit K, Triwatanawong J, Sumboonnanonda A. Long-term outcome in pediatric renal tumor survivors: experience of a single center. J Pediatr Hematol Oncol. 2013;35:610–3. https://doi.org/10.1097/MPH.0b013e3182a06265.
31. Israels T, Borgstein E, Pidini D, Chagaluka G, de Kraker J, Kamiza S, et al. Management of children with a Wilms tumor in Malawi, sub-Saharan Africa. J Pediatr Hematol Oncol. 2012;34:606–10. https://doi.org/10.1097/MPH.0b013e3182580921.
32. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. Semin Pediatr Surg. 2012;21:136–41. https://doi.org/10.1053/j.sempedsurg.2012.01.006.
33. Ekenze SO, Agugua-Obianyo NE, Odetunde OA. The challenge of nephroblastoma in a developing country. Ann Oncol. 2006;17:1598–600. https://doi.org/10.1093/annonc/mdl167.
34. Howard SC, Ortiz R, Baez LF, Cabanas R, Barrantes J, Fu L, et al. Protocol-based treatment for children with cancer in low income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)–part II. Pediatr Blood Cancer. 2007;48:486–90. https://doi.org/10.1002/pbc.20989.
35. Murphy AJ, Axt JR, de Caestecker C, Pierce J, Correa H, Seeley EH, et al. Molecular characterization of Wilms' tumor from a resource-constrained region of sub-Saharan Africa. Int J Cancer. 2012;131:E983–94. https://doi.org/10.1002/ijc.27544.
36. Rabeh W, Akel S, Eid T, Muwakkit S, Abboud M, El Solh H, et al. Wilms tumor: successes and challenges in management outside of cooperative clinical trials. Hematol Oncol Stem Cell Ther. 2016;9:20–5. https://doi.org/10.1016/j.hemonc.2015.12.006.