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HIGHLIGHTS

Incidence

- Malignancies of the kidney (renal cancers) represented 6.3% of cancer diagnoses among children younger than 15 years of age (incidence 7.9 per million) (Table VI.2) and 4.4% of cancer diagnoses for children and adolescents younger than 20 years of age (incidence of 6.2 per million).
- In the US approximately 550 children and adolescents younger than 20 years of age are diagnosed with renal tumors each year, of which approximately 500 are Wilms' tumor.
- Wilms' tumor was by far the most common form of renal cancer in children younger than 15 years of age, representing approximately 95% of diagnoses (Tables VI.1 and VI.2). Much less common were rhabdoid tumors of the kidney (1% of renal cancers) and clear cell sarcoma of the kidney (1.6% of renal cancers). Renal carcinomas, the most common form of renal cancer in adults, represented only 2.6% of renal cancers in children younger than 15 years of age.
- Wilms' tumor occurred most commonly among children younger than 5 years of age (Figure VI.1), with very low incidence for 10-14 and 15-19 year olds. The highest incidence for Wilms' tumor was in the first 2 years of life, followed by steadily decreasing rates with increasing age (Figure VI.2).
- Rhabdoid tumor of the kidney was diagnosed primarily in infants, while clear cell sarcoma of the kidney was diagnosed primarily during the first 4 years of life. Renal carcinomas, by contrast, occurred with highest incidence among 15-19 year olds (Figure VI.1).
- Females had slightly higher incidence than males for Wilms' tumor during the period 1975-95 (Table VI.3). For the recent period of 1990-95, however, incidence rates were similar by sex (Figure VI.3).
- Black children had somewhat higher incidence for Wilms' tumor than white children for the period 1975-95. For the time periods 1986-89 and 1990-95, however, incidence rates by race were similar (Figure VI.4).
- Incidence of Wilms' tumor showed neither substantial increases nor decreases during the 21-year period from 1975 to 1995 (FigureVI.5).

Survival

- The overall relative 5-year survival rate for children with Wilms' tumor was approximately 92% for cases diagnosed from 1985-94 (Figure VI.6), an improvement from the 81% survival rate for cases diagnosed from 1975-84. Relative survival rates were slightly higher for females than males and slightly higher for black children than for white children (Figure VI.6).

Risk factors

- Certain congenital anomalies and genetic conditions increase susceptibility for Wilms' tumor (Table VI.4). Suggestive, although not conclusive, data indicate that certain paternal occupations may be associated with increased Wilms' tumor risk.

INTRODUCTION

Renal tumors occurring in children comprise a spectrum of morphologic subtypes, including some with benign histopathology. Wilms' tumor (also called nephroblastoma or renal embryoma) is by far the most common form of renal cancer in children. Other rarer forms of childhood renal cancers are: clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, congenital mesoblastic nephroma, multilocular cystic renal tumor, renal cell carcinoma, and angiomyolipoma [1,2]. During 1975-95 in regions covered by SEER cancer registries, malignant forms of renal tumors represented 6.3% of total cancer diagnoses among children younger than 15 years of age and 4.4% for the younger than 20 years old population. The contribution of renal cancers to the overall childhood cancer burden was notably age-dependent, with renal cancers representing 9.7% of total incident malignancies diagnosed among children younger than 5 years of age, 5.4% in children 5-9 years of age, 1.1% in children 10-14 years of age, and only 0.6% in adolescents 15-19 years of age.

Wilms' tumor is believed to arise from primitive metanephric blastema (*i.e.*, the tissue from which the normal kidney arises), though this tumor type often contains tissues not occurring in the developing kidney, including skeletal muscle, cartilage, and squamous epithelium [3]. Wilms' tumor usually arises in only one of the affected child's kidneys, although approximately 12% of affected children may be diagnosed with Wilms' tumor that is multicentric in origin [4]. Approximately 7% of children with Wilms' tumor have involvement of both kidneys. Patients with bilateral forms are generally diagnosed at younger ages and are more likely to have associated developmental abnormalities than patients with unilateral forms [4]. In the US approximately 550 children and adolescents younger than 20 years of age are diagnosed with renal tumors each year, of which approximately 500 are Wilm's tumor.

Classification System

The International Classification for Childhood Cancers (ICCC) Group VI of Renal Cancers divides malignant neoplasms into three subgroups [5]:

a. Wilms' tumor, rhabdoid tumor of the kidney, and clear-cell sarcoma of the kidney
b. Renal carcinoma
c. Unspecified malignant renal tumors.

Table VI.1: Number of cases and percent distribution of renal cancers by histologic subtype and age group, all races, both sexes, SEER, 1975-95

Age (in years) at diagnosis	<5	5-9	10-14	15-19	<15	<20
Wilms' tumor	880 (96.2%)[1]	260 (95.9%)	39 (66.1%)	21 (35.0%)	1,179 (94.7%)	1,200 (92.0%)
Rhabdoid tumor of the kidney	12 (1.3%)	*	*	*	12 (1.0%)	12 (0.9%)
Clear cell sarcoma of the kidney	16 (1.8%)	*	*	*	19 (1.6%)	19 (1.6%)
Renal carcinoma	6 (0.7%)	7 (2.6%)	19 (32.2%)	38 (63.3%)	32 (2.6%)	70 (5.4%)
Unspecified renal cancer	*	*	*	*	*	*
Total renal cancers	915	271	59	60	1,245	1,305

[1] Number in parenthesis represents the percentage of all renal cancers for the age group that are represented by the histologic category.
*Less than 5 cases.

Table VI.2: Age-adjusted* incidence rates for renal cancer by race and sex, age <15, SEER, 1975-95

	Both sexes	Males	Females
Renal cancers (VI)			
All races	7.9	7.4	8.4
Whites	8.0	7.4	8.6
Blacks	9.5	9.5	9.6
Wilms' tumor (VIa)			
All races	7.6	7.1	8.1
Whites	7.9	7.3	8.4
Blacks	8.7	8.4	9.0

*Adjusted to the 1970 US standard population

The numbers of cases of these histologic diagnoses among children residing in the SEER areas for the period 1975-95 are shown in Table VI.1. Malignant forms of renal tumors were diagnosed in 1,245 children younger than 15 years of age and in 1,305 children younger than 20 years of age. Wilms' tumor was by far the most common form of renal cancer, accounting for 94.7% of the 1,245 renal cancers in children younger than 15 years of age and 92.0% of the 1,305 renal cancers among the younger than 20 year olds. Occurring much less commonly among the total 1,245 cases of renal cancer in children younger than 15 years of age were rhabdoid tumor of the kidney (12 cases representing 1.0% of renal cancers) and clear cell sarcoma of the kidney (19 cases representing 1.6% of renal cancers). For renal cell carcinoma, there were 32 cases among children younger than 15 years of age (2.6% of renal cancers) and 70 cases among children younger than 20 years of age (5.4% of renal cancers).

Wilms' tumor, rhabdoid tumor of the kidney, and clear cell sarcoma of the kidney are classified together in the ICCC category VIa, while the renal carcinomas are grouped together in the ICCC category VIb. In presenting incidence data, the ICCC category VIa (for which Wilms' tumor represents greater than 95% of cases for all age groups) is designated Wilms' tumor (ICCC VIa), since the incidence patterns and trends for this subcategory are largely determined by cases of Wilms' tumor. When Wilms' tumor is discussed as a single diagnosis, the term Wilms' tumor without any parenthetic modifier is used. Additionally, since incidence rates for renal cancers were low and based on very small numbers in children ages 15-19 (a total of 60 incident cases diagnosed in the SEER areas during 1975-95), presentation of incidence data are generally restricted to renal cancers diagnosed among children younger than 15 years of age.

INCIDENCE

The average annual age-adjusted incidence rates of renal cancer for the years 1975-95 was 7.9 per million for children younger than 15 years of age (Table VI.2) and 6.2 per million for children younger than 20 years of age in the SEER areas. As discussed in greater detail in subsequent paragraphs, incidence rates for renal cancers *in toto* and for Wilms' tumor (ICCC VIa) for the period 1975-95 were slightly higher for females than males and for black children compared to white children. However, for the most recent time period (1990-95), rates were similar for both sexes and for black children and white children.

Age-specific incidence

Age-specific incidence rates of renal cancers in 5-year age groups were highest among children younger than 5 years of age

Table VI.3: Age-specific incidence rates per million for renal cancer by age and race, SEER, 1975-95

	All races	Whites	Blacks
Males			
<5 years	17.8	18.2	21.5
5-9 years	4.9	4.9	6.7
10-14 years	1.2	1.1	2.2
Females			
<5 years	19.1	19.6	21.4
5-9 years	6.6	6.8	7.8
10-14 years	1.2	1.3	1.6

(Table VI.3). Incidence declined markedly with increasing age. The age-incidence pattern for renal cancer in children was driven by that for Wilms' tumor (ICCC VIa), as illustrated in Figure VI.1. Renal cell carcinomas (ICCC VIb) occurred very infrequently among each 5-year age group younger than 15 years of age, but for 15-19 year olds the incidence rate was higher (though still only 0.7 per million) (Figure VI.1). Among the 15-19 year old population, renal carcinomas represented the majority (63%) of cases of renal cancer.

Average annual incidence rates for Wilms' tumor by single year of age are presented in Figure VI.2 for the time periods 1976-84 and 1986-94.[1] The age-specific incidence rates were highest in the first two years of life at 21 per million, with incidence rates subsequently declining to levels less than 2 per million for children older than 9 years of age. Age-specific rates for the other renal cancers were much lower than those for Wilms' tumor. Rhabdoid tumors of the kidney was present almost exclusively in the first 2 years of life, with a peak in infancy of 1.0 per million. Clear cell sarcoma of the kidney also occurred much less frequently than Wilms' tumor, with age-specific incidence in the first 4 years of life ranging between 0.4 and 0.6 per million, and with very few cases occurring among children older than 3 years of age. Renal cell carcinoma was also uncommon among children of any age, with most cases occurring in adolescents 15-19 years of age, for which age-specific incidence rates varied between 0.5 and 0.9 per million.

[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

Sex-specific incidence

For the 21 year period from 1975 to 1995, renal cancer incidence rates among children younger than 15 years of age were minimally higher for females compared to males (13 percent higher among females) (Table VI.2). For Wilms' tumor (ICCC VIa), there was also a slight female predominance when the overall period 1975-95 was considered. However, incidence rates for Wilms' tumor (ICCC VIa) were the same for males and females for the most recent period evaluated (1990-95) (Figure VI.3). As illustrated in Figure VI.2, females had slightly higher rates of Wilms' tumor than males in infancy (22.6 per

Figure VI.1: Renal cancer age-specific incidence rates by ICCC subcategory, all races, both sexes, SEER, 1975-95

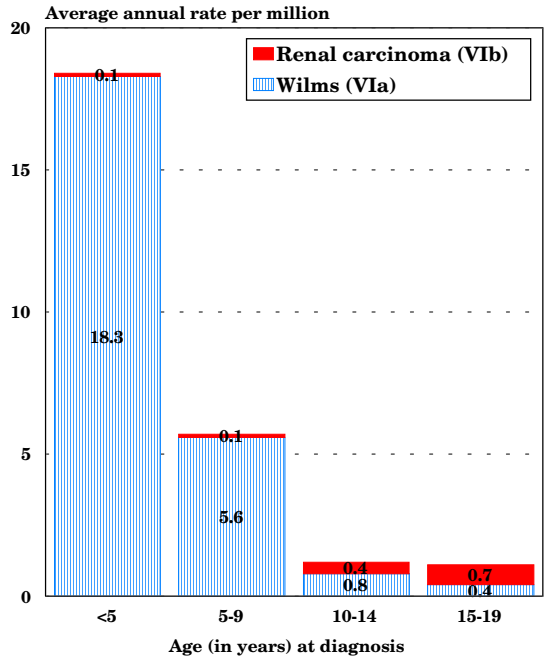


Figure VI.2: Wilms' tumor (VIa) age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94

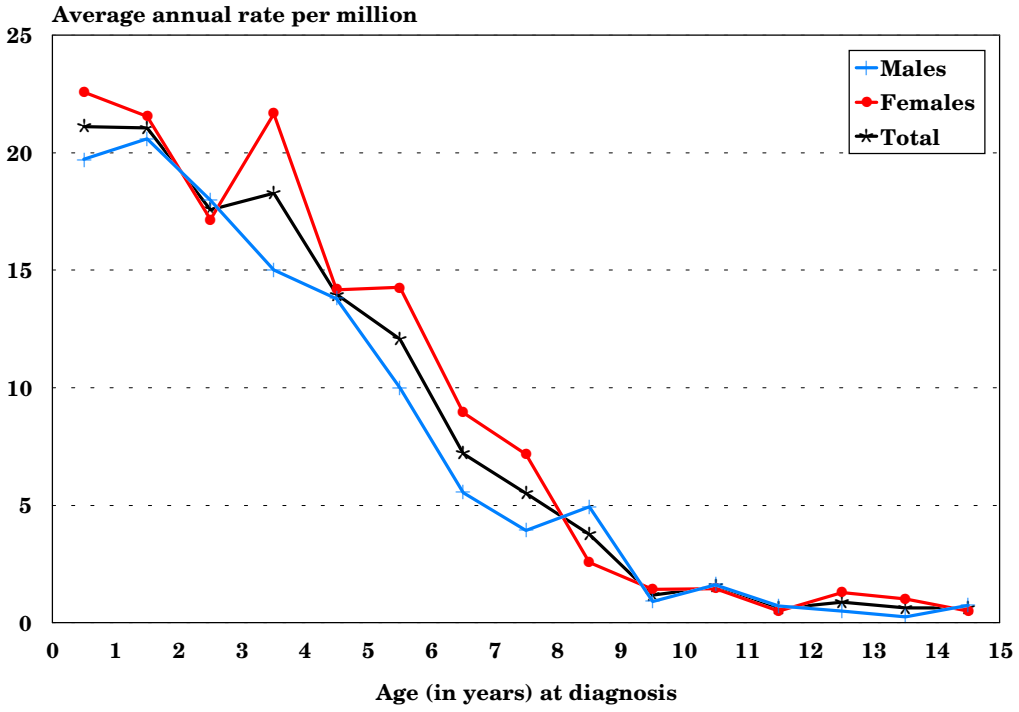
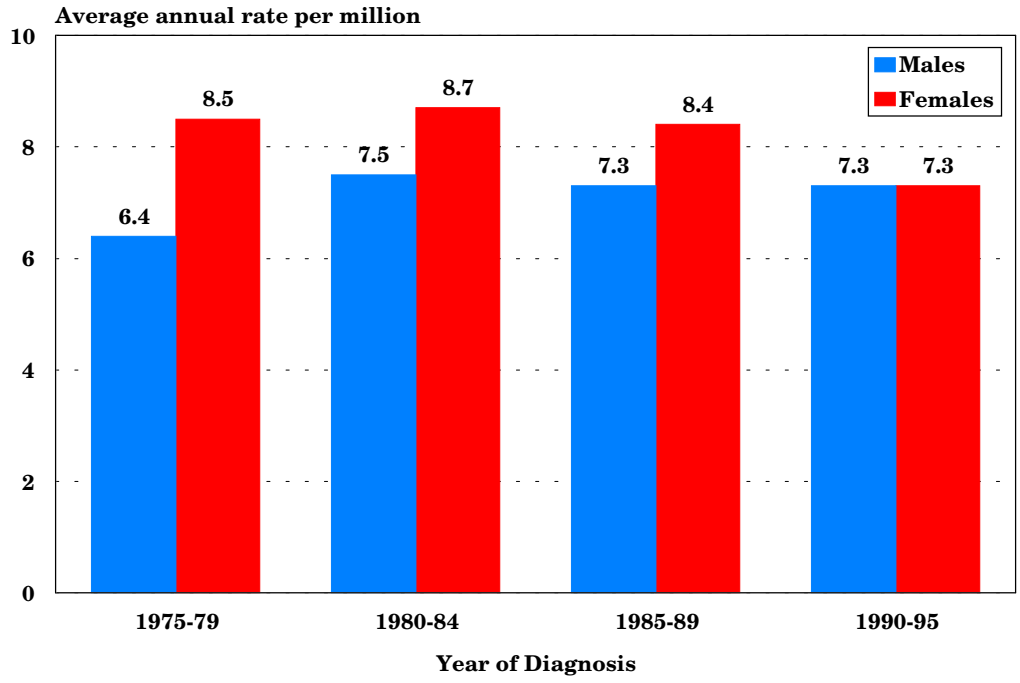
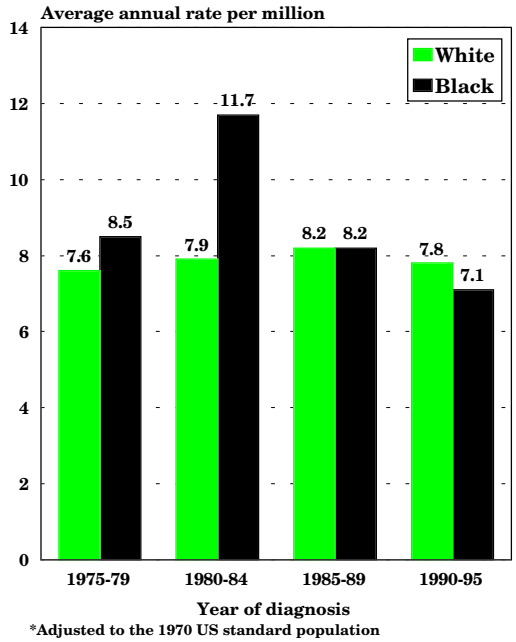


Figure VI.3: Wilms' tumor (VIa) age-adjusted* incidence rates by sex and year of diagnosis, age <15 all races, both sexes, SEER 1975-95



*Adjusted to the 1970 US standard population

Figure VI.4: Wilms' tumor (VIa) age-adjusted* incidence rates by race and year of diagnosis, age <15 both sexes, SEER, 1975-95



million versus 19.7 per million, respectively). Among children 3-8 years old, the age-specific incidence rates for females were generally equal to or greater than rates for males. For females, but not for males, the steady decline in Wilms' tumor incidence rates with increasing age after infancy was apparent except in the fourth year of life during which rates increased in females to levels approaching those seen in infancy, then subsequently declined linearly.

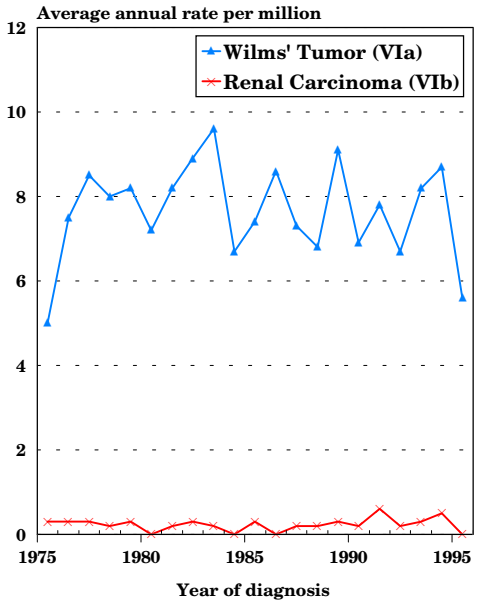
Black-white differences in incidence

Renal cancer and Wilms' tumor (ICCC VIa) incidence rates for the overall period 1975-95 were somewhat higher for black children than for white children (Table VI.2). For the two most recent five year periods (1985-89 and 1990-95), however, incidence rates for Wilms' tumor were similar for black children and white children (Figure VI.4).

TRENDS

The age-adjusted incidence rates for childhood renal cancers did not change significantly during the period 1975-95. Incidence rates for Wilms' tumor (ICCC VIa) varied from year to year (Figure VI.5), but there was no trend for increase or decrease during the 21-year period (estimated annual percentage change = -0.03%). The incidence of renal carcinoma was very low throughout the period (Figure VI.5). For the years 1975-79, Wilms' tumor (ICCC VIa) incidence rates for females (8.5 per million) were higher than for males (6.4 per million) (Figure VI.3). However, rates for males rose between 1975-79 and 1980-84 to 7.5 per million, and thereafter remained fairly stable. Rates for females declined, particularly between 1985-89 and 1990-95, so that females and males had the same incidence rate (7.3 per million) during 1990-95 (Figure VI.3). Incidence rates for Wilms' tumor (ICCC VIa) for white children did not vary much between each 5-6 year time period from 1975 to 1995. Black

Figure VI.5: Trends in renal cancer age-adjusted* incidence rates by type, age <15 all races, both sexes, SEER, 1975-95



children had higher incidence rates for Wilms' tumor (ICCC VIa) in 1975-79 and 1980-84 (8.5 and 11.7 per million, respectively), but the rates dropped for the years 1985-89 and 1990-95 (8.2 and 7.1 per million, respectively) to levels very similar to those for white children (Figure VI.4).

SURVIVAL

For children of all ages, both sexes, and all racial/ethnic groups residing in the SEER areas, the relative 5-year survival rate for children diagnosed with Wilms' tumor younger than 15 years of age during 1985-94 was 92%, compared with a rate of 81% among children diagnosed with this malignancy during 1975-84. Among cases diagnosed during 1985-94, 5-year survival was slightly better for females (94%) than males (91%). For 1985-94, black children had somewhat better outcome than white children (95% versus 92% 5-year survival) (Figure VI.6). Children with rhabdoid tumor are known to have a much poorer outcome than children with Wilms' tumor [44], and among the small number of children with rhabdoid tumor of the kidney followed for survival in SEER areas (n = 8), all either died (6) or were lost to follow-up (2). Children with clear cell sarcoma of the kidney are known to have a somewhat poorer prognosis than children with Wilms' tumor, with 6-year relapse-free survival rates of slightly above 60% based on data from the US National Wilms' Tumor Study Group [45,46]. There were only 13 children with clear cell sarcoma of the kidney evaluable for survival from the SEER areas for the time period 1975-94, and their relative 5-year survival rate was 84%. For children and adolescents with renal carcinomas, 5-year relative survival rates increased from 48% for cases diagnosed in 1975-84 to 83% for cases diagnosed in 1985-94 (although these estimates are

Figure VI.6: Wilms' tumor 5-year relative survival rates by race and sex, age <15, SEER (9 Areas), 1975-84 and 1985-94

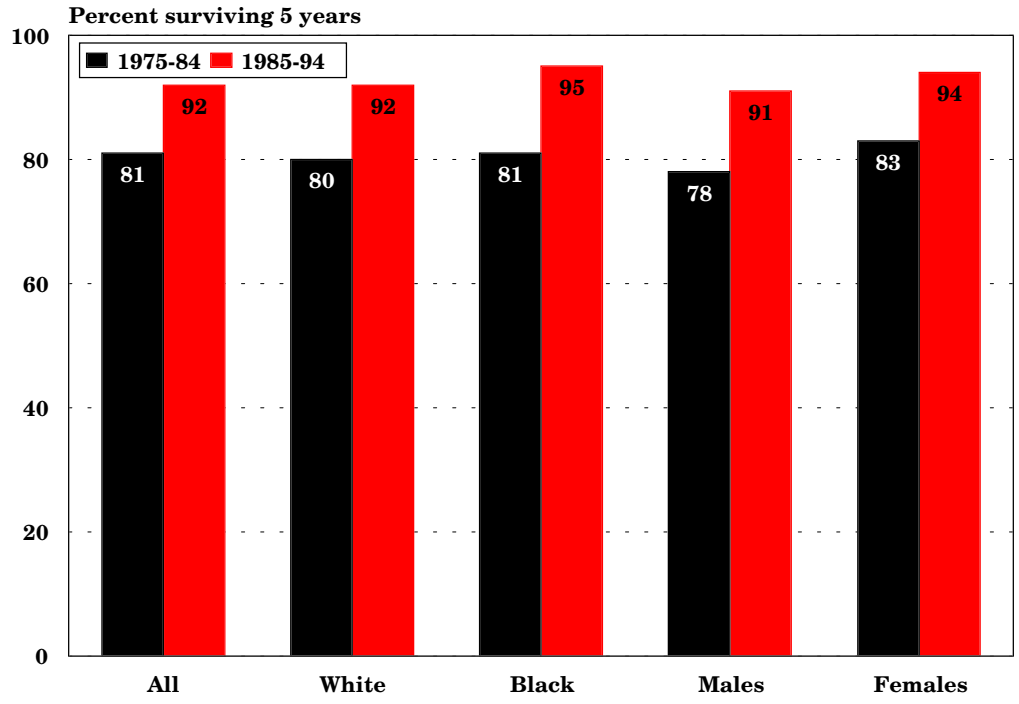


Table VI.4: Current knowledge on causes of Wilms' Tumor (WT)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	Incidence in Asians is about half that in blacks and whites.	10,11
Aniridia, genitourinary anomalies, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, mental retardation), Beckwith-Wiedemann syndrome, Perlman syndrome, Denys-Drash syndrome, Simpson-Golabi-Behmel syndrome	Risk is increased in children with these congenital anomalies and genetic conditions. The study of children with WAGR led to the identification of one of the WT genes.	12-22
Factors for which evidence is suggestive but not conclusive		
Paternal occupation	An increased risk for fathers employed as a welder or mechanic has been reported in several studies.	13,26,28
Factors for which evidence is inconsistent or limited		
High birth weight	Association with birth weight over 4,000 grams has been reported in some studies.	13,29,30
Parental exposure to pesticides	One study found an increased risk for parental occupational exposure to pesticides. Another study found an association with household insect extermination.	13,27,31-33
Ionizing radiation (in utero)	Prenatal diagnostic x-ray was associated with increased risk in one study.	34
Maternal consumption of coffee and tea during pregnancy	Three studies reported association with coffee and/or tea; another did not replicate this finding.	31,35,36
Maternal hair dye use during pregnancy	Use was associated with risk in one study, but not in others.	31,36
Maternal medication use during pregnancy	Studies reported associations with various drugs including hormones, antibiotics, dipyrone, metoclopramide, pethrane anesthesia during delivery. Most of these results were found in only a single study.	13,37,38
Maternal occupation	One study found an association with job groupings that included hairdressers, electronic and clothing manufacturing workers, laboratory workers, dental assistants.	26,39

based on only 23 and 29 cases, respectively, from these two time periods).

RISK FACTORS

Despite the rarity of renal cancer in children, a substantial body of epidemiologic, genetic, and molecular studies have contributed important insights to understanding its pathogenesis [3,6,7]. Historically, Wilms' tumor was thought to vary little in incidence throughout the world and was therefore proposed as an "index tumor" of childhood cancer [8]. However, international comparisons based on data through the 1980s showed a greater than threefold difference in age-adjusted incidence rates among populations, with highest rates observed in US and Nigerian blacks, followed by somewhat lower rates in Sweden and US whites, and lowest rates in Chinese and other Asians [9,10]. Data for the years 1973-88 from the US showed similar ethnic variation, with incidence in Asians about half that in blacks, and rates for blacks slightly higher than rates for whites [11] (Table VI.4).

A small proportion of Wilms' tumor cases appear to be heritable including: those patients with bilateral tumors, those occurring in association with aniridia and other congenital anomalies, and those few cases arising in the small number of families with one or more additional cases of Wilms' tumor in close family members [12,13]. Approximately 1.5% of patients in a large series had one or more family members (usually siblings or cousins) with Wilms' tumor based on interview data [14]. Congenital disorders that have been linked with Wilms' tumor include: the Beckwith-Wiedemann syndrome (an overgrowth syndrome associated with macrosomia, omphalocele, macroglossia, and visceromegaly and believed to be linked to an as yet unidentified gene(s) at chromosome region 11p15) [14,15]; the Simpson-Golabi-Behmel syndrome (an X-linked fetal overgrowth disorder caused by mutations in the glypican 3 gene) [15,16]; hemihypertrophy as an isolated abnormality; the Perlman and Sotos syndromes [17-19]; the Denys-Drash syndrome (associated with mutations of the Wilms' tumor suppressor gene WT1) [20-22]; and the WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation) that results from deletion of a number of contiguous genes on chromosome 11 including the aniridia gene PAX6 and the WT1 gene [12]. In addition to the heritable conditions cited above, inherited predisposition genes associated with some familial Wilms' tumor cases appear to exist at two other loci (and possibly others not yet identified) [23,24]. However, survivors of Wilms' tumor that is unilateral at diagnosis are at low risk for having children with Wilms' tumor [25].

Most of the analytical and epidemiologic investigations of childhood renal cancer have focused on Wilms' tumor, and very little is known about risk factors for childhood renal carcinoma or the other rarer childhood renal cancer subtypes. Several epidemiological studies have investigated occupational, environmental, and lifestyle characteristics as potential risk factors for Wilms' tumor, but findings to date have been inconsistent [13,26,27]. A few studies have suggested that children of fathers employed as welders or mechanics have increased risk of Wilms' tumor [13,28], but occupational exposure assessment was insufficient to draw firm conclusions [26]. Limited evidence implicates high birth weight in the etiology [29,30]. Parental and postnatal exposures to pesticides have also been linked with increased risk [27,31-33], but these associations were derived from interview data only and have not been confirmed with studies utilizing measurements. A large study in the United Kingdom has reported an association of Wilms' tumor with exposure of the mother to ionizing radiation from diagnostic x-rays

during pregnancy [34.] Some [31,32,35], but not all [36] investigations have found associations between maternal consumption of coffee and tea during pregnancy and risk of Wilms' tumor in offspring. Inconsistent reports have also implicated maternal hair dye use and various types of medications taken or anesthetics to which mothers have been exposed during pregnancy [13,37,38]. The role of maternal occupational exposures has received limited evaluation [26,39].

Most of the reported associations described in the preceding paragraph have not been consistently replicated in multiple, high quality studies in different populations. Future epidemiologic studies may benefit from more detailed exposure assessment, validated by environmental and biologic measurements. In addition, the role of genetic susceptibility and assessment of gene-environment interaction should be considered by evaluation of appropriate molecular markers to better define etiologic pathways for Wilms' tumor.

Recurring molecular abnormalities have been identified in the tumor cells of two of the uncommon renal cancers that occur in young children, rhabdoid tumor of the kidney and congenital mesoblastic nephroma. Rhabdoid tumor, which can develop in the central nervous system and extrarenal sites as well as in the kidney, is associated with tumor cell mutations in the INI1 gene located on chromosome 22 [40,41]. Evaluation of some children with rhabdoid tumors has revealed germline mutations of the INI1 gene [41]. Congenital mesoblastic nephroma is an infantile spindle cell tumor of the kidney with low malignant potential that is virtually identical morphologically to congenital fibrosarcoma [42]. The tumor cells of both of these tumors of infancy have been found to possess fusions of the ETV6 gene (also known as TEL) on chromosome 12 to the NTRK3 gene on chromosome 15 [42,43].

SUMMARY

The descriptive epidemiologic features of Wilms' tumor have been known for a number of years. Associated congenital anomalies and genetic factors have also been subject of much interest. More recent studies have further characterized the specific genetic loci and molecular alterations involved in the development of Wilms' tumor. Several epidemiologic studies have investigated occupational, environmental, and lifestyle factors as risk factors for Wilms' tumor. A number of parental and childhood exposures have been found to be associated with an increased risk of Wilms' tumor. Most of these associations have not been replicated in multiple high quality studies. However, some warrant further evaluation including paternal occupational exposures, pesticide exposure, and certain maternal exposures during pregnancy. Future epidemiologic studies may benefit from the inclusion of molecular markers that may better define etiologic pathways for Wilms' tumor.

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