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HIGHLIGHTS

Incidence

- Retinoblastoma accounted for approximately 11% of cancers developing in the first year of life, but for only 3% of the cancers developing among children younger than 15 years of age.
- In the US, approximately 300 children and adolescents younger than 20 years of age are diagnosed with retionblastomas each year.
- The vast majority of cases of retinoblastoma occur among young children, with almost two-thirds (63%) of all retinoblastomas occurring before the age of two years and 95% occurring before the age of five years.
- The incidence of bilateral tumors was strongly age dependent with 42% of the retinoblastomas occurring in children less than one year of age being bilateral compared to 21% of those among children aged one year, and only 9% among older children.
- Rates of retinoblastoma were essentially equal among males (3.7 per million) and females (3.8 per million) and among whites (3.7 per million) and blacks (4.0 per million) (Table V.2)
- There was no substantial sustained change in retinoblastoma incidence during the 21-year period, 1975-95 (Figure V.3 and Table V.2).

Survival

- Survival for children with retinoblastoma was quite favorable, with more than 93% alive at five years after diagnosis. Males and females had similar 5-year survival rates for the period 1976-94 (93-94%). Black children had slightly lower 5-year survival rates than white children (89% versus 94%) (Figure V.5).

Risk factors

- A retinoblastoma gene has been identified. Each child of a parent with familial bilateral retinoblastoma has a 50% risk of inheriting the retinoblastoma gene. Some patients develop the gene as the result of a new mutation (sporadic heritable retinoblastoma) and can pass the gene on to their children even though they did not inherit the gene from their parents. Children who inherit the retinoblastoma gene have a 90% risk of developing retinoblastoma. Genetic retinoblastomas are more likely to be bilateral and to occur during the first year of life. Little is know about non-genetic (sporadic) retinoblastomas (Table V.3).

INTRODUCTION

Retinoblastoma is a tumor of childhood which arises in the retina of the eye and extremely rarely in the pineal gland [1]. Two types of retinoblastomas have been described: those linked to genetic mutations and the so-called sporadic retinoblastomas. The genetic-linked retinoblastomas are divided into two groups, those which arise in children who carry the retinoblastoma gene inherited from one or both parents (familial retinoblastoma) and those in which the disease occurs as the result of a new mutation, usually in their father's sperm but sometimes in their mother's egg (sporadic heritable retinoblastoma) [2,3]. Both familial retinoblastomas and sporadic

Table V.1: Number of retinoblastomas by laterality, sex, and race, age <15 SEER, 1975-95

	Total	Unilateral		Bilateral		Unknown	
	No.	No.	%	No.	%	No.	%
Total	625	453	72.5	154	24.6	18	2.9
Males	314	226	72.0	76	24.2	12	3.8
Females	311	227	73.0	78	25.1	6	1.9
Whites	474	341	71.9	116	24.5	17	3.6
Blacks	86	61	70.9	25	29.0	-	-

heritable retinoblastomas are more likely to be bilateral and to occur during the first year of life, while the sporadic retinoblastomas are more likely to be unilateral and occur after the first year of life.

The importance of retinoblastoma to cancer research far exceeds the low incidence of this uncommon tumor, since it was through careful analysis and insightful mathematical modeling of the age distribution of unilateral and bilateral cases that the "tumor suppressor gene" concept was initially developed [4,5]. Subsequent work led to the localization of the gene responsible for retinoblastoma to a small region on the long arm of chromosome 13 [6], and eventually to isolation of the gene itself [7]. The retinoblastoma gene product is now recognized as a critical element in controlling progression through the cell cycle, and abnormalities of the retinoblastoma gene are among the most common occurring in all types of cancer cells [5,8]. In the US, approximately 300 children and adolescents younger than 20 years of age are diagnosed with retionblastomas each year.

INCIDENCE

Table V.1 shows the distribution of retinoblastomas diagnosed among residents of the SEER areas during 1975-95 by laterality, race, and sex. Approximately one-fourth of all retinoblastomas were bilateral. All bilateral disease is hereditary whereas unilateral disease may or may not be hereditary. The percentage of unilateral and bilateral tumors were similar for black children and white children and for males and females.

The vast majority of cases of retinoblastoma occur among young children (Figure V.1), with almost two-thirds (63%)

Figure V.1: Unilateral and bilateral retinoblastoma age-specific incidence rates, all races both sexes, SEER, 1976-84 and 1986-94

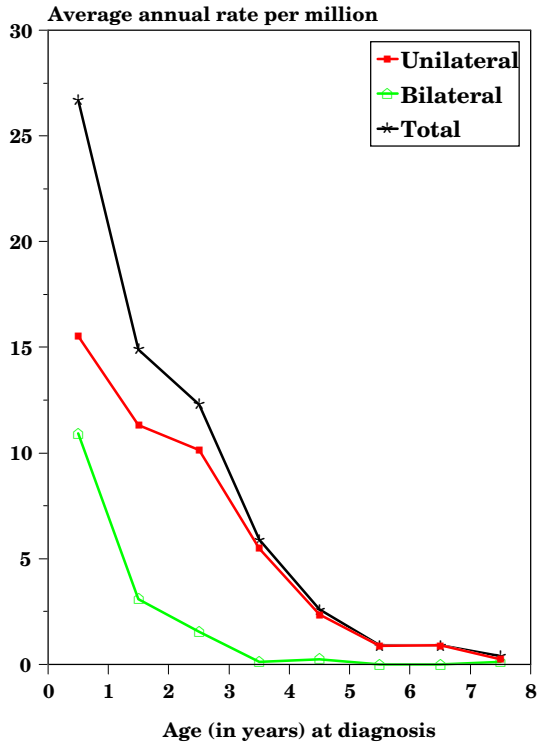
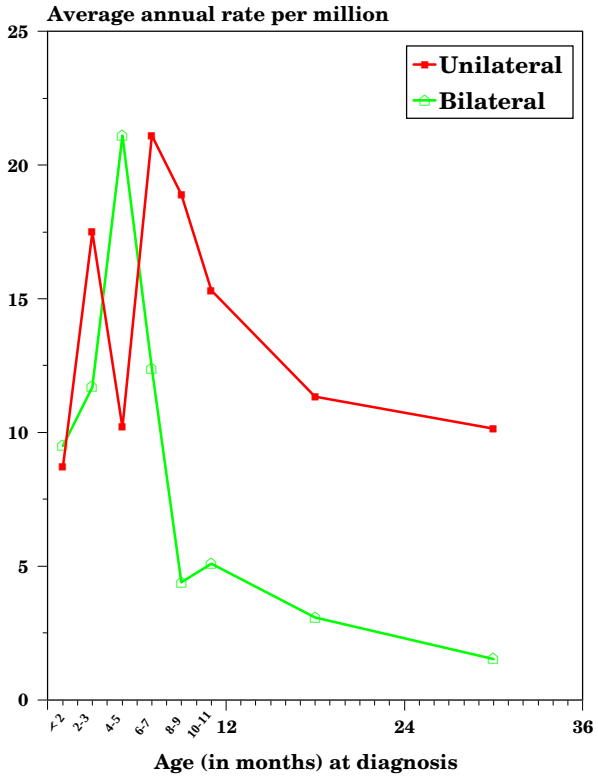


Figure V.2: Unilateral and bilateral retinoblastoma age-specific incidence rates, age <3, all races both sexes,SEER, 1976-84 and 1986-94



of all retinoblastomas diagnosed between 1975-95 among children residing in the SEER areas occurring before the age of two years and with 95% occurring before the age of five years. Since retinoblastoma was extremely rare after the age of five years (only 28 childhood retinoblastomas reported to SEER areas as having been diagnosed younger than 20 years of age occurred in children aged 15-19 years in comparison to 625 cases in children younger than 15 years of age), information presented in this chapter will be limited to children younger than 15 years of age.

The incidence of bilaterality was strongly age dependent, with 42% (103/248) of the retinoblastomas occurring in children less than one year of age being bilateral compared to 21% (31/147) of those among children aged one year, and only 9% (20/230) among older children. The incidence rates for both unilateral and bilateral retinoblastoma decrease as age increases. The incidence rate for bilateral retinoblastoma drops to almost zero after age 2, while the rate for unilateral retinoblastoma remains higher until after age 7 (Figure V.1). Figure V.2 provides a more detailed view of incidence in the first 3 years of life, with incidence for the first year of life being estimated by two month age intervals. For bilateral tumors, the peak incidence is at 4-5 months of age, with a sharp decline thereafter and with very low rates by the third year of life. For unilateral tumors, peak incidence is also in the first year of life (at 6-7 months), but the decline in incidence with increasing age is much more gradual than for bilateral tumors, with rates remaining above 10 per million children for the first 3 years of life.

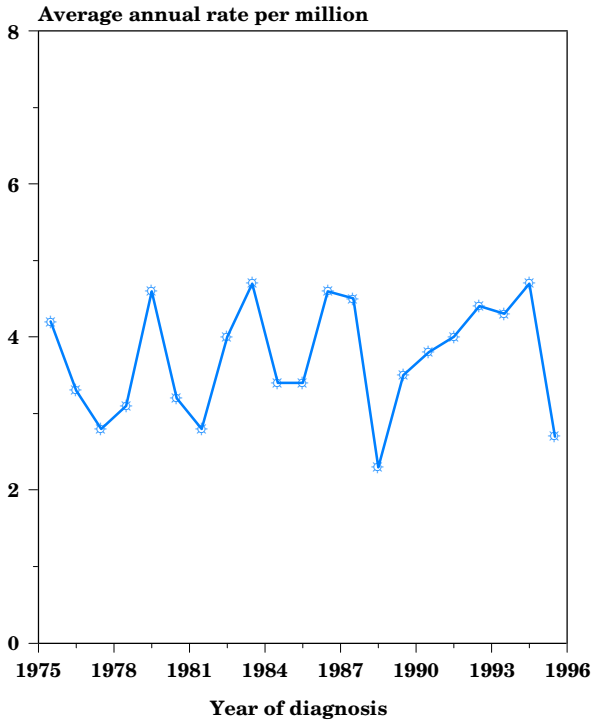
The incidence rate of retinoblastoma for the period 1975-95 was 3.8 per million (Table V.2). Retinoblastoma accounted for approximately 11% of the cancers developing in the first year of life, but for only 3% of the cancers developing among children younger than 15 years of age. Rates of retinoblastoma among males (3.7 per million) and females (3.8 per million) were essentially equal. Rates for whites (3.7 per million) and blacks (4.0 per million) were also similar.

Table V.2: Average annual age-adjusted* incidence rates per million of retinoblastoma, by time period, race, and sex, age <15 SEER, 1975-95

	1975-95	1975-79	1980-84	1985-89	1990-95
All races, Both sexes	3.8	3.6	3.6	3.7	4.0
Male	3.7	3.6	3.3	3.4	4.2
Female	3.8	3.6	4.0	4.0	3.8
White	3.7	3.3	3.5	3.7	4.0
Black	4.0	4.6	4.0	3.7	3.8

* Adjusted to the 1970 US standard population

Figure V.3: Trends in retinoblastoma age-adjusted* incidence rates, age <15, all races both sexes, SEER 1975-1995



*Adjusted to the 1970 US standard population

TRENDS

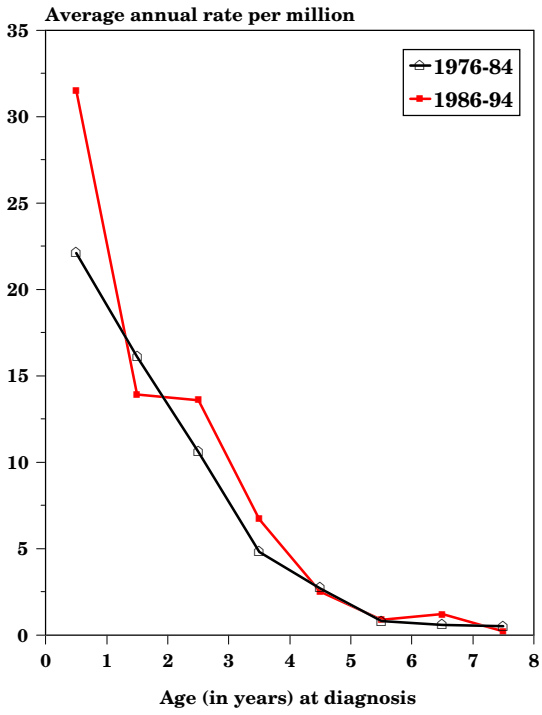
Figure V.3 shows the incidence for retinoblastoma among children younger than 15 years of age for 1975-95. Because of the relatively small numbers of children with retinoblastoma diagnosed in SEER areas annually (approximately 20 per year), there was considerable variability in the year-to-year rates. There was no substantial sustained change in retinoblastoma incidence during this 21 year period.

Table V.2 shows the incidence rate for retinoblastoma among children younger than 15 years of age for four specific time periods between 1975-95 by sex and race. Rates were slightly higher in the last time period for males and for whites. The estimated overall annual percent change was about one-half of one percent per year (0.6%). The change was greater for males (1.2%) than for females (0.2%), but neither change was significant. The rates for blacks were higher than whites for the earlier time period but by the late 1980s were similar. Figure V.4 shows the incidence of retinoblastoma by year of age for an early time period (1976-84) and for a recent time period (1986-94) and illustrates that the small increase that did occur between these two time periods was primarily the result of increased diagnosis of retinoblastoma in the first year of life.

SURVIVAL

Figure V.5 shows that survival for children diagnosed with retinoblastoma in the period 1975-94 was quite favorable, with more than 93% alive at five years after diagnosis. Males and females had similar 5-year survival rates for the period 1975-94 at 93-94%, while black children had slightly lower 5-year survival rates than white children (89% versus 94%).

Figure V.4: Retinoblastoma age-specific incidence rates by time period, all races, both sexes SEER, 1976-84 and 1986-94



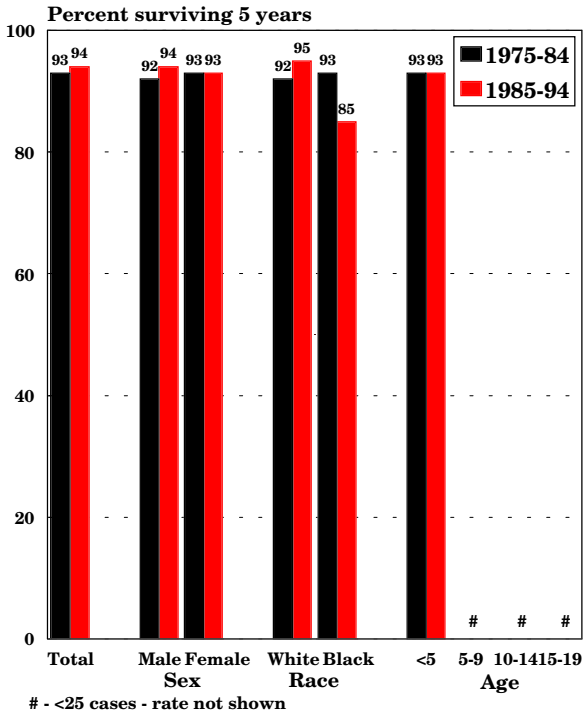
RISK FACTORS

While the genetics of retinoblastoma are well understood, there is much less known about the role of non-genetic factors in retinoblastoma (Table V.3). Each child of a parent with familial bilateral retinoblastoma has a 50% risk of inheriting the retinoblastoma gene. Patients with sporadic heritable retinoblastoma carry the gene for retinoblastoma and can also pass the gene on to their children even though they did not inherit the gene from their parents. Children who inherit the retinoblastoma gene have a 90% risk of developing retinoblastoma. Sporadic (nonheritable) retinoblastoma results from post-conception events and has been associated in a single study with parental occupation (Table V.3) [9].

SUMMARY

Retinoblastomas occur among very young children, usually before the age of five years. The incidence is about equal among males and females and among black children and white children. Rates have changed little over the 21-year period,

Figure V.5: Retinoblastoma 5-year relative survival rates, by sex, race, age and time period SEER (9 areas), 1975-84 and 1985-94



- <25 cases - rate not shown

Table V.3: Current knowledge of causes of retinoblastoma

Exposure or Characteristic	Comments	References
Known risk factors		
Parent with history of bilateral retinoblastoma	Each child has a 50% risk of inheriting the retinoblastoma gene. If the gene is inherited, the risk of retinoblastoma is over 90%. A small proportion of unilateral patients also carry the gene and can pass it on to their children.	4,10
13q deletion syndrome	Recognition of this syndrome led to the identification of the retinoblastoma gene.	10
Factors for which evidence is inconsistent or limited		
Paternal occupation	There is a single report of association with employment in the military, metal manufacturing, and as welder, machinist, or related occupation.	9

1975-95. Familial and sporadic heritable retinoblastomas are caused by genetic mutations and both usually result in the bilateral form of the disease. Little is known about the causes of sporadic non-heritable retinoblastomas. Survival rates are greater than 90% for children with retinoblastoma.

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