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HIGHLIGHTS

Incidence

- The age of peak cancer incidence among children occurred during the first year of life (Figure XII.1).
- Malignancies of infancy represented 10% of all cancer that was diagnosed among children younger than 15 years of age. The average annual incidence rate of all infant cancer combined was 233 per million infants, which was 12% higher than the age (2 years) with the next highest incidence.
- The rate among females (234 per million infants) was essentially the same as that in males (232 per million infants). This is notable because infancy was the only age among children younger than 15 years of age in which female rates were not lower than male rates.
- Neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants).
- The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases (Figure XII.2).
- Central nervous system malignancies comprised 13% of infant cancer, with an average annual incidence rate of nearly 30 per million infants.
- The average annual incidence rates for malignant germ cell and malignant soft tissue tumors were essentially the same at 15 per million infants. Each comprised about 6% of infant cancer (Figure XII.2).
- Leukemias accounted for a substantial proportion of the racial difference, in that the average annual rate for white infants (48.7 per million) was 66% higher than for black infants (29.4 per million).

Survival

- The prognosis for infants with cancer is often worse than in children of older ages, even when comparing the same histologic diagnosis. For instance, the 5-year relative survival for children younger than 15 years of age who were diagnosed with acute lymphoid leukemia from 1975-94 was well over 70%, but for infants the survival rate was 33%.
- Over 80% of children diagnosed with neuroblastoma during infancy were alive 5 years following diagnosis. In contrast, for children diagnosed with neuroblastoma at age 1 year or older, the 5-year relative survival was about 45%.

INTRODUCTION

Adult cancers usually form in epithelial tissues and are believed often to be the result of a long biological process related to the interaction of exogenous exposures with genetic and other endogenous characteristics among susceptible people. However, in young children, particularly infants, the aberrant genetic processes that fail to safeguard against the clonal proliferation of cells with unregulated growth potential occur very early in life and progress very quickly. Due to the unique clinical, genetic, and epidemiologic characteristics of cancers in infants [1,2], it is becoming increasingly

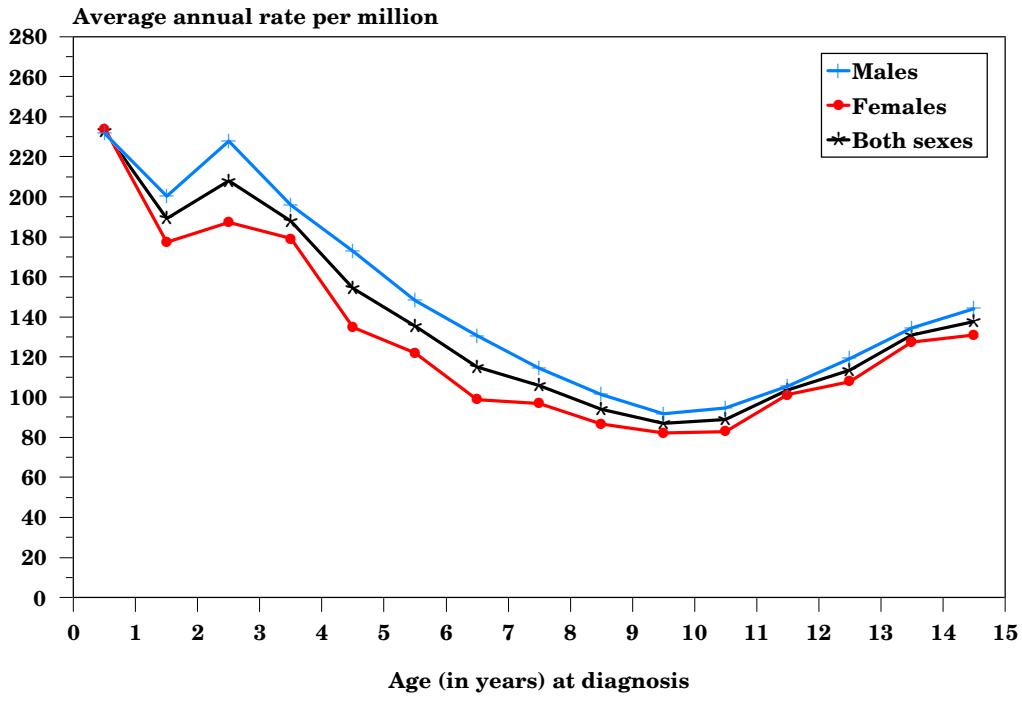
apparent that the study of infant cancer may lead to further understanding of the mechanisms of carcinogenesis. With that in mind, this chapter will briefly summarize and discuss data on cancer that occurs among children who are diagnosed within the first year of life.

INCIDENCE

The cancer cases used to calculate incidence rates in this discussion were limited to primary malignancies that were registered in SEER areas of the United States during the time periods 1976-84 and 1986-94. This time restriction was imposed because enumeration of the population at risk by single years of age was available only for the census years of 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.

The age of peak cancer incidence among children occurred during the first year of life, as shown in Figure XII.1. Malignancies of infancy represented 10% of all cancer that was diagnosed among children younger than 15 years of age. The incidence rate of all infant cancer combined was 233 per million infants, which was 12% higher than the age (2 years) with the next highest incidence. The rate among females (234 per million infants) was essentially the same as that in males (232 per million infants). This is notable because infancy was the only age among children younger than 15 years of age in which female rates were not lower than male rates. Differences in rates by sex will be discussed in more detail below.

Figure XII.1: Total childhood cancer age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94 combined



Histology-specific incidence

Figure XII.2 illustrates the incidence rate for the most predominant types of infant cancer. Although neuroblastoma represented less than 8% of cancer cases among children younger than 15 years of age, neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants). The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases. As with older children, acute lymphoid leukemia was the most frequently occurring leukemia. The average annual incidence rate of acute lymphoid leukemia was 21 per million infants, while the rate for the acute non-lymphoid leukemias was 11 per million infants. For juvenile chronic myeloid leukemia, which by international consensus is now called juvenile myelomonocytic leukemia (JMML), the average annual incidence rate was 3 per million infants. The combined rate for other and unspecified leukemias was about 5 per million infants.

Central nervous system malignancies comprised 13% of infant cancer, with an incidence rate of nearly 30 per million infants. Astrocytomas and other gliomas (combined) accounted for half of the CNS malignancies (15 per million), followed by primitive neuroectodermal tumors/medulloblastomas (PNET, 9 per million infants) and ependymomas (5 per million). Retinoblastoma and Wilms' tumor followed CNS cancer in order of occurrence among infants. Retinoblastoma accounted for about 12% of infant cancer and Wilms' tumor an additional 9%.

The incidence rates for malignant germ cell tumors (including intracranial) and malignant soft tissue tumors were essentially the same at 15 per million infants.

Figure XII.2: Infant age-specific incidence rates by type, all races, both sexes, SEER, 1976-84 and 1986-94 combined

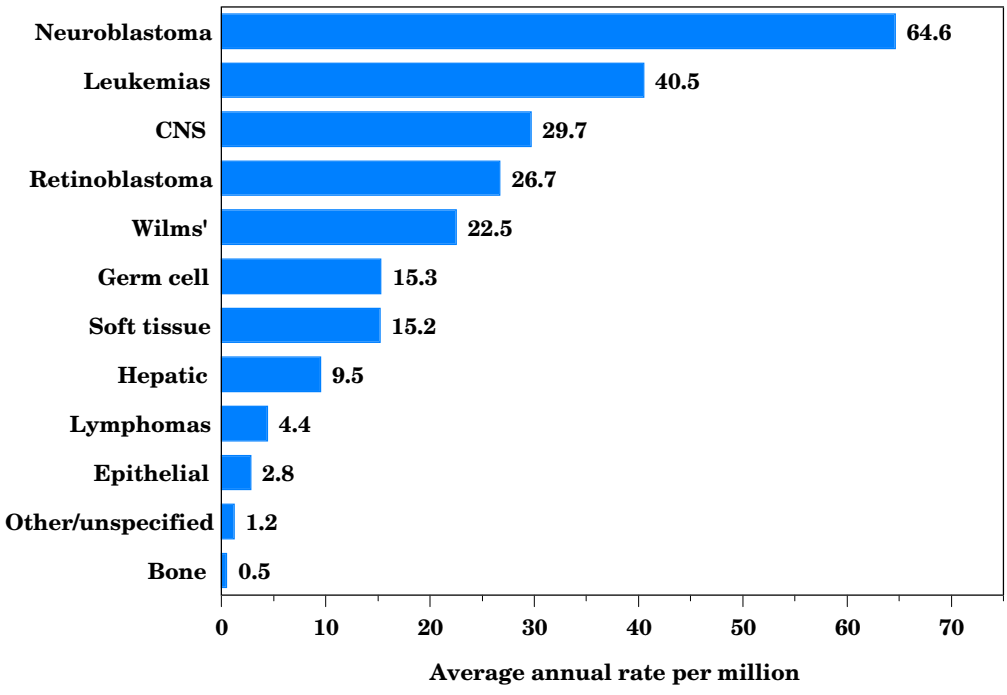
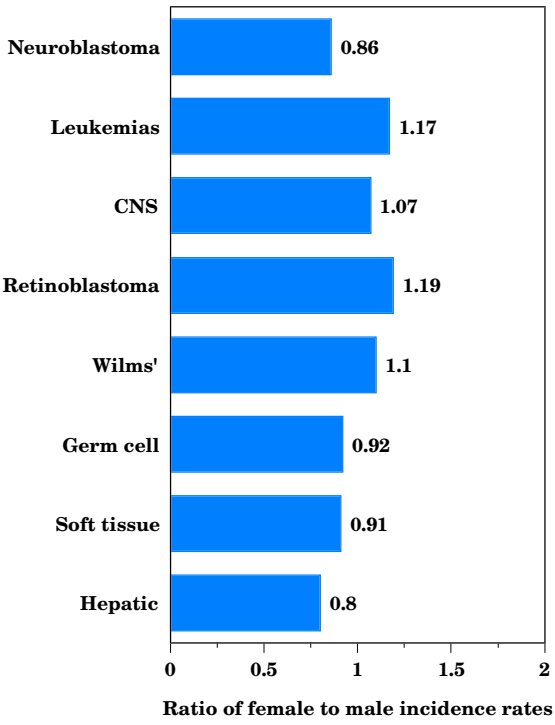


Figure XII.3: Ratios of female to male cancer incidence rates among infants by type, all races SEER, 1976-84 and 1986-94 combined

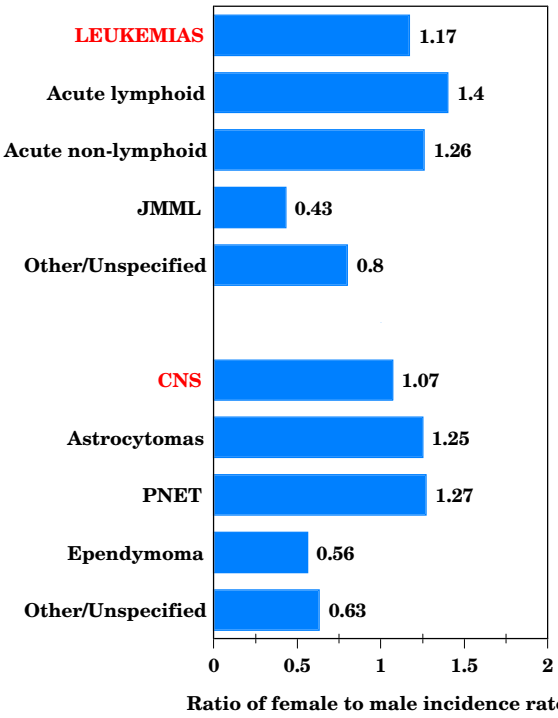


Each comprised about 6% of infant cancer. About 29% of the germ cell malignancies diagnosed during infancy were gonadal, which is half the percentage that occurs overall in children younger than 15 years of age. Unlike soft tissue tumors in older children, the rate of fibrosarcomas (5 per million infants) was similar to that of rhabdomyosarcomas (6 per million infants). This contrasts with the rhabdomyosarcoma and fibrosarcoma rates among children younger than 15 years of age of 4.6 per million and 2.3 per million, respectively. The rate for malignancies of the liver, almost exclusively hepatoblastoma, was 9.5 per million infants. Hepatoblastoma is similar to neuroblastoma, retinoblastoma, and Wilms' tumor (nephroblastoma) in that it is an embryonal malignancy with the age of peak incidence occurring during very early childhood. Lymphomas and especially bone cancers, which are quite important cancers among adolescents, are extremely rare in infants.

Sex-specific incidence

The female to male ratios of incidence rates for selected cancer types are illustrated in Figure XII.3. None of the sex differences were very pronounced. For leukemias and CNS cancer, however, the sex ratios differed by histologic subtype. Figure XII.4 provides female to male ratios for major subgroups of leukemia and CNS cancer. This illustration reveals that most types of infant leukemia and CNS cancer were more common in females than males, but JMML and ependymoma were notable exceptions. For both types of neoplasms, there is around a 2-fold higher average annual incidence in males than in females. The JMML rates were 4.0 per million male infants compared with 1.7 per million female infants. The ependymoma rates

Figure XII.4: Ratios of female to male cancer incidence rates among infants by type, all races SEER, 1976-84 and 1986-94 combined



were 6.2 per million male infants compared with 3.5 per million female infants.

Black-white differences in incidence

Figure XII.5 demonstrates the substantial discrepancy in black-white cancer incidence rates among children, especially young children. During infancy this racial variation is quite pronounced, in that white children (275 per million white infants) had a 40% higher malignancy rate than black children (196 per million black infants). This difference does not appear to be a result of earlier diagnosis for white children, based on the similar age pattern of incidence that is illustrated in Figure XII.5. The ratios of incidence rates for white relative to black infants are shown for selected cancer types in Figure XII.6. Leukemias accounted for a substantial proportion of the racial difference, in that the average annual rate for white infants

Figure XII.5: Total childhood cancer age-specific incidence rates by race, both sexes SEER, 1976-84 and 1986-94 combined

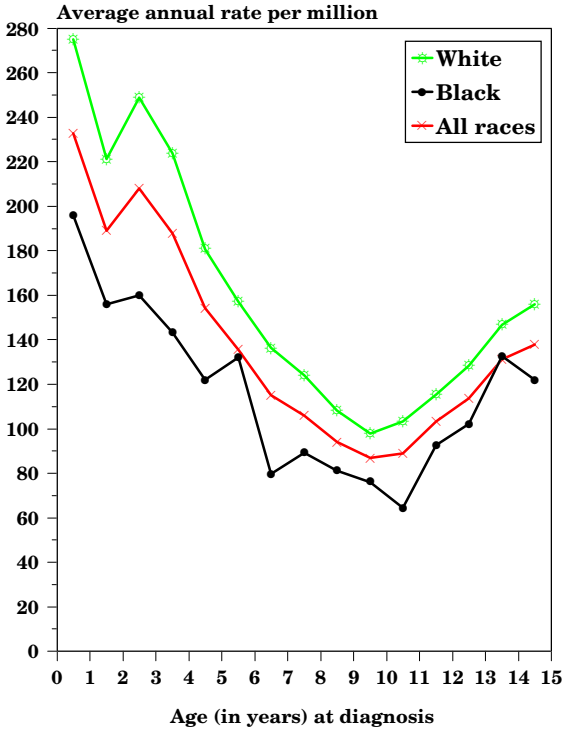
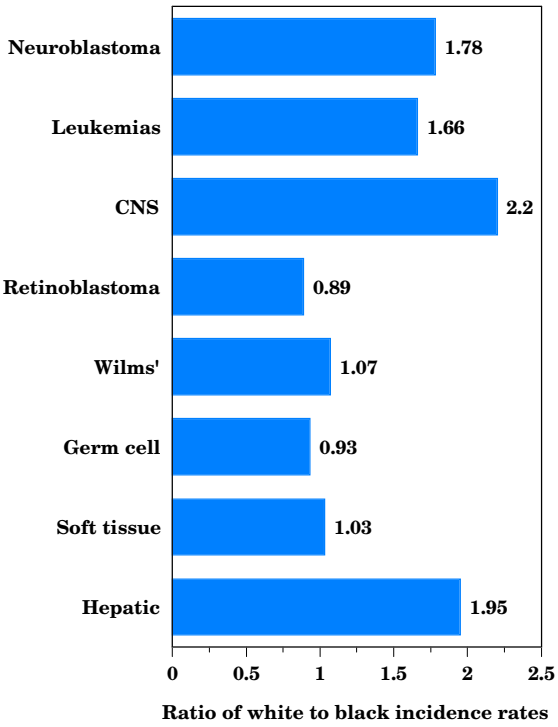


Figure XII.6: Ratios of white to black incidence rates among infants by type, both sexes SEER, 1976-84 and 1986-94 combined



(48.7 per million) was 66% higher than for black infants (29.4 per million). For neuroblastoma, white rates were 78% higher than black rates (79.0 vs. 44.5 per million, respectively). The relative difference was even greater for both liver cancer and CNS cancer. The infant incidence rate for hepatoblastoma was 95% higher in whites than in blacks (11.1 vs. 5.7 per million, respectively) and for CNS malignancies the rate was 120% higher for whites (37.7 per million) than for blacks (17.1 per million). Of the more common infant cancers, only rates of malignant germ cell tumors and retinoblastoma were higher in black infants, and these differences were slight. The small number of cases for black infants precluded reliable subgroup comparisons for the CNS cancers and leukemias.

Distribution by month of age at diagnosis

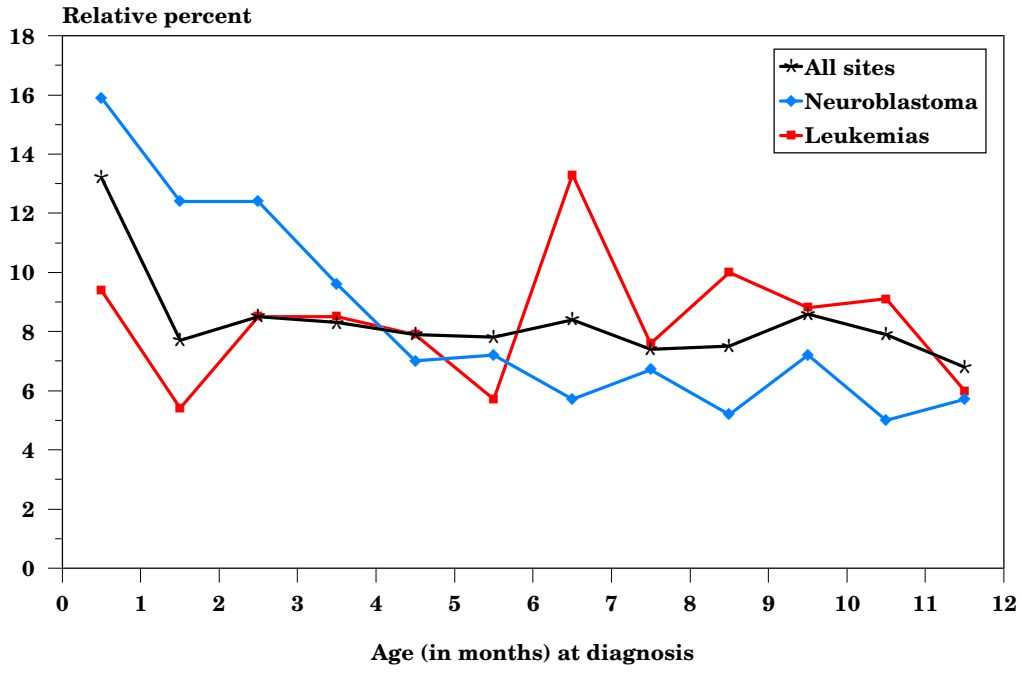
Although we lack a valid denominator (the number of children at risk by month of

age) to accurately calculate month-specific age incidence rates, the percentage of cancer cases (all types combined) by month of age at diagnosis is presented in Figure XII.7. This distribution shows that 13% of the infant malignancies were diagnosed during the first month following birth. Separate distributions for all leukemias combined and for neuroblastoma are also illustrated. Approximately half of neuroblastomas were diagnosed within the first 4 months of life, with 16% diagnosed during the month following birth. In fact, many of these tumors were likely detected *in utero*. Unlike neuroblastoma, the pattern of diagnosis for leukemias shows that the peak month of diagnosis occurred during the latter part of infancy, in the 7th month of life. Although not shown in the figure, the majority of infant germ cell tumors (56%) were diagnosed very soon after birth, before 2 months of age. There was no other cancer type that presented with such a large percentage of cases so early after birth.

TRENDS

As discussed in a previous report of trends in infant cancer [2], considerable caution must be exercised when interpreting temporal changes in rates for a single age group. Any trend analysis of incidence rates may be confounded by changes in population characteristics, the accuracy of census estimates, screening practices, diagnostic technology, morphology classifications, and case ascertainment. One or more of these factors could effectively conspire to show increasing incidence over time that is not reflective of more cancer, but rather of earlier diagnosis or better case identification. Neuroblastoma is an excellent example of this because of the recent introduction of (controversial) screening practices for earlier detection in Japan and Canada [3,4] and because of the

Figure XII.7: Percent distribution of infant cancer cases by month of age at diagnosis and type, all races both sexes, SEER, 1976-84 and 1986-94 combined



fairly recent advent of fetal ultrasound diagnosis [5]. With that caveat in place, a table of incidence rates for two time periods (1976-84 and 1986-94) is presented. (Table XII.1) The percentage change in the incidence rates is also shown.

These data imply that incidence rates of infant cancer were higher during the time period 1986-94 than the time period 1976-84. To what degree these data represent a true increase in cancer incidence in the US, compared with the influence of the potentially misleading factors that were mentioned above, has not been determined and requires more detailed assessment. For instance, the 125% increase in germ cell tumors is largely concentrated among nongonadal malignancies (primarily sacrococcygeal and pelvic) among female infants (see the monograph chapter entitled: "Germ Cell, Trophoblastic and Other Gonadal Tumors" for additional details). While this could indicate a true increase in the incidence of this disease, it is likely that a substantial proportion of the increase reflects changes over time in the identification by pathologists of malignant elements in teratomas with an otherwise benign appearance, leading to increased reporting of malignant teratomas among infants [6]. Likewise, the increase in reported rates of infant neuroblastoma, a disease with an exceptionally high survival rate and with a propensity for spontaneous regression, may reflect increased diagnoses and reporting of tumors that previously regressed before being detected [7].

Table XII.1: Average annual incidence rates per million by type, age <1, all races both sexes, SEER, 1976-84 and 1986-94

Cancer type	1976-84	1986-94	% Change
All cancer	197.9	269.3	36
Neuroblastoma	55.2	74.4	35
All leukemia	35.9	45.4	26
All CNS	23.3	36.5	57
Retinoblastoma	22.1	31.5	43
Wilms'	21.4	23.6	10
Germ cell	9.5	21.3	124
Soft tissue	13.6	16.6	22
Hepatic	7.6	11.4	50
Lymphoma	4.5	4.2	- 7
Epithelial	2.6	3.0	15
Other/Unspecified	1.4	1.0	-29
Bone	0.5	0.5	0

SURVIVAL

The prognosis for infants with cancer is often worse than in children of older ages, even when comparing the same histologic diagnosis. For instance, the 5-year relative survival for children younger than 15 years of age who were diagnosed with acute lymphoid leukemia from 1975-94 was well over 70%, but for infants the survival rate was 35%. Survival was bleak at all ages for acute non-lymphoid leukemia, but it was the poorest for infants, with a relative 5-year survival of 30%. This pattern was also evident for rhabdomyosarcomas and CNS tumors, particularly ependymomas and PNET. For ependymomas, 5-year relative survival for infants was less than 20% and for PNET it was less than 30%. Infant neuroblastoma was an exception. Over 80% of children diagnosed with neuroblastoma during infancy were alive 5 years following diagnosis. In contrast, for children diagnosed with neuroblastoma at age 1 year or older, the 5-year relative survival was about 45%. The 5-year survival from 1975-94 was also very good for children diagnosed with Wilms' tumor (86%) and retinoblastoma (over 90%).

SUMMARY

The age of peak incidence of cancer in children occurs during the first year of life. Neuroblastoma is the most common infant malignancy, followed by the leukemias and the CNS cancers. Female infants and male infants have essentially the same overall cancer incidence rates. White infants have substantially higher cancer rates than black infants for most cancer types. Inci-

dence rates were notably higher for the period 1986-94 compared with 1976-84, although many factors other than a real increase in incidence may be influencing this trend. Relative survival for infants is very good for neuroblastoma, Wilms' tumor and retinoblastoma, but not for most other types of cancer.

The distribution of malignant disease in infants is quite different from that which is found in older children, adolescents, or adults. For instance, embryonal tumors such as neuroblastoma, Wilms' tumor, retinoblastoma, medulloblastoma and hepatoblastoma are more prevalent in infants than in humans of any other age. The descriptive epidemiologic data that is presented here may serve to stimulate ideas for further etiologic research into the multifactorial nature of cancer occurrence. For example, the initial two-hit theory for carcinogenesis was developed primarily from clinical observations of a higher frequency of bilaterality of retinoblastoma in infants than in older children [8,9]. The study of infant cancer can aid in developing new hypotheses related to how aberrant genetic processes, early developmental abnormalities and gene-environment interactions contribute to the carcinogenic process. The study of retinoblastoma, and later of Wilms' tumor, led to the discovery of two important tumor suppressor genes that are related to adult as well as pediatric malignancy [10]. Recent work has shown that hematologic malignancies manifest differently in infants than in older children [11]. All these factors speak to the importance of further research into the epidemiology and biology of cancer in very young children.

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