

HIGHLIGHTS

Incidence

- ◆ In the US, approximately 700 children and adolescents younger than 20 years of age are diagnosed with tumors of the sympathetic nervous system each year, of which approximately 650 are neuroblastomas.
- ◆ Sympathetic nervous system tumors accounted for 7.8% of all cancers among children younger than 15 years of age.
- ◆ Over 97% of sympathetic nervous system tumors are neuroblastomas, embryonal malignancies of the sympathetic nervous system that occur almost exclusively in infants and very young children.
- ◆ Regardless of age, neuroblastomas most commonly occurred in the adrenal gland. Mediastinal tumors were more frequent in infants than in older children, while the opposite age pattern was observed for CNS tumors (Figure IV.1).
- ◆ The average age-adjusted annual incidence rate for all sympathetic nervous system cancers was 9.5 per million children.
- ◆ The occurrence of sympathetic nervous system malignancies was strongly age-dependent (Figure IV.2). For neuroblastomas alone, the incidence rate for both sexes combined during the second year of life (29 per million) was less than half that of infancy (64 per million).
- ◆ Neuroblastomas were by far the most common cancer of infancy, with an incidence rate almost double that of leukemia, the next most common malignancy that occurred during the first year of life.
- ◆ Sixteen percent of infant neuroblastomas were diagnosed during the first month following birth and 41% were diagnosed during the first 3 months of life (Figure IV.3).
- ◆ Over the 21-year observation period, there was little indication of an increase in the overall incidence of sympathetic nervous system malignancies (Figure IV.4). The estimated annual percent change in age-adjusted incidence rates was 0.4%.

Survival

- ◆ For children aged 1 to 4 years at diagnosis, 5-year survival rate improved from 35% during 1975-84 to 55% during 1985-94. Survival at 5 years from diagnosis was essentially unchanged over these time intervals among infants (83%) and children 5 years or older (40%).

Risk factors

- ◆ Relatively little is known about the etiology of sympathetic nervous system tumors (Table IV.3). The young age at onset of most cases illustrates the need to investigate exposure events occurring before conception and during gestation.

Table IV.1: Number of cases and age-adjusted* incidence rates per million by ICCC categories of sympathetic nervous system malignancies and sex, age <15, all races, SEER, 1975-95

Tumor Type	Males		Females		Total	
	No.	Rate	No.	Rate	No.	Rate
Neuroblastomas	787	9.4	705	8.9	1492	9.1
Other sympathetic nervous system	28	0.4	22	0.3	50	0.3
Total	815	9.8	727	9.2	1542	9.5

*Adjusted to the 1970 US standard population

INTRODUCTION

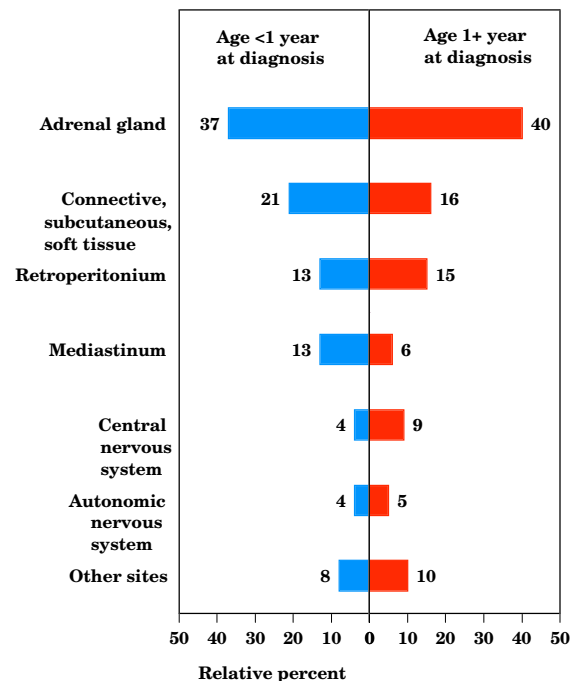
Neuroblastoma is an embryonal malignancy of the sympathetic nervous system that is derived from primordial neural crest cells and occurs almost exclusively in infants and young children [1]. Other childhood malignancies of the sympathetic nervous system include ganglioneuroblastoma, which is a more differentiated variant of neuroblastoma, and the histogenetically related pheochromocytoma [2]. Malignant paragangliomas, medulloepitheliomas, neuroepitheliomas and olfactory neurogenic tumors are also cancers of the sympathetic nervous system, although they are extremely rare in children and will not be emphasized. To follow the convention of the International Classification of Childhood Cancer system [3], data for neuroblastoma and ganglioblastoma are grouped together as one category (henceforth called neuroblastomas), and all other sympathetic nervous system malignancies as a second category. Because of important distinctions in biological characteristics and prognosis of neuroblastomas in infants (less than 1 year at diagnosis) compared with older children (older than 1 year of age at diagnosis) [1], data are provided to highlight the epidemiology of both age groups individually. Additionally, because the occurrence of neuroblastomas and other sympathetic nervous system malignancies are so rare in adolescents, the rate calculations and discussion are limited to children

younger than 15 years of age. In the US, approximately 700 children and adolescents younger than 20 years of age are diagnosed with tumors of the sympathetic nervous system each year, of which approximately 650 are neuroblastomas.

INCIDENCE

During the 21-year period from 1975 through 1995, 1,542 children were diagnosed with sympathetic nervous system malignancies in the SEER areas (Table IV.1). This represented 7.8% of all cancer

Figure IV.1 Percent distribution of neuroblastomas by primary site and age, all races, both sexes SEER, 1975-95



in this age group. The majority (97%) of these malignancies were neuroblastomas; only 50 children were diagnosed with any other histological type. Within the neuroblastoma category, ganglioneuroblastomas comprised 15% of tumors (8% among infants and 20% among those 1-14 years of age).

The distribution of neuroblastomas by primary site is shown in Figure IV.1. Regardless of age, neuroblastomas most commonly occurred in the adrenal gland. Mediastinal tumors were more frequent in infants than in older children, while the opposite age pattern was observed for CNS tumors.

Age-specific incidence

The incidence rate for all sympathetic nervous system cancers was 9.5 per million children. The occurrence of sympathetic nervous system malignancies, however, was strongly age-dependent. Figure IV.2 illustrates the incidence rates by single year of

Figure IV.2: Sympathetic nervous system age-specific incidence rates by sex, all races SEER, 1976-84 and 1986-94

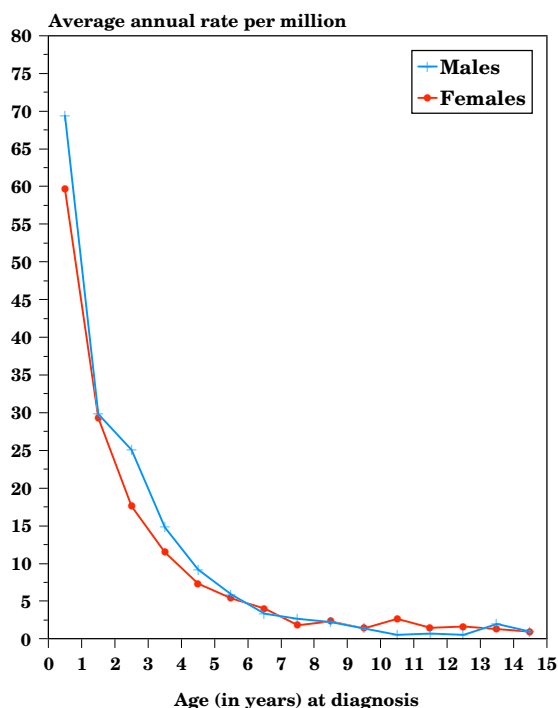
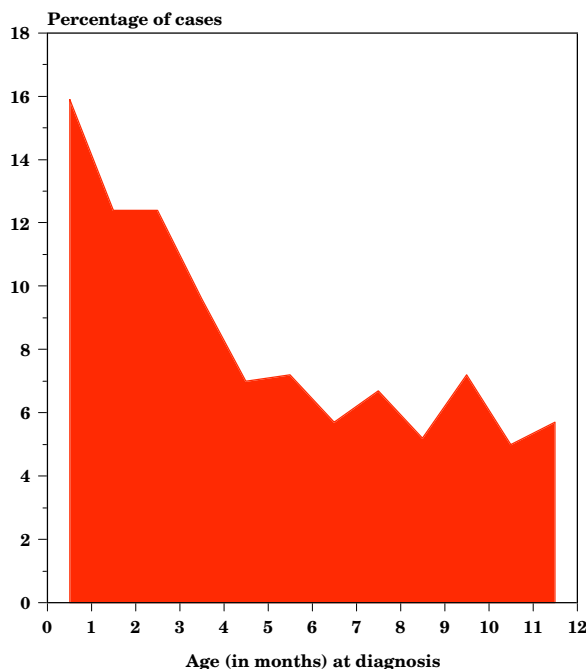


Figure IV.3: Percent distribution of infant neuroblastomas by month of age, all races, both sexes, SEER, 1975-95



age¹ and sex, and shows the predominance of neuroblastomas during infancy. For neuroblastomas alone, the incidence rate for both sexes combined during the second year of life (29 per million) was less than half that of infancy (64 per million). The rates for sympathetic nervous system tumors other than neuroblastomas were 1.2 per million for infants, and less than 1 per million for all other single years of age.

Neuroblastomas were by far the most common cancer of infancy with an incidence rate almost double that of leukemia, the next most common malignancy that occurs during the first year of life [4]. As shown in Figure IV.3, 16% of infant neuroblastomas were diagnosed during the first month following birth and 41% were diagnosed during the first 3 months of life.

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.

Table IV.2: Average annual age-specific incidence rates per million for all sympathetic nervous system tumors by age, sex, and race SEER 1975-95

Age (in years) at diagnosis	Males			Females		
	White	Black	All	White	Black	All
<1	83.6	50.5	69.3	74.1	38.4	59.6
1-14	8.2	7.4	7.3	7.6	6.5	6.5
<15*	10.1	8.8	9.8	9.6	8.6	9.2

* Adjusted to the 1970 US standard population

Sex and race-specific incidence

Figure IV.2 also demonstrates that the incidence of sympathetic nervous system cancer was slightly higher among males than females. For neuroblastomas, overall male rates (9.8 per million) were 6.5% higher than female rates (9.2 per million) with the greatest difference occurring during infancy (69.3 per million versus 59.6 per million for males and females, respectively). There was no discernable sex difference for sympathetic nervous system malignancies other than neuroblastomas.

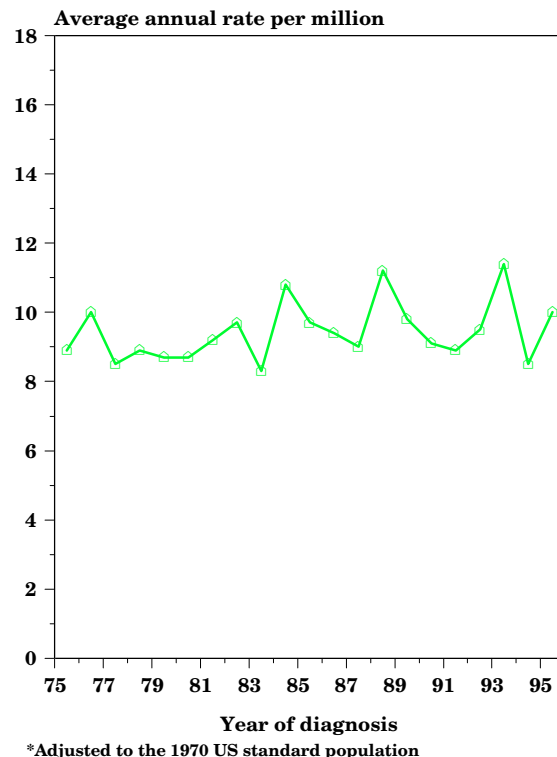
White infants of both sexes had a higher incidence of sympathetic nervous system tumors than did black infants, but little difference by race was observed among older children (Table IV.2). The ratio of white to black incidence rates among infants was 1.7:1 for males and 1:9:1 for females. In Table IV.2, “all races” includes whites, blacks, and children of other identified racial or ethnic backgrounds. There were too few cases of sympathetic nervous system among any other races to calculate reliable incidence rates.

TRENDS

Over the 21-year observation period, there was little indication of a linear trend in the overall incidence of sympathetic nervous system malignancies (Figure IV.4). The estimated annual percent change in

age-adjusted incidence rates was 0.37% ($p > 0.05$). Rates, however, have increased somewhat among infants during recent years. Figure IV.5 shows incidence rates of neuroblastomas by year of age at diagnosis for the periods 1976-84 versus 1986-94. Among infants, the rate in the earlier time period was 53 per million compared to 74 per million in the later time period. No differences in rates between the time

Figure IV.4: Trends in sympathetic nervous system age-adjusted* incidence rates by year of diagnosis age <15, all races, both sexes, SEER, 1975-95



periods occurred for children either 1 or 2 years of age at diagnosis. Thus, it does not appear that the increase among infants can be explained by a shift towards earlier age at diagnosis. The increase among infants, however may be a result of *de facto* fetal and neonatal screening. Mass screening of infants for neuroblastoma has been evaluated in recent years in Japan, Canada, and some countries in Europe [5,6]. Although systematic screening for neuroblastoma is not conducted in the United States, the awareness of screening in other countries and the recent widespread availability of non-invasive diagnostic tests for neuroblastoma may have resulted in US physicians diagnosing cases of neuroblastoma with minimal clinical symptomatology that previously were undetected. The documented ability of some fetal and infant

Figure IV.5: Neuroblastoma age-specific incidence rates by age, all races, both sexes SEER, 1976-84 and 1986-94

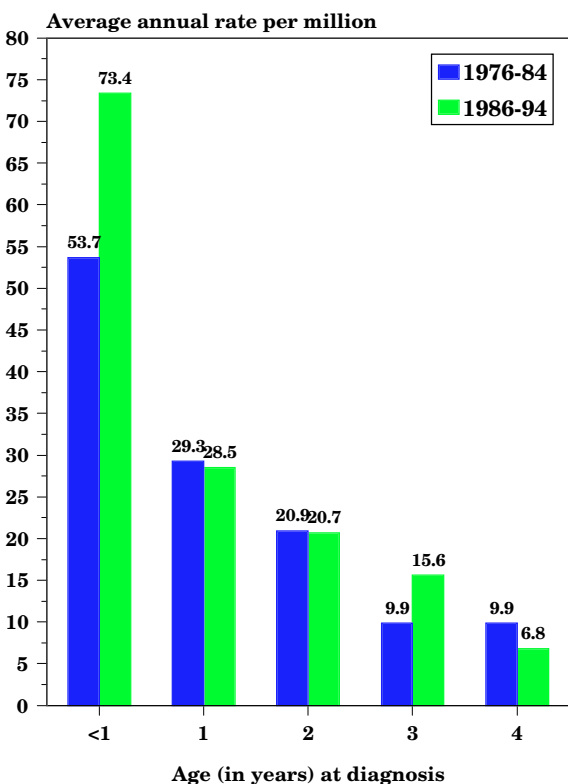
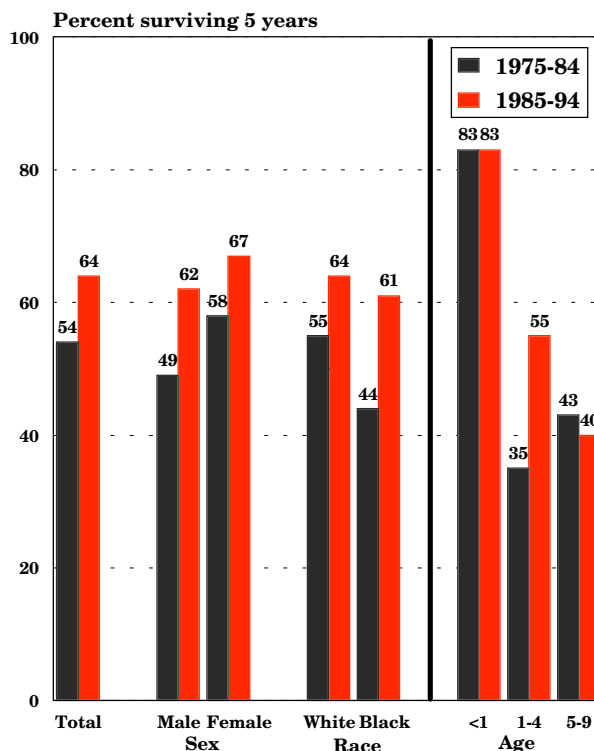


Figure IV.6: Neuroblastoma 5-year relative survival rates by sex, race, age, and time period SEER (9 areas), 1975-84 and 1985-94



neuroblastomas to spontaneously regress is consistent with the hypothesis that the increased incidence among infants is the result of detection of cases that were previously not diagnosed [1,9,10]. Also consistent with this hypothesis is the recent widespread use of prenatal ultrasound testing with coincidental detection of adrenal neuroblastomas [7,8].

SURVIVAL

Prognosis for neuroblastomas is dependent on age, stage of disease, and the molecular biologic and cytogenetic characteristics of the tumor [1]. Figure IV.6 illustrates the more favorable prognosis for infants with neuroblastoma (5-year relative survival rate, 83%) compared to children older than 1 year of age. The favorable outcome for infants with neuroblastoma no doubt reflects the favorable biological

Table IV.3: Current knowledge on causes of neuroblastoma (NB)

Exposure or Characteristic	Comments	References
Factors for which evidence is inconsistent or limited		
Medications	Two studies have reported increased risk when mothers took medications during pregnancy such as amphetamines, diuretics, tranquilizers, or muscle relaxers or for vaginal infection. Other studies have reported an association with maternal phenytoin treatment.	11,12,13
Hormones	Two studies reported that sex hormones were associated with an increase in risk. One of the studies reported a 10-fold increased risk for fertility drug use prior to pregnancy.	12,13,14
Birth characteristics	One study reported increased risk associated with low birth weight and protective effect for preterm delivery. This was not confirmed in two other studies.	13,15,16
Congenital anomalies	A variety of congenital anomalies has been reported to occur with NB in a small number of cases, but no consistent pattern of association has been shown.	11
Previous spontaneous abortion/fetal death	Previous spontaneous abortion was associated with increased risk in one study and decreased risk in another.	13,16
Alcohol	One study reported a dose-response relationship between frequency of alcohol use during pregnancy and NB, but another reported no effect. An association with fetal alcohol syndrome has also been reported.	12,13,17
Tobacco	An early study reported no effect of maternal smoking on risk. However, a later study suggested a weak dose-response relationship between level of maternal smoking during pregnancy and NB risk.	12,13
Paternal occupational exposures	Three studies have reported conflicting results on the risk associated with paternal employment in electronics, agriculture, and packaging and materials handling. Specific associated occupational exposures include electromagnetic fields, pesticides, hydrocarbons, dusts, rubber, paint, and radiation.	18-20

characteristics of neuroblastomas arising in this age group [1]. For children aged 1 to 4 years at diagnosis, the 5-year survival rate improved from 35% during 1975-84 to 55% during 1985-94. Survival was essentially unchanged during these time intervals for children older than 4 years of age (40%). There were no substantive differences in survival by sex or race (Figure IV.6).

RISK FACTORS

Relatively little is known about the etiology of sympathetic nervous system tumors (Table IV.3). The young age at onset of most cases illustrates the need to investigate exposure events occurring before conception and during gestation. The few epidemiological investigations of

neuroblastoma have not had sufficient statistical power or detailed data collection to provide convincing evidence of etiologic risk factors. Medications [11,12,13] and hormones used during pregnancy [12,13,14] are among the most suggestive factors suspected to increase the risk of neuroblastoma. Certain birth characteristics, pesticide exposure, and parental occupational exposure to electromagnetic fields [13,15,16,18-20] have been evaluated, but with conflicting results. In addition, clinical and molecular characteristics, such as amplification of the *nmyc* oncogene, loss of heterozygosity of the short arm of chromosome 1, and hyperdiploidy, may be useful in establishing homogenous disease subgroups for future epidemiological investigations of neuroblastoma [1].

SUMMARY

Sympathetic nervous system malignancies, of which neuroblastomas comprised 97% of the total, represented 7.8% of cancer in children younger than 15 years of age. The incidence rate was 9.5 per million children, however rates were strongly age-dependent. The incidence rate of sympathetic nervous system malignancies among infants was 65 per million, and the rate dropped by half in the second year of life. Overall, incidence rates did not change substantially during the study period. Among infants, however, there was an increase in incidence rates from 1986-94 compared with the period 1976-84. This increase was not noted in older children, thus excluding earlier age at diagnosis as a likely explanation for the trend. Rather, the increase likely arose from identification of previously undetected cases with minimal clinical symptomatology through widespread application of fetal ultrasound testing and noninvasive diagnostic tests for neuroblastoma. The known propensity of the neuroblastomas of infancy to undergo spontaneous regression supports this explanation. Five-year relative survival of

neuroblastomas was 83% for infants, 55% for children 1-4 years of age, and 40% for older children. Unfortunately, there is very little known about why neuroblastoma occurs, or what factors increase risk for occurrence.

Reference List

1. Brodeur GM, Castleberry RP. Neuroblastoma. In: Pizzo PA, Poplack DG, Editors. Principles and Practices of Pediatric Oncology. 3rd ed. Philadelphia, PA: Lippencott-Raven; 1997:761-797.
2. Russell DS, Rubinstein LJ. Pathology of Tumours of the Nervous System, 5th edition. Williams & Wilkins, Baltimore, MD, 1989; 898-943.
3. Kramarova E, Stiller CA. The international classification of childhood cancer. *Int J Cancer*. 1996;68:759-765.
4. Gurney JG, Ross JA, Wall DA, Bleyer WA, Severson RK, Robison LL. Infant cancer in the U.S.: histology-specific incidence and trends, 1973-1992. *J Pediatr Hematol Oncol* 1997; 19:428-432.
5. Woods WG, Tuchman M, Robson LL, Bernstein M, Leclerc JM, Brisson LC, Brossard J, Hill G, Shuster J, Luepker R, Byrne T, Weitzman S, Bunin G, Lemieux. A population-based study of the usefulness of screening for neuroblastoma. *Lancet* 1996; 348:1682-1687.
6. Parker L, Powell J. Screening for neuroblastoma in infants younger than 1 year of age: review of the first 30 years. *Med Pediatr Onc* 1998; 31:455-469.
7. Moore RM, Jeng LL, Kaczmarek RG, Placek PJ. Use of diagnostic imaging procedures and fetal and monitoring devices in the care of pregnant women. *Public Health Rep* 1990;105: 471-475.
8. Archarya S, Jayabose S, Kogan SJ, Tugal O, Beneck D, Leslie D, Slim M. Prenatally diagnosed neuroblastoma. *Cancer* 1997; 80:304-310.
9. Carlsen NLT. Neuroblastoma: epidemiology and pattern of regression. Problems in interpreting results of mass screening. *J Pediatr Hemat Oncol* 1992;14:103-110.
10. Evans AE, Chatten J, D'Angio GJ, Gerson JM, Robinson J, Schnauffer L. A review of 17 IV-S neuroblastoma patients at the Children's Hospital of Philadelphia. *Cancer* 1980;45:833-9.
11. Bodeur GM. Neuroblastoma and other peripheral neuroectodermal tumors. Chapter 24. In: Clinical Pediatric Oncology, 4th Ed. Fernbach DJ, Vietti TJ (Eds.). Mosby Yearbook, St. Louis, MO., 1991.

12. Kramer S, Ward E, Meadows AT, and Malone KE. Medical and drug risk factors associated with neuroblastoma: A case control study. *J Natl Cancer Inst* 1987;78:797-804.
13. Schwartzbaum JA. Influence of mother's prenatal drug consumption on risk of neuroblastoma in the child. *Am J Epidemiol* 1992;135:1358-1367.
14. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, and Mahoney MC. Gravid health status, medication use, and risk of neuroblastoma. *Am J Epidemiol* 1996;143:996-1001.
15. Johnson CC and Spitz MR. Neuroblastoma: A case control analysis of birth characteristics. *J Natl Cancer Inst* 1985;74:789-192.
16. Neglia JP, Smithson WA, Gunderson P, King FL, Singher LJ, and Robison LL. Prenatal and perinatal risk factors for neuroblastoma. A case-control study. *Cancer* 1988;61:2202-2206.
17. Kinney H, Faix R, and Brazy J. The fetal alcohol syndrome and neuroblastoma. *Pediatrics* 1980;66:130-132.
18. Bunin GR, Ward E, Kramer S, Rhee CA, and Meadows AT. Neuroblastoma and parental occupation. *Am J Epidemiol* 1990;131:776-780.
19. Spitz MR and Johnson CC. Neuroblastoma and paternal occupation. *Am J Epidemiol* 1985;121:924-929.
20. Wilkins JR and Hundley VD. Paternal occupational exposure to electromagnetic fields and neuroblastoma in offspring. *Am J Epidemiol* 1990;131:995-1008.