Residential Pesticide Exposure and Neuroblastoma

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Neuroblastoma is the most common neoplasm in children under 1 year of age. We examined the relation between residential exposure to pesticides and neuroblastoma, using data from a case-control study of risk factors for neuroblastoma. Incident cases of neuroblastoma (N = 538) were identified through the Pediatric Oncology Group and the Children's Cancer Group. One age-matched control was identified for each case by random digit dialing. Telephone interviews with each parent collected information on residential exposure to pesticides. Pesticide use in both the home and garden were modestly associated with neuroblastoma [odds ratio (OR) = 1.6 (95% confidence interval [95% CI] = 1.0–2.3, and OR = 1.7 (95% CI = 0.9–2.1), respectively]. Compared with infants [OR = 1.0 (95% CI = 0.6–2.0)], stronger associations were found for garden pesticides in children diagnosed after 1 year of age [OR = 2.2 (95% CI = 1.3–3.6)], which suggests that pesticides may act through a mechanism more common for neuroblastomas in older children. There was no evidence of differential pesticide effects in subgroups of neuroblastoma defied by MYCN oncogene amplification or tumor stage. (Epidemiology 2001;12:20–27)

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Neuroblastoma is a neoplasm derived from embryonic neural crest cells. It is the most common tumor occurring in the first year of life and accounts for 8–10% of all childhood tumors.[1] In the United States, neuroblastoma occurs in approximately 1 of every 7,000 live births, contributing about 550 new cases each year, with an annual incidence rate of 9.2 cases per million children under 15 years of age.[1] At diagnosis, more than half of these children are under 2 years of age, and approximately 80% are under 4 years of age; rarely is neuroblastoma diagnosed in children older than 10 years of age.

The severity of neuroblastoma ranges from asymptomatic tumors that spontaneously regress to rapidly progressing tumors that respond poorly to aggressive treatment and often lead to death.[2] Clinical and biological subgroups of neuroblastoma have been characterized by the age at diagnosis, tumor stage at diagnosis, and specific genetic alterations such as MYCN oncogene amplification.[2,3] These disease subgroups are known to have prognostic significance but may also be of etiologic relevance.

Relatively little is known about etiologic factors for neuroblastoma. The young age at onset of most cases emphasizes the need to investigate exposures and events occurring before conception and during gestation in addition to genetic contributions to neuroblastoma.[4] Previous studies have reported positive associations between farm residence or parental employment in agriculture and neuroblastoma, but findings have been inconsistent.[5–8] The results from these studies, combined with reports from studies of occupational and residential pesticides and other childhood cancers and birth outcomes, have prompted this investigation. To assess the potential effects of residential pesticides on neuroblastoma, we conducted a large case-control study of neuroblastoma and collected detailed information from parents on parental and childhood residential pesticide exposures.

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Subjects and Methods

STUDY POPULATION

The details of this study are provided elsewhere.[13] Briefly, children diagnosed with neuroblastoma between May 1, 1992, and April 30, 1994, at one of 139 participating hospitals throughout the United States and Canada were eligible to participate if their biological mother was available for telephone interview and spoke English or Spanish. Fathers were eligible only if mothers also provided interviews. Five hundred thirty-eight case mothers (73% of eligible) and 405 case fathers (76% of eligible) provided interviews. Controls were identified through telephone random digit dialing and individually matched to cases by telephone number (area code and exchange) and on the date of birth (±6 months for cases diagnosed under 3 years of age, ±1 year for cases diagnosed over 3 years of age). Five hundred four control mothers (72% of eligible) and 304 control fathers (61% of eligible) completed interviews.

DATA SOURCES

Two collaborative clinical trial groups, Children's Cancer Group and Pediatric Oncology Group, confirmed the diagnosis of neuroblastoma and provided information on the clinical stage at diagnosis (International Neuroblastoma Staging System; INSS) and *MYCN* amplification status for case children. Telephone interviews with both case and control mothers and fathers collected information about family medical histories, vitamin and medication use, parental job histories, occupational exposures, residential pesticide use, and other factors.

Each parent was separately asked about pesticides used in the home and garden and by professional exterminators during the time period from 1 month before conception to the date of diagnosis. Interviews queried the type of pesticide, as well as the purpose, frequency, and timing of use relative to dates of the child's conception and birth. Because both parents were interviewed independently, maternal and paternal reports of pesticide use or timing of use sometimes differed. Among households in which parents did not agree, it was not possible to determine which parent more accurately recalled the details about pesticide use. Thus, for each pesticide category, information from both parents was combined to create two exposure indicator variables representing the following: (1) either the mother or father reported pesticide use, but the other parent reported no use, or (2) both parents in the household reported pesticide use. Both were compared with a reference group in which both parents reported no pesticide use. Both parents reporting an exposure does not necessarily indicate that the exposure was greater but may indicate a greater probability that the exposure actually occurred. This classification method was possible only when both parents provided information.

To determine whether the timing of exposure was associated with neuroblastoma, exposures were evaluated in two time windows representing the period from 1 month before conception through the end of pregnancy and the period from birth to diagnosis. Exposures during the childhood period were evaluated only for children older than 3 months of age at diagnosis. To evaluate whether the effects of pesticide exposure differed in clinical and biological subgroups of neuroblastoma, which might define etiologically homogeneous subgroups, analyses were stratified by the child's age, and for cases, the tumor's stage and MYCN amplification status.

ANALYSIS

The relation between residential pesticide exposures and neuroblastoma was evaluated by estimating the odds ratios (ORs) for both parents reporting use (OR_2) and either parent reporting use (OR_1) and 95% confidence intervals (CIs) using unconditional logistic regression. The matching factor, child's age, was assessed as a continuous variable and as a group of indicator variables categorizing age into 6-month strata. Because the continuous form of age adequately accounted for the effects of age and met the linearity requirements of logistic models, it was included in all models. The potential confounding effects of race, household income, maternal age, and education were also evaluated. Of these, only household income was retained in the final analyses, based on the change in the OR with its inclusion and on its weak association with pesticide use and neuroblastoma in these data.

To assess potential bias due to missing paternal information, analyses were conducted that used only maternal reports of pesticide use and stratified by whether the father completed an interview.

Results

Demographic characteristics were similarly distributed between cases and controls in the total study (Table 1). Twenty-five per cent of cases and 39% of controls were excluded because the father was not interviewed. Mothers of these children had slightly lower household income and education, were younger, and were less likely to be white compared with those included. Thirty cases and 18 controls were also excluded because of missing information about household income, leaving 390 cases and 296 controls available for the residential pesticide analyses.

In the total study population, pesticide use was common from the month before conception to the reference date; 65% of parents reported using pesticides in or around the home, 47% reported using lawn and garden pesticides, and 29% reported professional extermination. The proportion of mothers and fathers reporting use of these pesticides in their individual interviews was similar, but the level of agreement when both parents participated ranged from weak [home pesticides *Kappa* (K) = 0.21 to moderate (extermination K = 0.6, garden pesticides K = 0.4). Parental agreement was similar for cases as compared with controls. In general, subjects

TABLE 1. Demographic Distribution of Cases (Ca) and Controls (Co), Based on Maternal Information

	Total Study		Pesticide Investigation			
			Participants		Exclusions*	
	Ca N = 538	Co N = 504	Ca N = 390	Co N = 296	Ca N = 148	Co N = 208
Child's age, years						
<1	38	39	40	43	35	33
1	22	22	22	22	22	21
2–4	30	29	28	27	34	33
≥5	9	10	10	8	9	13
Maternal age, years						
<20	9	7	4	3	20	13
20–30	61	63	62	63	61	62
≥31	30	30	34	34	19	25
Household income						
≤$10,000	18	11	11	6	39	19
>$10,000	82	89	89	94	61	81
Maternal education						
<High school	11	10	7	6	22	16
≥High school	68	63	68	62	69	64
≥College	21	27	25	32	9	20
Maternal race						
White non-Hispanic	79	78	85	86	62	67
Other	21	22	15	14	38	33

Data are presented as percentages.
* Exclusions are children missing paternal interview or household income information.

whose parents agreed in their reports of pesticide use were demographically similar to those whose parents disagreed, although parents in disagreement about extermination were of slightly lower income.

When both parents reported use of pesticides, the use of professional extermination was associated with neuroblastoma [OR, = 1.4 (95% CI = 0.9–2.1)], as were household pesticides [ORB = 1.6 (95% CI = 1.0–2.3)] and garden pesticides [OR, = 1.7 (95% CI = 0.9–2.1)]. These associations were not evident when only one parent reported use (Table 2). Effect estimates associated with each type of pesticide were slightly stronger for use during the childhood period than during pregnancy; however, pesticide use tended to be correlated across the two time periods. In most households, when at least one parent reported pesticide use during pregnancy, pesticide use was also reported during childhood (63% for home pesticides and 62% for garden pesticides), limiting the ability of this study to evaluate further the independent effects of pesticide exposure during specific time periods.

Although few parents reported the brand or chemical name of the pesticides used, many reported the purpose of pesticide use. The most commonly reported purpose for using pesticides in the home was to control for ants or roaches (41%), which was associated with neuroblastoma [ORB = 1.8 (95% CI = 1.0–3.1)]. Less frequently reported reasons for using home pesticides included treatment for flies (10%), fleas (11%), and termites (<1%). Among the specific types of pesticides used in the garden, herbicides were more strongly associated with neuroblastoma [ORB = 1.9 (95% CI = 1.1–3.2)] than were insecticides [ORB = 1.3 (95% CI = 0.7–2.3)].

TABLE 2. Residential Pesticide Use and the Risk of Neuroblastoma by Period, as Reported by Either One or Both Parents, of Exposure

	Ever				Preconception-Pregnancy				Childhocdt			
	Ca_N	Co_N	OR*	95% CI	Ca_N	Co_N	OR*	95% CI	Ca_N	Co_N	OR*	95% CI
Extermination												
Unexposed‡	261	211	1.0		227	176	1.0		227	176	1.0	
Either	61	43	1.1	0.8–1.7	29	23	0.9	0.5–1.6	37	24	1.1	0.6–2.0
Both	63	38	1.4	0.9–2.1	23	15	1.0	0.5–2.1	46	25	1.5	0.8–2.6
Home pesticide												
Unexposed‡	90	87	1.0		83	76	1.0		83	76	1.0	
Either	141	108	1.2	0.8–1.8	82	70	0.9	0.5–1.4	94	71	1.2	0.8–1.9
Both	150	92	1.6	1.0–2.3	93	52	1.3	0.8–3.3	92	50	1.4	0.9–2.2
Garden pesticide												
Unexposed‡	145	126	1.0		123	109	1.0		123	109	1.0	
Either	114	91	1.2	0.8–1.7	72	54	1.4	0.8–1.9	68	62	0.8	0.5–1.3
Both	113	66	1.7	0.9–2.1	65	39	1.3	0.8–2.0	74	36	1.8	1.0–3.1

* Odds ratios (ORs) adjusted for household income and child's age. ORs for "Either" reflect either mother or father reponing pesticide use, ORs for "Both" reflect both mother and father reporting pesticide use.
† Children <3 months of age were excluded from models of childhood period.
‡ Reference category reflects both parents reporting no pesticide use.

TABLE 3. Residential Pesticide Use, as Reported by Either One or Both Parents, and the Risk of Neuroblastoma by Age at Diaenosis

	Age <1				Age 1+			
	Ca_N	Co_N	OR*	95% CI	Ca_N	Co_N	OR*	95% CI
Extermination								
Unexposedt	111	101	1.0		150	110	1.0	
Either	19	12	1.4	0.6–3.0	42	31	0.9	0.5–1.6
Both	22	14	1.5	0.7–3.0	41	24	1.3	0.7–2.3
Home pesticide								
Unexposed†	51	46	1.0		39	41	1.0	
Either	57	48	1.1	0.6–1.9	84	60	1.5	0.8–2.5
Both	44	32	1.2	0.7–2.2	106	60	1.9	1.1–3.2
Garden aesticide								
Unexposed†	70	59	1.0		75	67	1.0	
Either	47	37	1.1	0.6-2.0	67	54	1.2	0.7–2.0
Both	31	27	1.0	0.6-2.0	82	39	2.2	1.3–3.6
Garden pesticide type								
Herbicide								
Either	17	14	1.0	0.5–2.3	29	22	1.3	0.7–2.6
Both	12	9	1.2	0.5–3.1	39	18	2.2	1.1-4.3
Insecticide								
Either	23	17	1.2	0.6–2.5	31	33	1.0	0.6–1.9
Both	10	11	0.8	0.3–2.2	24	14	1.7	0.8–3.6

* Odds ratios (ORs) adjusted for household income and child's age. OR for "Either" reflects either mother or father reporting pesticide use. OR for "Both" reflects both parents reporting pesticide use.
t Reference category reflects both parents reporting no pesticide use.

Few parents reported the reason for professional extermination, which precluded meaningful analysis.

The effects of pesticides were generally stronger among children diagnosed at 1 year of age or older than among those diagnosed under 1 year of age (Table 3). Home pesticides were not notably associated with neuroblastoma in children under 1 year of age [OR, = 1.2 (95% CI = 0.7–2.2)]; however, among children 1 year of age and older the effect was nearly doubled [OR, = 1.9 (95% CI = 1.1–3.2)]. This pattern was found for specific uses of pesticides, such as the treatment of ants, roaches, and flies in the home. Garden pesticides were also more strongly associated with neuroblastoma among the older children [OR, = 2.2 (95% CI = 1.3–3.6)] than among children under 1 year of age [OR_B = 1.0 (95% CI = 0.6–2.0)], including garden pesticides specified as herbicides or insecticides. This age-specific pattern was not evident in relation to professional extermination.

Estimated associations between neuroblastoma and professibnal extermination or garden pesticides were slightly stronger among case children with amplified MYCN status than those with normal MYCN status; however, the confidence intervals in the two groups overlapped substantially (Table 4). This was also the case for comparison of pesticide effects in early- vs late-stage neuroblastoma compared with controls. MYCN amplification and late-stage disease were correlated with the age at diagnosis (1 year and older).

We evaluated the independent effects of home pesticides, garden pesticides, and professional extermination by adjusting each for the others. Adjustment for multiple pesticide use had no effect on the overall results (data

TABLE 4. The Effect of Pesticides, as Reported by Either One or Both Parents, in Subgroups of Neuroblastoma Cases Stratified by the International Neuroblastoma Staging System (INSS) and MYCN Oncogene Amplification Status

	MYCN Normal				MYCN Amplified			INSS 1, 2, and 4S			INSS 3 and 4		
	Co_N*	Ca_N	OR†	95% CI	Ca_N	OR†	95% CI	Ca_N	OR†	95% CI	Ca_N	OR†	95% CI
Extermination													
Unexposed$	211	178	1.0		30	1.0		82	1.0		139	1.0	
Either	43	34	0.9	0.6–1.5	6	0.8	0.3–2.2	19	1.3	0.7–2.4	32	0.9	0.5–1.5
Both	38	34	1.1	0.6–1.8	9	1.9	0.8–4.4	14	1.1	0.5–2.1	36	1.3	0.8–2.2
Home pesticide													
Unexposed$	87	52	1.0		11	1.0		30	1.0		44	1.0	
Either	108	94	1.5	0.9–2.3	15	1.1	0.5–2.5	43	1.3	0.7–2.2	79	1.3	0.8–2.1
Both	92	98	1.8	1.1–2.8	18	1.6	0.7–3.5	44	1.5	0.9–2.7	80	1.5	0.9–2.4
Garden pesticide													
Unexposed$	126	89	1.0		18	1.0		50	1.0		69	1.0	
Either	91	83	1.3	0.9–2.0	8	0.7	0.3–1.7	41	1.2	0.7–2.1	60	1.3	0.8–2.1
Both	66	66	1.4	0.9–2.3	15	2.0	0.9–4.4	25	1.2	0.7–2.2	71	2.2	1.3–3.5

*, tEach case (Ca) group was compared with all controls (Co).
† Odds ratios (ORs) adjusted for household income and child's age. ORs for "Either" reflect either mother or father reporting pesticide use. OR for "Both" reflects both parents reporting pesticide use.
‡ Reference category reflects both parents reporting no exposure.

not shown). Home pesticide use was often reported in addition to garden pesticides (77%) or professional exterminators (74%), but there was no evidence of interaction among these three categories of residential pesticides.

Parents reporting garden pesticide use were asked who applied the chemical. Many mothers and fathers reported that the father applied the pesticides (57% and 78%, respectively). When the mother reported that she applied the pesticides, the neuroblastoma effect estimate was higher [OR = 2.2 (95% CI = 1.3–3.8)] than when she reported the father applying pesticides [OR = 1.5 (95% CI = 1.1–2.1)] or when the father reported that he applied the pesticide [OR = 1.1 (95% CI = 0.8–1.5)]. To evaluate the effect of missing paternal pesticide data, we used only the pesticide information reported by the mother, stratified by the presence of paternal information. The association between home pesticides and neuroblastoma was similar when paternal information was [OR = 1.3 (95% CI = 0.9–1.7)] and was not [OR = 1.3 (95% CI = 0.8–2.1)] available. Results for extermination were also similar. The association with garden pesticides, however, was slightly higher when the father's information was available [OR = 1.8 (95% CI = 1.3–2.5)] than when it was not [OR = 1.2 (95% CI = 0.7–2.2)], after adjustment for maternal age, education, and income.

Discussion

When pesticides are used, children have great potential for exposure, owing to the amount of time they spend on the floor, in the yard, and with pets, which are all associated with higher levels of pesticides.[14–16] Residential pesticide use during pregnancy and childhood was common in this study. Pesticides used in the home by parents and professional exterminators were essentially insecticides. Garden pesticides included both herbicides and insecticides.

Pesticides used in both the home and garden were moderately associated with increased neuroblastoma. The strongest associations were for garden pesticides in children diagnosed after 1 year of age. The stronger effect in older children may reflect either a longer period of pesticide exposure and time for the action of pesticides to contribute to neuroblastoma or different effects of pesticides in an etiologic pathway marked by an older age at diagnosis. Mobile children can access more floor and yard areas where pesticides have been applied, compared with infants, who are typically restricted to a protected area and may have lower opportunity for exposure. Alternately, the clinical heterogeneity of neuroblastoma may reflect etiologic differences whereby pesticides may act through a biological pathway more common to the type of neuroblastoma in older children. Age, tumor stage, and MYCN amplification status are commonly used to distinguish clinical subgroups of neuroblastoma.[3] Because the effects of pesticides were not greatly modified by MYCN amplification status, these data do not support the potential for pesticides to act through a pathway directly involving MYCN amplification. Further evaluation of the effects of pesticides in biological subgroups of disease was limited by sparse data representing combinations of age, stage at diagnosis, and MYCN amplification status and lack of data on other biological characteristics.

Although pesticides could be involved in the development of neuroblastoma by initiating either germ-line or somatic cell mutations, few are known mutagens.[17–19] Nonmutagenic theories include the possibility that pesticides are involved in carcinogenesis through tumor promotion. Some pesticides (for example, chlordane, lindane, and chlorpyrifos) are known to affect the immune system, potentially contributing to neuroblastoma development by decreasing regulation of cell proliferation or surveillance for dysfunctional or undifferentiated neural crest cells.[20–23] Other pesticides demonstrate estrogen-mimicking properties or otherwise disrupt endogenous hormonal activity. These pesticides could alter the proliferation or differentiation of neural cells that continue to be regulated by hormones into the neonatal period.[19,24–31]

Although the mechanisms described are plausible means by which pesticides could contribute to the development of neuroblastoma, further interpretation of the positive yet imprecise associations reported here requires consideration of measurement and design issues. In this study, exposure measurement was based on parents' self-report of residential pesticide use. This measurement assumes that parents can remember and report their prior use of pesticides and that the quality of recall and reporting does not differ by case status. Most parents in this study were asked to recall pesticide use from 1 to 5 years earlier. While this interval is shorter than for most cancer studies, it was still a long time to remember the details about the pesticides used, especially details concerning the timing of exposure relative to pregnancy and the child's birth.

To improve the validity of the exposure classification, we considered whether only one parent or both parents reported exposure. Both parents' agreement that a pesticide was used would not necessarily indicate greater exposure than reports by only one parent, but confirmation from both parents increased our confidence that the reported pesticide was really used. Thirty-five per cent of the couples in our data disagreed about whether pesticides were used, underscoring the problem of error in recall or reporting. Yet, because concordance in pesticide reporting between mothers and fathers did not differ by case status, it does not appear that case parents conferred with each other or otherwise put greater effort toward recalling pesticide use than control parents. Thus, it seems unlikely that differential recall based on motivation of case parents might have resulted in an overestimate of the exposure effect in this study.[32] Nevertheless, we do not know whether the category that requires both parents to report is truly more or less sensitive to recall bias than exposures reported by only one parent.

Although requiring both parents to contribute to the exposure classification may have reduced bias in the effect estimates, it also reduced the study size by excluding children with information from only one parent. To assess potential selection bias owing to missing paternal information, we conducted analyses using only the mothers' reports of pesticides, stratified by whether or not the father provided an interview. Although the association between mother's report of garden pesticide use and neuroblastoma was higher when the father was interviewed than when he was not, effect estimates associated with home pesticide use and professional extermination were similar between the two groups. It remains unclear why maternal reports of garden pesticide use would differ by the joint distribution of case status and paternal participation. It is possible that because fathers were more likely to apply garden pesticides in these data, if the father was absent from the home, either garden pesticides were not used or the mother was less likely to remember their use.

Even when parents accurately report the use of pesticides and the timing of use with respect to pregnancy or childhood, use does not necessarily confer exposure to the child. The chemical properties of the pesticides, method of application, use of protective equipment, activity of the child, and consequently the exposure pathways (dermal, ingestion, and inhalation) may be important determinants of the type and degree of pesticide exposure. Furthermore, pesticides are not a homogenous group of chemicals. Grouping home pesticides by the method of application (sprays, solids, and traps) did not reveal substantial differences in associations with neuroblastoma; effect estimates for each application method followed patterns similar to those of general home pesticide use, but estimates were much less stable. Although some parents reported the brand name or the purpose for using pesticides, few reported the chemical. Because multiple chemicals may be found in products of the same brand, there was not enough information to evaluate the effects of specific chemicals in these data. There was also no way to account for pesticides used in other settings such as daycare or for pesticide exposure from environmental sources such as ground or surface water or dusts from regional spraying. Exposure assessment methods that account for details surrounding exposure specific to the home and individual are necessary to advance our understanding of the effects of pesticides.[33]

Few other studies have evaluated the possible relation between pesticides and neuroblastoma in any detail. In a prospective study of farming families in Norway, Kristensen et al[5] inferred pesticide exposure through farm residence and pesticide purchase records. This study reported elevated rates of neuroblastoma among children whose families resided on farms around the time of birth [OR = 2.5 (95% CI = 1.0–6.1)]. Among the few studies of occupational exposures, only one collected specific information about pesticide exposure, reporting increased risk of neuroblastoma when either the mother or father used pesticides on the job.[34] The other occupational studies, which produced equivocal results, based pesticide exposure on the parent's job title rather than specific pesticide exposure information.[6–8]

This study was large and appeared to accurately represent children with neuroblastoma. Case children were referred through Children's Cancer Group and Pediatric Oncology Group, which are estimated to see nearly 95% of all children diagnosed with neuroblastoma in the United States.[35] Furthermore, the age distribution of children in this study was similar to that of the children with neuroblastoma identified through the Surveillance, Epidemiology, and End Results Program, a population-based registry system representing 10% of the U.S. population.[36] Nevertheless, it is possible that the use of random digit dialing to select controls may have resulted in similar distributions of pesticide exposure among cases and controls, based on pesticide use patterns by geographic region. If this occurred in our study, the effect of pesticides estimated may be underestimated.

The amount of information on residential pesticides in this study has allowed a more detailed evaluation of the relation between pesticides and neuroblastoma than previous studies. The differing effects of pesticide in age subgroups of neuroblastoma suggest that pesticides may be involved in etiologic pathways specific to the types of neuroblastoma in older children.

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Appendix

Participating Principal Investigators: Children's Cancer Group

Institutions	Investigators	Grant No.
Children's Cancer Group		
Group Operations Center (Arcadia, CA)	W. Archie Bleyer Anita Khayat Harland Sather Mark Krailo Joanie Stuckley Daniel Stram Richard Sposto	CA13539
University of Michigan Medical Center (Ann Arbor, MI)	Raymond Hutchinson	CA02971
University of California Medical Center (San Francisco, CA)	Katherine Matthay	CA17829
University of Wisconsin Hospital (Madison, WI)	Diane Puccetti	CA05436
Children's Hospital and Medical Center (Seattle, WA)	J. Russell Geyer	CA10382
Rainbow Babies and Children's Hospital (Cleveland, OH)	Eric Kodish	CA20320
Children's National Medical Center (Washington, D.C.)	Gregory Reaman	CA03888
Children's Hospital of Los Angeles (Los Angeles, CA)	Paul Gaynon	CA02649
Children's Hospital of Columbus (Columbus, OH)	Frederick Ruymann	CA03750
Columbia Presbyterian College of Physicians and Surgeons (New York, NY)	Michael Weiner	CA03526
Children's Hospital of Pittsburgh (Pittsburgh, PA)	A. Kim Ritchey	CA36015
Vanderbilt University School of Medicine (Nashville, TN)	James Whitlock	CA26270
Doembecher Memorial Hospital for Children (Portland, OR)	H. Stacy Nicholson	CA26044
University of Minnesota Health Sciences Center (Minneapolis, MN)	Joseph Neglia	CA07306
Children's Hospital of Philadelphia (Philadelphia, PA)	Beverly Lange	CA11796
Memorial Sloan-Kettering Cancer Center (New York, NY)	Peter Steinherz	CA42764
James Whitcomb Riley Hospital for Children (Indianapolis, IN)	Philip Breitfeld	CA13809
University of Utah Medical Center (Salt Lake City, UT)	William Carroll	CA10198
University of British Columbia Vancouver, BC, Canada	Paul Rogers	CA29013
Children's Hospital Medical Center (Cincinnati, OH)	Robert Wells	CA26126
Harbor/UCLA and Miller Children's Medical Center (Torrance/Long Beach, CA)	Jerry Finklestein	CA14560
University of California Medical Center (UCLA) (Los Angeles, CA)	Stephen Feig	CA27678
University of Iowa Hospitals and Clinics (Iowa City, IA)	Raymond Tannous	CA29314
Children's Hospital of Denver (Denver, CO)	Lorrie Odom	CA28851
Mayo Clinic and Foundation (Rochester, MN)	Gerald Gilchrist	CA28882
University of North Carolina (Chapel Hill, NC)	Stuart Gold	
University of Medicine and Dentistry of New Jersey (Camden, NJ)	Richard Drachtman	
Children's Mercy Hospital (Kansas City, MO)	Maxine Hetherington	
Wyler Children's Hospital (Chicago, IL)	James Nachman	
M.D. Anderson Cancer Center (Houston, TX)	Beverly Raney	
New York University Medical Center (New York, NY)	Aaron Rausen	
Children's Hospital of Orange County (Orange, CA)	Violet Shen	
Pediatric Oncology Group		
Operations Office (Chicago, IL)	Sharon B. Murphy	CA30969
Statistical Office (Gainesville, FL)	Jonathan J. Shuster	CA29139
Baylor (Waco, TX)	C. Philip Steuber	CA03161
Hackensack Medical Center (Hackensack, NJ)	Michael B. Harris	
Boston Floating Hospital (Boston, MA)	Cynthia Sweetnam Kretschmar	
East Carolina University (Greenville, NC)	Charles W. Daeschner	CA69177
Medical University of South Carolina (Charleston, SC)	Joseph Laver	CA69177

Institutions	Investigators	Grant No.
Children's Hospital Michigan (Detroit, MI)	Yaddanapudi Ravindranath	CA29691
St. Johns Hospital (Detroit, MI)	Hadi Sawaf	CA29691
Children's Memorial Hospital (Chicago, IL)	Morris Kletzel	CA07431
Dana-Farber Cancer Institute (Boston, MA)	Holcombe E. Grier	CA41573
Maine Children's (Scarborough, ME)	Craig Hurwitz	CA41573
Duke University (Durham, NC)	Joanne Kurtzberg	CA15525
West Virginia University (Morgantown, WV)	A. Kim Ritchey	CA15525
University of Maryland (Baltimore, MD)	Christopher Franz	CA69428
Yale University (New Haven, CT)	Peter Beardsley	CA69428
Emory University (Atlanta, GA)	Andrew Yeager	CA20549
All Children's Hospital (St. Petersburg, FL)	Jerry Levey Barbosa	
Joe DiMaggio Children's (Hollywood, FL)	Philippa G. Sprinz	
Tampa Children's Hospital (Tampa, FL)	Cameron K. Tebbi	
Hospital for Sick Children (Toronto, Ontario, Canada)	Mark Greenberg	
Medical College Virginia (Richmond, VA)	Edward C. Russell	
Miami Children's Hospital (Miami, FL)	Enrique Escalon	
SUNY Stony Brook (Stony Brook, NY)	Robert Ingalls Parker	CA29293
University of Vermont (Burlington, VT)	Joseph D. Dickerman (New Orleans, LA)	CA29293
Ochsner Clinic (New Orleans, LA)	Rafael Sanchez Ducos	
University of Oklahoma (Oklahoma City, OK)	Sharon B. Murphy	CA30969
Cook Children's Medical Center (Ft. Worth, TX)	W. Paul Bowman	CA33625
St. Jude Children's (Memphis, TN)	Ching-Hon Pui	CA31566
University of Alabama (Birmingham, AL)	Robert Castleberry	CA25408
Nemours Children's Clinic (Jacksonville, FL)	Paul A. Pitel	
University of Florida (Gainesville, FL)	Paulette Mehta	
University of Kansas (Kansas City, KS)	Robert C. Trueworthy	
University of Miami (Miami, FL)	Narayana Gowda	
United States Air Force Medical Center (Keesler, MS)	Gary D. Crouch	CA15898
University of Mississippi Medical Center (Jackson, MS)	Jeanette Pullen	CA15989
University of California-Davis (Davis, CA)	Jonathan M. Ducore	
Children's Hospital (San Diego, CA)	Richard P. Kadota	CA28439
University of Texas-San Antonio (San Antonio, TX)	Paul Jan Thomas	
Naval Medical Center (Portsmouth, NH)	Paulette Charese Bryant	
Tripler Army Medical Center (Tripler, HI)	Bruce A. Cook	
Walter Reed Army Medical, (Washington, DC)	David A. Maybee	
Washington University (St. Louis, MO)	Michael Rugledge Debaun	CA05587
Presbyterian Hospital (Charlotte, NC)	Barry L. Golembe	CA69177
Wake Forest University School of Medicine (Winston-Salem, NC)	Allen Chauvenet	