



Day Care, Childhood Infections, and Risk of Neuroblastoma

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Neuroblastoma is the most common cancer in infants worldwide, but little is known about its etiology. Infectious etiologies involving the immune system have been hypothesized for some childhood cancers, especially leukemia, but the role of infectious agents in neuroblastoma has not been fully investigated. The authors used data from a large case-control study conducted by the Children's Oncology Group in the United States and Canada in 1992–1994 to investigate whether there was any relation among day-care attendance, childhood infections, allergies, and neuroblastoma. They interviewed mothers of 538 case children and 504 age-matched control children by telephone about several factors, including pregnancy, medical history, lifestyle, and childhood medical conditions and exposures. The results suggested decreased risks associated with day-care attendance (odds ratio (OR) = 0.81, 95% confidence interval (CI): 0.56, 1.17), childhood infectious diseases (chickenpox, mumps, red measles, and German measles) (OR = 0.60, 95% CI: 0.39, 0.93), and allergies (OR = 0.68, 95% CI: 0.44, 1.07). The authors found reduced neuroblastoma risk associated with markers of potential childhood infections. This suggests a possible role of infectious agents in neuroblastoma etiology. Future epidemiologic studies should incorporate more direct data on infection.

child; day care; hypersensitivity; infection; neuroblastoma

Abbreviations: CI, confidence interval; OR, odds ratio.

Neuroblastoma is an embryonal malignancy of the sympathetic nervous system that derives from primordial neural crest cells. It is the third most common cancer in children and the most common tumor in infants (1). In an analysis of Surveillance, Epidemiology, and End Results incidence data, 41 percent of infant neuroblastomas were diagnosed during the first 3 months of life (2). Little is known about the etiology of neuroblastoma, and the relatively young age at onset has led researchers to investigate a possible influence of parental factors prior to conception or during gestation. These factors have included occupation, smoking, alcohol consumption, medication use during pregnancy, pregnancy history, and birth characteristics (3). Associations between these factors and neuroblastoma risk have been inconsistent (2, 3).

Infections are suspected to play a role in the etiology of some childhood cancers, especially childhood acute leukemia and Hodgkin's disease (4–6). Kinlen et al. (7–9) postulated that childhood leukemia is a rare response to a specific infection and that the risk of infection increases through the mixing of populations. Greaves (10, 11) hypothesized that childhood leukemia may result from a two-step process, with a first step possibly being an in-utero mutation in a small population of cells. The second step, a postnatal event, may be an additional mutation or proliferation of the initially mutated cell population. It has been suggested that the second event may result from exposure to an infectious agent. By contributing to the normal maturation of the immune system and the establishment of immunocompetence, early common infections or factors that favor infections in early childhood would protect the child against

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TABLE 1. Demographic characteristics of persons under age 19 years diagnosed with neuroblastoma at one of 139 participating hospitals and age-matched controls, United States and Canada, 1992–1994

	Cases (n = 538)		Controls (n = 504)		Odds ratio*	95% confidence interval
	No.	%	No.	%		
Gender						
Male	301	56	251	50	1.0†	
Female	237	44	253	50	0.8	0.6, 1.0
Mother's age (years) at birth						
<20	48	9	35	7	1.3	0.8, 2.1
20–24	119	22	110	22	1.1	0.8, 1.5
25–30	212	39	206	41	1.0†	
31–39	148	28	146	29	1.0	0.7, 1.3
≥40	11	2	7	1	1.5	0.6, 3.9
Mother's race						
White	429	80	396	79	1.0†	
Black	42	8	39	8	1.0	0.6, 1.6
Hispanic	49	9	54	11	0.8	0.5, 1.2
Other	18	3	15	3	1.1	0.5, 2.2
Mother's education						
Less than high school	60	11	51	10	1.4	0.9, 2.2
High school	366	68	318	63	1.4	1.0, 1.9
Any college	112	21	135	27	1.0†	
Household income during child's birth year‡						
<\$10,000	89	18	54	11	2.2	1.4, 3.4
\$10,000–\$20,000	92	18	91	19	1.3	0.9, 2.0
\$21,000–\$30,000	87	17	114	23	1.0†	
\$31,000–\$40,000	79	16	86	18	1.2	0.8, 1.9
\$41,000–\$50,000	54	11	52	11	1.4	0.9, 2.2
>\$50,000	107	21	89	18	1.6	1.1, 2.4

* Unmatched odds ratio adjusted for child's diagnosis reference age.

† Reference category.

‡ Thirty cases and 18 controls had missing data on household income.

leukemia, while relative isolation would make the child more vulnerable (10, 11). In fact, several studies observed that the risk of childhood leukemia might be reduced by day-care attendance (12–14), breastfeeding (6, 13, 15–19), early common infections (14, 20, 21), or population mixing (22–26). Moreover, a recent analysis of data from the present neuroblastoma study found a reduced odds ratio for breastfeeding (27). In this context, factors that influence a child's immune system are of special interest. To our knowledge, the relation between neuroblastoma and factors related to the immune system has never been investigated fully. This paper focuses on markers of childhood infection and immune response, including the relations of day-care attendance, birth order, childhood infections, and allergies to neuroblastoma.

MATERIALS AND METHODS

Study population

Details on this study have been published elsewhere (28). Cases were children and young adults under age 19 years who were newly diagnosed with neuroblastoma between May 1, 1992, and April 30, 1994, at any of 139 participating hospitals in the United States and English-speaking Canada. The hospitals were members of one of two collaborative pediatric clinical trials groups, the Children's Cancer Group and the Pediatric Oncology Group (29). The two groups merged to form the Children's Oncology Group. Treating physicians gave us permission to approach the parents of patients about participation in the study. Criteria for inclusion of eligible cases were availability of the biologic mother for interview, a telephone in the home, and the ability of the

TABLE 2. Relation of day-care attendance to risk of neuroblastoma (year before diagnosis excluded), United States and Canada, 1992–1994

	Cases		Controls		Odds ratio*	95% confidence interval
	No.	%	No.	%		
Any day-care attendance						
No	340	78	269	72	1.00†	
Yes	97	22	103	28	0.81	0.56, 1.17
Age (months) at starting day care						
No day care	340	78	269	74	1.00†	
<6	55	13	52	14	0.90	0.57, 1.41
≥6	36	8	42	12	0.72	0.43, 1.22
Duration of day-care attendance (months)						
No day care	340	78	269	72	1.00†	
<6	9	2	7	2	1.01	0.36, 2.83
≥6	88	20	99	26	0.75	0.52, 1.10
Total day-care exposure (hours)‡						
No day care	340	78	269	72	1.00†	
<500	15	3	12	3	0.99	0.44, 2.22
≥500	82	19	94	25	0.74	0.51, 1.09

* Unmatched odds ratio adjusted for child's diagnosis reference age, mother's race, mother's education, and household income during child's birth year.

† Reference category.

‡ Total hours of day-care exposure took into account both duration of day-care attendance and number of hours of day care per week.

mother to speak English or Spanish. Among 741 potentially eligible cases, 538 (73 percent) case mothers were interviewed successfully. Reasons for nonparticipation of mothers included physician refusal ($n = 90$; 12 percent), maternal refusal ($n = 57$; 8 percent), untraceability ($n = 44$; 6 percent), and other reasons ($n = 12$; 2 percent).

One control was selected for each case using a random digit dialing method based on the first eight digits of the case's telephone number (30). Controls were individually matched to cases by telephone number and date of birth (± 6 months for cases diagnosed at 3 years of age or less; ± 1 year for cases diagnosed at more than 3 years of age). The parents of cases and controls were interviewed about exposures and events prior to a common reference date, the case's date of diagnosis. The household random digit dialing screening response proportion was 74 percent (31). Among 703 eligible control mothers, 504 (72 percent) completed interviews.

Data collection

Mothers of cases and controls were contacted after signed consent forms were received from the responsible physicians. After initial contact, parents were sent packets that contained consent forms and interview guides to facilitate recall and increase interview efficiency. Telephone interviews with parents were conducted by trained interviewers. Parents of both cases and controls were asked about demographic characteristics, occupational history, pregnancy

history, birth characteristics, medication use, children's illnesses and conditions, lifestyle, and other factors. Data related to infections and factors potentially promoting infections included history of day-care attendance, the birth order of the index child, history of selected childhood infections, history of ear infections, and history of other infections. Information on history of children's illnesses and conditions was also collected by maternal self-report. Day-care variables considered included attendance at day care (ever/never), age at starting day care, age at ending day care, and number of hours spent in day care per week. Selected childhood infections included chickenpox, mumps, red measles, and German measles. Mothers were asked to report conditions diagnosed by physicians. Other conditions of interest were disorders such as asthma, hay fever, eczema, and other allergies (ear, nose, and throat allergy (e.g., rhinitis and sinusitis); dermatologic allergy (e.g., urticaria); contact dermatitis; food dermatitis; and hypersensitivity to drugs).

Statistical analysis

All analyses were performed using SAS software (version 8.1; SAS Institute, Inc., Cary, North Carolina). Odds ratios and 95 percent confidence intervals were estimated using unconditional logistic regression. The original matching factor, reference age at diagnosis, was taken into account in the unmatched analyses using a six-level categorical variable (<1 year, 1–2 years, 3–4 years, 5–6 years, 7–10 years, or ≥ 11 years). Mothers' demographic characteristics, such as educa-

tional level (less than high school, high school, or any college), maternal race/ethnicity (White, Black, Hispanic, or other), and maternal report of annual total household income during the child's birth year (<\$10,000, \$10,000–\$20,000, \$21,000–\$30,000, \$31,000–\$40,000, \$41,000–\$50,000, or >\$50,000), were also included in the analyses as potential confounders. Results from conditional logistic regression using the 504 matched pairs did not differ materially from the results of the unconditional logistic regression analyses. Day-care attendance was defined as participation in any day care outside the home. We used four different variables: a dichotomous variable (ever/never), age at which the child started attending day care, duration of day care, and total hours of day-care exposure, which combined day-care duration and number of hours of attendance per week. We analyzed the day-care measures after excluding the year before diagnosis to eliminate the potential of the disease to affect day-care utilization. The year before diagnosis was excluded for both cases and controls; the year before diagnosis for controls was the year before the reference date. Childhood infections and allergies were analyzed in children aged 1 year or older. We included 538 cases and 504 controls in the analysis.

RESULTS

Among case children, 38 percent were under 1 year of age at diagnosis, 35 percent were 1–2 years of age, 17 percent were 3–4 years of age, and 10 percent were 5 or more years of age. Slight case-control differences were found for gender, maternal race, and maternal age at birth (table 1). More case mothers than control mothers had a low level of education (for less than high school vs. college, odds ratio (OR) = 1.4, 95 percent confidence interval (CI): 0.9, 2.2). The proportions of cases from lower-income households (<\$10,000 annually) and higher-income households (>\$50,000 annually) were higher than among controls.

Twenty-two percent of case children and 28 percent of control children had ever attended day care (OR = 0.81, 95 percent CI: 0.56, 1.17) (table 2). Decreased risks of neuroblastoma were suggested for a day-care duration of 6 months or more (OR = 0.75, 95 percent CI: 0.52, 1.10) and 500 or more total hours of day-care exposure (OR = 0.74, 95 percent CI: 0.51, 1.09). Results were more pronounced when the year before diagnosis was not excluded (ever use of day care vs. never: OR = 0.74, 95 percent CI: 0.55, 0.99; day-care duration of 6 months or more: OR = 0.66, 95 percent CI: 0.48, 0.90; ≥ 500 total hours of day-care exposure: OR = 0.65, 95 percent CI: 0.47, 0.89). The analyses were adjusted for child's diagnosis reference age, household income, and mother's education; all results remained unchanged after adjustment.

We found a strong inverse association among children who were breastfed and had ever attended day care, with an odds ratio of 0.46 (95 percent CI: 0.28, 0.74) (table 3), while odds ratios were 0.63 (95 percent CI: 0.41, 0.96) and 0.73 (95 percent CI: 0.44, 1.20), respectively, for children who were breastfed only and children who had ever attended day care only. Moreover, an odds ratio of 0.36 (95 percent CI: 0.16, 0.81) was observed for children who attended day care

TABLE 3. Relation of day-care attendance, breastfeeding, and infectious diseases to risk of neuroblastoma, United States and Canada, 1992–1994

	Odds ratio*	95% CI†
Day care attendance and breastfeeding‡		
No day care, no breastfeeding	1.0§	
Day care, no breastfeeding	0.73	0.44, 1.20
No day care, breastfeeding	0.63	0.41, 0.96
Day care, breastfeeding	0.46	0.28, 0.74
No day care, breastfeeding for ≤ 6 months	1.0§	
Day care, breastfeeding for ≤ 6 months	0.82	0.46, 1.47
No day care, breastfeeding for > 6 months	0.90	0.52, 1.55
Day care, breastfeeding for > 6 months	0.43	0.20, 0.92
Day care duration and breastfeeding‡		
No day care, breastfeeding for ≤ 6 months	1.0§	
Day-care duration < 6 months, breastfeeding for ≤ 6 months	1.68	0.61, 4.63
Day-care duration ≥ 6 months, breastfeeding for ≤ 6 months	0.65	0.35, 1.21
No day care, breastfeeding for > 6 months	0.89	0.52, 1.53
Day-care duration < 6 months, breastfeeding for > 6 months	0.99	0.19, 5.33
Day-care duration ≥ 6 months, breastfeeding for > 6 months	0.36	0.16, 0.81
Infantile disease and day care¶		
Infantile disease, no day care	0.52	0.28, 0.95
Infantile disease, day care	0.73	0.37, 1.41
Ear infections and day care¶		
Ear infections, no day care	1.99	0.69, 3.24
Ear infections, day care	1.43	0.46, 2.81
Other infections and day care¶		
Other infections, no day care	1.43	1.23, 2.94
Other infections, day care	1.04	0.73, 2.34
Infantile disease and breastfeeding¶		
Infantile disease, no breastfeeding	0.37	0.18, 0.76
Infantile disease, breastfeeding	0.93	0.49, 1.76
Ear infections and breastfeeding¶		
Ear infections, no breastfeeding	2.29	1.17, 4.50
Ear infections, breastfeeding	1.65	0.96, 2.86
Other infections and breastfeeding¶		
Other infections, no breastfeeding	1.92	0.74, 4.96
Other infections, breastfeeding	0.80	0.37, 1.74

* Unmatched odds ratio adjusted for child's diagnosis reference age, mother's race, mother's education, and household income during child's birth year.

† CI, confidence interval.

‡ Analyses were conducted in children older than 6 months.

§ Reference category.

¶ Analyses were conducted among children aged 1 year or older.

for 6 months or more and also were breast-fed for more than 6 months (table 3). We did not find any association between birth order and neuroblastoma (for three or more siblings vs. one sibling, OR = 0.94, 95 percent CI: 0.67, 1.31).

TABLE 4. Relation of infectious diseases and allergies to risk of neuroblastoma among children over 1 year of age, United States and Canada, 1992–1994

	Cases		Controls		Odds ratio*	95% confidence interval
	No.	%	No.	%		
Infectious diseases						
Selected childhood infections†						
Yes vs. no	57	17	72	24	0.60	0.39, 0.93
0	273	83	231	76	1.00‡	
1	55	17	64	21	0.66	0.42, 1.02
≥2	2	0.6	9	3	0.13	0.02, 0.65
Ear infections						
Yes vs. no	254	80	210	69	1.76	1.20, 2.58
0	65	20	95	31	1.00‡	
<1 per month	190	61	167	55	1.62	1.09, 2.41
≥1 per month	55	18	39	13	2.13	1.24, 3.66
Other infections (yes vs. no)§	39	12	29	9	1.26	0.74, 2.11
Allergies						
Asthma	18	5	25	8	0.69	0.36, 1.34
Hay fever	8	2	17	6	0.43	0.18, 1.04
Eczema	19	6	21	7	0.82	0.41, 1.62
Any allergy¶	45	14	58	19	0.68	0.44, 1.07

* Unmatched odds ratio adjusted for child's diagnosis reference age, mother's race, mother's education, and household income during child's birth year.

† Included chickenpox, mumps, German measles, and red measles.

‡ Reference category.

§ Included infections of the upper and lower respiratory tract, digestive tract, and kidney (ear infection was excluded).

¶ Included asthma; hay fever; other ear, nose, and throat allergy such as rhinitis and sinusitis; eczema; and other dermatologic allergy as urticaria, contact dermatitis, food dermatitis, or hypersensitivity to drugs.

We found an inverse association between any selected childhood infections (chickenpox, mumps, German measles, and red measles) and neuroblastoma (OR = 0.60, 95 percent CI: 0.39, 0.93) (table 4). The association was stronger for children who had had two or more infectious diseases (OR = 0.13, 95 percent CI: 0.02, 0.65), though the result was based on small numbers. Ear infections were associated with an elevated odds ratio (OR = 1.76, 95 percent CI: 1.20, 2.58). Decreased risk was found for a history of hay fever (OR = 0.43, 95 percent CI: 0.18, 1.04), asthma (OR = 0.69, 95 percent CI: 0.36, 1.34), or any allergy (OR = 0.68, 95 percent CI: 0.44, 1.07). There was a general pattern of lower risk for day care and breastfeeding with ear infections and other infections but not with infantile disease (table 3).

DISCUSSION

Our results suggested that day-care attendance, selected childhood infections, and certain allergic disorders were associated with a reduced risk of neuroblastoma, though odds ratios for ear infection and other infections were elevated. The strengths of our study included a large sample, a detailed interviewer-administered questionnaire, and collection of extensive information on covariates. However,

our results should be considered in the light of potential study limitations.

Response proportions in the case and control groups were below 75 percent, which might indicate selection bias. We did not have direct information with which to characterize nonrespondents. Potential differences in the response proportions among mothers of cases and controls could have resulted in differences related to socioeconomic status. Day-care attendance is more common among children of women with higher educations and incomes. Control mothers who participated in this study had slightly higher educational attainment and household income than cases. The results remained unchanged after adjustment for these socioeconomic factors, but we cannot rule out the possibility that residual confounding by socioeconomic status or other unmeasured characteristics associated with participation among controls influenced our results.

Another concern is maternal recall, especially differential recall patterns. Maternal recall bias related to day-care information seems unlikely, but recall of childhood diseases and infections may have led to misclassification. Ten years ago, a British study investigated mothers' reports of childhood infections and their concordance with general practitioner records. Questions of two types were asked about infections:

closed-ended questions were used for specific childhood infections such as chickenpox, mumps, red measles, and German measles, and open-ended questions were posed for other infections. Specific childhood infections were systematically reported more often by mothers in comparison with general practitioners' records. Mothers' reports might be considered the preferred data source for these specific infections, which often do not require consultation with a physician. However, for reports of other infections obtained through open-ended questions, the accuracy of mothers' recall was poor. In our study, questions about infections were posed using closed-ended questions for specific infections (chickenpox, mumps, red and German measles, and ear infections) and open-ended questions for other infections. Thus, with respect to misclassification, we could consider our results concerning specific infections to be more valid than results for other infections. Another potential bias is that the cases' diseases might have reduced their day-care attendance. We excluded the year before diagnosis to minimize potential for this bias.

To our knowledge, this was the first study to evaluate the effect of markers of childhood infections and immune responses on risk of neuroblastoma. A recent analysis of data from the present neuroblastoma study found reduced odds ratios for children who were breastfed (27) and encouraged us to investigate the leukemia "infectious hypothesis" for neuroblastoma. Interestingly, we found a decreased risk of neuroblastoma for children who attended day care. Some recent studies of childhood acute leukemia found similar inverse associations with breastfeeding (6, 13, 15–19) and day care (12–14). Day-care attendance and breastfeeding together further reduced the risk of neuroblastoma. Some of the results for infection and breastfeeding indicated a reduced risk but were based on small numbers of subjects. Our previous analysis of breastfeeding and neuroblastoma found a pattern of reduced risk with breastfeeding (27). The results of this study and the earlier report suggest that breastfeeding in combination with other factors deserves further investigation.

We observed reduced odds ratios for the usual childhood infectious diseases (chickenpox, mumps, and German and red measles), whose relation to neuroblastoma has never before been investigated. Results on associations between conditions such as chickenpox, measles, rubella, and mumps and childhood leukemia have been mixed (14, 15, 20, 21, 32, 33). Allergic disorders were also of interest, because they involve challenges to the immune system. We observed reduced odds ratios with hay fever and asthma. An inverse association between allergies and neuroblastoma was also found by Schuz et al. (34).

Biologic mechanisms that might explain our findings are unclear at present. An infectious etiology or immunologic modifiers for neuroblastoma development have not been prominent hypotheses. Nonetheless, there are several lines of laboratory research that provide some clues. There has been significant interest in the mechanisms responsible for the high rate of spontaneous regression of neuroblastoma (the second highest of any human cancer). One possible mechanism involves immunologic factors, and in recent studies investigators reported that the presence of natural

immunoglobulin M antibodies was cytotoxic for human neuroblastoma cells in vitro and in vivo (35, 36). Another relevant research area involves investigation of viral etiology. A recent study suggested that the BK polyomavirus was associated with neuroblastoma. The virus produces a relatively common childhood infection without symptoms, but latent or persistent infection may become reactivated. The study found BK virus DNA in the tumor cells of 17 of 18 neuroblastomas but not in any of five normal adrenal medullas (37). Another common early childhood polyomavirus, the human neurotrophic JC virus, has been associated with pediatric medulloblastoma (38, 39). Although these disparate findings are far from definitive, they suggest that infectious agents and immune responses may influence children's risk of developing solid tumors.

Future epidemiologic studies should incorporate more direct measures of infection. Additional laboratory studies evaluating immunologic influences on the development, progression, and regression of neuroblastoma are also warranted.

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Contributing Children's Cancer Group and Pediatric Oncology Group investigators, institutions, and grant numbers are given in Appendix tables 1 and 2.

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(Appendix tables 1 and 2 follow)

APPENDIX TABLE 1. Participating principal investigators—Pediatric Oncology Group

Institution	Principal Investigator	Grant no.
Baylor College of Medicine	Dr. C. Philip Steuber	CA-03161
Hackensack Medical Center	Dr. Michael B. Harris	
Boston Floating Hospital	Dr. Cynthia Sweetnam Kretschmar	
East Carolina University	Dr. Charles W. Daeschner	CA-69177
Medical University of South Carolina	Dr. Joseph Laver	CA-69177
Children's Hospital Michigan	Dr. Yaddanapudi Ravindranath	CA-29691
St. John's Hospital	Dr. Hadi Sawaf	CA-29691
Children's Memorial Hospital (Chicago)	Dr. Morris Kletzel	CA-07431
Dana-Farber Cancer Institute	Dr. Holcombe E. Grier	CA-41573
Maine Children's Hospital	Dr. Craig Hurwitz	CA-41573
Duke University	Dr. Joanne Kurtzberg	CA-15525
West Virginia University, Morgantown	Dr. A. Kim Ritchey	CA-15525
University of Maryland	Dr. Christopher Franz	CA-69428
Yale University	Dr. Peter Beardsley	CA-69428
Emory University	Dr. Andrew Yeager	CA-20549
All Children's Hospital	Dr. Jerry Levey Barbosa	
Joe DiMaggio Children's Hospital	Dr. Philippa G. Sprinz	
Tampa Children's Hospital	Dr. Cameron K. Tebbi	
Hospital for Sick Children	Dr. Mark Greenberg	
Medical College Virginia	Dr. Edward C. Russell	
Miami Children's Hospital	Dr. Enrique Escalon	
State University of New York, Stony Brook	Dr. Robert Ingalls Parker	CA-29293
University of Vermont	Dr. Joseph D. Dickerman	CA-29293
Ochsner Clinic	Dr. Rafael Sanchez Ducos	
Oklahoma University	Dr. Ruprecht Nitschke	CA-11233
Pediatric Oncology Group Operations Office	Dr. Sharon B. Murphy	CA-30969
Cook-Fort Worth Children's Medical Center	Dr. W. Paul Bowman	CA-33625
St. Jude Children's Research Hospital	Dr. Ching-Hon Pui	CA-31566
Pediatric Oncology Group Statistical Office	Dr. Jonathan J. Shuster	CA-29139
University of Alabama	Dr. Robert Castleberry	CA-25408
Nemours Children's Clinic	Dr. Paul A. Pitel	
University of Florida	Dr. Paulette Mehta	
University of Kansas	Dr. Robert C. Trueworthy	
University of Miami	Dr. Narayana Gowda	
Keesler Air Force Base Hospital	Dr. Gary D. Crouch	CA-15898
University of Mississippi Medical Center	Dr. Jeanette Pullen	CA-15989
University of California, Davis	Dr. Jonathan M. Ducore	
Children's Hospital (San Diego)	Dr. Richard P. Kadota	CA-28439
University of Texas, San Antonio	Dr. Paul Jan Thomas	
Naval Medical Center, Portsmouth	Dr. Paulette Charese Bryant	
Tripler Army Medical Center	Dr. Bruce A. Cook	
Walter Reed Army Medical Center	Dr. David A. Maybee	
Washington University	Dr. Michael Rugledge Debaun	CA-05587
Presbyterian Hospital	Dr. Barry L. Golembe	CA-69177
Wake Forest University School of Medicine	Dr. Allen Chauvenet	

APPENDIX TABLE 2. Participating principal investigators—Children's Cancer Group

Institution	Principal Investigator(s)	Grant no.
Children's Cancer Group Operations Center	Drs. W. Archie Bleyer, Anita Khayat, Harland Sather, Mark Krailo, Jonathan Buckley, Daniel Stram, and Richard Sposto	CA-13539
University of Michigan Medical Center	Dr. Raymond Hutchinson	CA-02971
University of California Medical Center	Dr. Katherine Matthay	CA-17829
University of Wisconsin Hospital	Dr. Diane Puccetti	CA-05436
Children's Hospital and Medical Center	Dr. J. Russell Geyer	CA-10382
Rainbow Babies and Children's Hospital	Dr. Susan Shurin	CA-20320
Children's National Medical Center	Dr. Gregory Reaman	CA-03888
Children's Hospital of Los Angeles	Dr. Paul Gaynon	CA-02649
Children's Hospital of Columbus	Dr. Frederick Ruymann	CA-03750
Columbia Presbyterian College of Physicians and Surgeons	Dr. Leonard H. Wexler	CA-03526
Children's Hospital of Pittsburgh	Dr. A. Kim Ritchey	CA-36015
Vanderbilt University School of Medicine	Dr. John Lukens	CA-26270
Doernbecher Memorial Hospital for Children	Dr. H. Stacey Nicholson	CA-26044
University of Minnesota Health Sciences Center	Dr. Joseph Neglia	CA-07306
Children's Hospital of Philadelphia	Dr. Beverly Lange	CA-11796
Memorial Sloan-Kettering Cancer Center	Dr. Peter Steinherz	CA-42764
James Whitcomb Riley Hospital for Children	Dr. Philip Breitfeld	CA-13809
University of Utah Medical Center	Dr. Richard O'Brien	CA-10198
University of British Columbia	Dr. Christopher Fryer	CA-29013
Children's Hospital Medical Center	Dr. Robert Wells	CA-26126
Harbor/UCLA* and Miller Children's Medical Center	Dr. Jerry Finklestein	CA-14560
University of California Medical Center (University of California, Los Angeles)	Dr. Stephen Feig	CA-27678
University of Iowa Hospitals and Clinics	Dr. Raymond Tannous	CA-29314
Children's Hospital of Denver	Dr. Lorrie Odom	CA-28851
Mayo Clinic and Foundation	Dr. Gerald Gilchrist	CA-28882
University of North Carolina	Dr. Joseph Wiley	
University of Medicine and Dentistry of New Jersey	Dr. Richard Drachtman	
Children's Mercy Hospital	Dr. Maxine Hetherington	
Wyler Children's Hospital	Dr. James Nachman	
M. D. Anderson Cancer Center	Dr. Beverly Raney	
New York University Medical Center	Dr. Aaron Rausen	
Children's Hospital of Orange County	Dr. Violet Shen	

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