Editorial

Pediatric Cancer in the United States: The Children's Oncology Group Epidemiology Research Program

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Childhood Cancer—The Problem

Over 8,500 children under age 15 years are diagnosed with cancer each year in the United States (1). Unlike adults, where epithelial tumors predominate, the most common types of cancer in children include the leukemias and lymphomas and the tumors of the central and sympathetic nervous systems, soft tissue, bone, and kidney. The overall incidence rate for childhood cancers has increased significantly by almost 33% during the period 1975 to 2001 (1), although, in more recent years, the rate has been leveling off. Only ~5% of childhood cancers can primarily be attributed to a genetic predisposition (2). With the exception of a few known risk factors including *in utero* exposure to radiation and prior chemotherapeutic agents (3), the etiology of most childhood cancer is unknown. Because of its rarity, epidemiologic studies of childhood cancer are challenging. In particular, using a case-control approach necessitates careful assembly of well-characterized cases, which requires cooperation among many hospitals and institutions and the identification of a feasible and valid control group. In this editorial, we highlight the current challenges and approaches to advancing our understanding of the etiology of childhood cancer.

Cooperative Clinical Trials Groups: Children's Oncology Group

Most previous epidemiologic studies of childhood cancer in the United States were conducted through the former Children's Cancer Group (see Table 1), which consisted of approximately half of the hospitals and institutions that treated children with cancer (4). In 2000, the Children's Oncology Group (COG), an international consortium of hospitals and institutions in the United States, Canada, and elsewhere, was established through the merger of four pediatric oncology clinical trial groups, including Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and International Rhabdomyosarcoma Study Group. It is estimated that ~90% of children diagnosed with cancer in the United States are treated by a member institution of the COG (4). In addition to an Operations Center, a Research and Statistical Data Center, a Group Chair's Office (currently, Dr. Gregory H. Reaman), and nearly 250 affiliated COG institutions who are committed to participate in therapeutic and nontherapeutic trials, scientific and discipline standing committees are charged with proposing innovative research in their respective fields.

The COG Epidemiology Steering Committee (n = 12) consists of epidemiologists, molecular biologists, pediatric oncologists, nurses, and other health professionals.[3] Moreover, ~30 individuals from various disciplines around the world are associate members of the committee. Several key areas for future initiatives have been identified by members, including (*a*) addressing important methodologic issues (including control selection and exposure assessment), (*b*) expanding studies of gene-environment interactions, and (*c*) developing educational materials. Current examples of the former two are discussed briefly below. Finally, because of the nationwide coverage of COG, a North American pediatric cancer registry is being proposed.

Addressing Important Methodologic Issues (e.g., Control Selection). To date, most national epidemiology studies of pediatric cancer have used random digit dialing for control selection. However, with the telemarketing burden and the increasing use of answering machines, cellular telephones, and caller identification, the efficiency of random digit dialing is decreasing. Further, concerns about the validity of this method are increasing. Our most recent experience with random digit dialing suggests overall response rates (5) of <40%. The COG Epidemiology Steering Committee held a workshop in 2002 to discuss the pros and cons of alternative control groups. Smaller-scale studies conducted in New York and California have successfully recruited controls through birth certificates (6-8). Although response rates are similar to random digit dialing, the ability to characterize nonresponders to evaluate potential selection bias is a distinct advantage. In 2003, our committee surveyed all 52 birth registrars in the United

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[3] Dr. Ross is Chair and Dr. Olshan is a member of the COG Epidemiology Steering Committee.

Table 1. Children's Cancer Group/COG etiology of childhood cancer studies

Protocol	Title	Cases (*n*)	Chairperson	Source of funds
E01	Case-control study of osteogenic sarcoma	200	T. Pendergrass	Local
E02	Case-control study of hepatoblastoma	75	J. Buckley	Local
E03	Case-control study of Ewing's sarcoma	170	L. Robison	NIH
E04	Self-administered questionnaire	3,500	J. Buckley	Local
E05	Case-control study of acute nonlymphoblastic leukemia	204	L. Robison	NIH
E06	Case-control study of Wilms' tumor*	240	A. Olshan	March of Dimes
E07	Case-control study of retinoblastoma	270	A. Meadows	NIH
E08	Case-control study of non-Hodgkin's lymphoma	249	J. Buckley	NIH
E09	Case-control study of infant leukemia	302	L. Robison	NIH
E10	Case-control study of rhabdomyosarcoma*	300	S. Grufferman	NIH
E11	Twin concordance study	850	J. Buckley	American Cancer Society
E12	Case-control study of primitive neural ectodermal tumor and astrocytoma	321	G. Bunin	NIH
E13	Case-control study of Hodgkin's disease*	300	S. Grufferman	NIH
E14	Case-control study of acute nonlymphoblastic leukemia	525	M. Steinbuch	NIH
E15	Case-control study of childhood acute lymphoblastic leukemia	1,915	L. Robison	NIH
E16	Parental occupation and childhood cancer	3,500	G. Bunin	March of Dimes
E18	Case-control study of neuroblastoma*	640	A. Olshan	NIH
E21	Case-control study of primitive neural ectodermal tumor	700	G. Bunin	NIH
AE22†	Case-control study of germ cell tumors	600	X. Shu	NIH
B955	Environmental exposures and Ras mutations in childhood leukemia	2,440	J. Perentesis	NIH
B956	Glutathione *S*-transferase genotype in childhood leukemia	2,440	S. Davies	NIH
AE23†	Case-control study of Down syndrome-leukemia and Down syndrome	160	J. Ross	NIH
AE24†	Case-control study of infant leukemia	480	J. Ross	NIH
A0026†	Case-control study of Wilms' tumor	600	A. Olshan	NIH
AADM01P1†	Pilot for the Childhood Cancer Research Network	1,400	J. Ross	NIH
AE27†	Case-control study of hepatoblastoma	600	L. Spector	Pending, NIH

*Collaborative study with the Pediatric Oncology Group.
†COG study (others were Children's Cancer Group studies unless otherwise noted).

States and found that >70% could release identifying information from birth certificates. This method for control selection will be used in the expansion of the epidemiology of infant leukemia study as well as the proposed hepatoblastoma study. Further, members of the committee plan to submit a grant proposal to test and characterize the feasibility of using birth certificates for recruiting controls up to age 15 years.

Expanding Studies of Gene-Environment Interactions. Childhood cancer studies are only beginning to incorporate single nucleotide polymorphisms and haplotypes into studies of gene-gene and gene-environment interactions (9-13). A few of the studies in Table 1 have and will be incorporating susceptibility markers into analyses (E14, E15, AE24, and AE27). However, these types of studies require large sample sizes. It is expected that a national pediatric cancer registry will help facilitate this type of research through the expeditious acquisition of diverse biological samples from both parents and children. The committee is hosting a workshop on gene-environment interactions in childhood cancer in October 2004 to discuss various study design issues to consider once a registry is in place.

North American Pediatric Cancer Registry

Because COG treats the vast majority of children with cancer in the United States (4), it makes sense to consider using COG as the basis for a national pediatric cancer registry. Importantly, individual institution ethical and review boards are requiring local investigators to contact and obtain signed consent forms from parents before they are approached to consider participation in COG-wide epidemiology, biology, and other nontherapeutic studies. (This is in addition to the mandatory institutional review board approval and informed consent that is required by the institution(s) and investigator(s) actually conducting the nontherapeutic study.) For COG epidemiologic studies, this can present a huge hurdle, as often with only one or two cases at a specific institution, it is necessary to obtain institutional review board approval at 200(!) or more institutions. Further, because local institutional investigators are often overworked and understaffed, there is a tendency to delay submitting nontherapeutic studies through institutional review boards and, once approved, difficulty in tracing and locating parents for consent to be interviewed.

Investigators within COG and the National Cancer Institute have initiated a pilot protocol called the Childhood Cancer Research Network (COG protocol AADM01P1) to determine the feasibility of establishing a registry. The protocol capitalizes on the mandatory registration (no personal identifiers) of all pediatric cancer patients that COG requires of institutions to maintain membership. The additional requirements for the protocol are simple: institutions are asked to (*a*) obtain consent from parents (and children if they are age

eligible) for release of personal identifiers at the time of diagnosis and (*b*) obtain consent for possible future contact to consider taking part in a nontherapeutic study. That future study would be separately explained and consented by the individuals conducting the study.

Ten percent of COG institutions were randomly selected for the pilot protocol for the Childhood Cancer Research Network. All of them obtained institutional review board approval for the protocol. Of the 1,364 parents/patients approached thus far, 96% have agreed to both levels of consent. Additional piloting efforts are under way, including selecting a sample of parents to determine the feasibility of interviewing them and obtaining a biological specimen from them and their child.

Childhood Cancer—The Future

The previous case-control studies of risk factors for childhood cancer (Table 1) and those conducted in Canada, United Kingdom, France, and elsewhere have provided several leads and suggestive associations with factors such as infections, parental occupational exposures, medication use, pregnancy and birth conditions, diet, and pesticides (3). To sort out these findings and advance knowledge, a new generation of focused and sophisticated studies is needed. These studies require systematically identified cases, acquisition of diverse biological specimens, precise exposure assessment, and a feasible and valid comparison group. As we have described, the COG Epidemiology Steering Committee has several initiatives to address some of these issues. Other investigations, such as the Northern California Childhood Leukemia Study (6, 14) and the United Kingdom Childhood Cancer Study (15), have taken up the challenge to develop and implement new studies to overcome previous limitations. It is only through these collaborative efforts that we will begin to unlock the etiology of these important cancers.

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