Assessment of Environmental and Genetic Factors in the Etiology of Childhood Cancers: The Childrens Cancer Group Epidemiology Program

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The occurrence of cancer during childhood represents one of the leading causes of death within the pediatric and adolescent age group. It is estimated that approximately 8000 children will be diagnosed annually with cancer in the United States. Epidemiologic research addressing the etiology of childhood cancer has been limited because of the difficulties in identifying a sufficiently large study population. Moreover, the use of retrospectively ascertained childhood cancer cases in epidemiologic investigations has restricted the incorporation of biological and clinical parameters. The Childrens Cancer Group has developed an active program in epidemiologic research, with over a decade of experience demonstrating the feasibility and strengths of conducting analytic epidemiologic studies within a cooperative clinical trials network. The availability of detailed clinical and biologic data on cases diagnosed within the cooperative group facilitates the transfer of state-of-the-art technology to epidemiologic research. — Environ Health Perspect 103(Suppl 6):111–116 (1995)

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Introduction

Approximately 8000 children in the United States are diagnosed annually with cancer (*1*). The incidence of cancer in children less than 15 years of age is approximately 13 per 100,000 for whites and 11 per 100,000 for blacks. While the absolute number of childhood cancer cases is low, when compared to the number of adult cancers, U.S. mortality data demonstrate that cancer is the second leading cause of death in children, second only to accidents (*2*). It can be estimated that approximately one in every 400 individuals living in the United States will develop cancer before age 15.

Data from the Surveillance Epidemiology and End Results Program indicate a gradual but continuous increase in the incidence rates of childhood cancers (*3,4*). These increases are most apparent for leukemia and brain tumors, the two diagnoses that comprise approximately 50% of cases in the 0 to 14 age group. There has been considerable speculation on the cause(s) of the observed increase. Possibilities include random variations in the pattern of occurrence of cancer, improvements in access to medical care and/or medical detection, more complete case ascertainment by registries, new or more extensive environmental exposures, or iatrogenically induced secondary cancers. A recent analysis has demonstrated that secondary cancers do not account for the increase (*5*).

The types and distributions of the malignancies seen in the pediatric and adolescent age groups differ substantially from those seen in adults. Although childhood cancers represent less than 2% of all cancers that occur in the United States, the unique clinical and biologic features of pediatric malignancies have contributed substantially to our understanding of cancer. Most of the contribution of pediatric cancers has been in providing insights into the genetic events associated with malignant transformation. Tumor suppressor genes, first identified in retinoblastoma (a tumor with an annual incidence of less than 5 per million), have now been described in Wilms' tumor, rhabdomyosarcoma, and some adult malignancies (*6–8*). Childhood cancers have also provided important information on familial cancer associations and syndromes (*9–10*). In contrast to these genetic and familial findings, childhood cancers have contributed much less to the understanding of the environmental aspects of cancer.

Recognizing the difficulties of conducting epidemiologic studies of childhood cancer, the Childrens Cancer Group (CCG) established an Epidemiology Committee to propose and develop a program for conducting studies within the structure of the existing clinical trials cooperative group. Following is a summary of the program that currently exists in CCG.

The Childrens Cancer Group Epidemiology Program

The Division of Cancer Therapy of the National Cancer Institute supports a program of collaborative cooperative clinical trials groups. Presently there are two pediatric groups, Childrens Cancer Group and Pediatric Oncology Group. Collectively, the members of these two large multi-institutional programs diagnose and treat greater than 90% of cases of childhood cancer in the United States and essentially 100% of cases diagnosed before 5 years of age (*11*). It is a requirement in CCG that all pediatric oncology patients seen at a

Authors represent the Childrens Cancer Group Epidemiology Committee.

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member institution be registered with the group Operations Office, whether or not the patient is entered into a clinical trial.

Recognizing the limitations imposed by the relative rarity of childhood cancers and the strengths of the cooperative group mechanism, the CCG initiated development of a program to conduct epidemiologic research within the existing clinical trials infrastructure. The CCG Epidemiology Committee functions as the primary source of expertise in areas related to childhood cancer etiology and the conduct of epidemiologic/etiologic investigations. The overall objectives of the Epidemiology Committee are to investigate environmental and genetic factors related to childhood cancer etiology. The committee is responsible for establishing long-range strategies and priorities, initiating new proposals, reviewing proposed study concepts, preparing and submitting study-specific grant applications, protocol development, monitoring study progress, and reporting and publishing study results. Close collaboration with the clinical and other CCG committees (e.g., study committees, strategy groups, and discipline and scientific committees) is required to carry out these functions.

Previous and Current Activities

Since the Epidemiology Committee was established in 1982, CCG has initiated 17 epidemiologic protocols and has proposed three studies (Table 1). The majority of CCG epidemiology studies have been case–control designs. A methodology has been successfully established (Figure 1) using telephone interviews with parents of cases and controls. Controls are selected using a method of random digit dialing (*12*).

The 12-year history of the CCG Epidemiology Committee has clearly demonstrated the feasibility and advantages of conducting epidemiologic research within the CCG. These include *a*) identification of large numbers of cases, *b*) extremely high participation rates, *c*) integration of clinical and biologic data into study designs, and *d*) the ability to compete successfully for NIH and private research funding.

Using the large case population available from CCG, studies of some of the less common pediatric tumors [e.g., hepatoblastoma, retinoblastoma, acute myeloid leukemia (AML), Ewing's sarcoma, osteosarcoma] have been conducted. Moreover, for common childhood cancers, it has been possible to target studies within distinct subsets of cases [e.g., immunophenotype in acute lymphoblastic leukemia (ALL), young age in brain tumors, etc.]. By and large these studies would not have been feasible outside of a cooperative group setting. Provided in Table 2 are the average numbers of new patients registered each month with the CCG Operations Office.

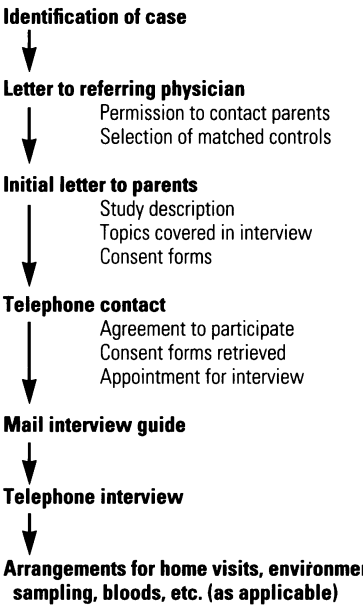

Figure 1. General procedure for Childrens Cancer Group case–control studies.

Table 1. Summary of Childrens Cancer Group epidemiology studies.

Status/ Protocol	Title	No. cases	Chairperson	Source of funding
Completed				
E-01	Case–control study of osteogenic sarcoma	200	T Pendergrass	Local
E-02	Case–control study of hepatoblastoma	75	J Buckley	Local
E-03	Case–control study of Ewing's sarcoma	170	L Robison	NIH
E-05	Case–control study of ANLL	204	L Robison	NIH
E-06	Case–control study of Wilms' tumor[a]	240	A Olshan	March of Dimes
E-07	Case–control study of retinoblastoma	270	A Meadows	NIH
E-11	Twin concordance study	850	J Buckley	ACS
E-12	Case–control study of PNET and astrocytoma	321	G Bunin	NIH
Closed/analysis				
E-04	Self-administered questionnaire	3500	J Buckley	Local
E-08	Case–control study of non-Hodgkin's lymphoma	240	J Buckley	NIH
E-09	Case–control study of infant leukemia	290	L Robison	NIH
E-10	Case–control study of rhabdomyosarcoma[a]	300	S Grufferman	NIH
E-16	Parental occupation and childhood cancer	3500	G Bunin	March of Dimes
Active				
E-13	Case–control study of Hodgkin's disease[a]	300	S Grufferman	NIH
E-14	Case–control study of ANLL	600	M Steinbuch	NIH
E-15	Case–control study of childhood ALL	1950	L Robison	NIH
E-17	Role of EBV in Hodgkin's disease[a]	400	S Grufferman	NIH
E-18	Case–control study of neuroblastoma[a]	640	A Olshan	NIH
Proposed				
	Maternal diet in PNET		G Bunin	NIH
	Etiology of 11q23 abnormalities		L Robison	Pending
	Case–control study of germ cell tumors		X Shu	Pending

[a]Collaborative study with the Pediatric Oncology Group.

Experience in CCG has shown that using the methodologic approach adopted, case–control studies designed to test specific hypotheses and/or generate hypotheses within selected childhood cancers can be successfully conducted. Impressively high rates of participation (both physician and parent) have been achieved. For example, in the current case–control study of childhood ALL (E-15), where over 2300 cases have been identified, permission to contact parents was received from physicians of 98.4% of eligible cases. Physician refusal occurred in only 1.1% and parent refusal, via the physician, in 0.5%. Of the parents contacted, 97.5% participated in the study. Using the method of random digit dialing for control selection, the participation rate in CCG studies has averaged approximately 80%.

In addition to the availability of the large numbers of cases, one of the major advantages of conducting epidemiologic studies in CCG is the clinical and biological data that can be incorporated into the design of the epidemiologic investigation. Table 3 summarizes the CCG epidemiology studies incorporating the use of clinical/biological data in the study design and/or analysis.

Funding of CCG epidemiologic studies has been successfully obtained through NIH R01-supported grants as well as private

Table 2. Average monthly accrual of cases registered with Childrens Cancer Group.

Cancer type	No. cases
ALL	88
AML	21
Brain tumors	62
Neuroblastoma	23
Wilms' tumors	19
Soft tissue sarcoma	24
Lymphoma	38
Bone tumors	20
Retinoblastoma	5
Others	22
Total	323

foundations (i.e., American Cancer Society, March of Dimes). All the 12 R01 grant applications that have undergone the NIH peer-review process have received priority ratings resulting in funding.

Completed CCG Epidemiology Studies

Listed below are some of the findings of completed epidemiology studies conducted by CCG (*13–29*):

- Identified risk factors for retinoblastoma differed according to the two nonfamilial forms studied (sporadic heritable and nonheritable). Paternal occupational exposure to metals was associated with the sporadic heritable form, while employment as a welder or machinist was associated with an increased risk of nonheritable retinoblastoma. (CCG-E07)
- Gestational factors including exposure to X-rays and use of morning sickness medications were significantly associated with an increased risk of nonheritable retinoblastoma, while vitamin use during the first trimester of pregnancy was associated with a decreased risk in both nonfamilial forms of retinoblastoma. (CCG-E07)
- Risk of astrocytic glioma is associated with a history of seizures and epilepsy in first or second degree relatives (OR = 2.4). The association is strongest when the relative experienced seizures in childhood. (CCG-E12)
- Maternal intake of dietary substances relevant to the nitrosamine hypothesis in childhood brain tumors was not found to be associated with an increased risk for astrocytic glioma or primitive neuroectodermal tumor (PNET) in young children. However, for PNET a protective effect existed for vegetables, fruits, folate, and vitamin C, and for use of multivitamins early in pregnancy. (CCG-E12)
- For cases diagnosed before age 6, a striking difference exists in identified risk factors for cases of PNET versus astrocytic glioma. (CCG-E12)
- A previously reported association between parental cigarette smoking and risk of rhabdomyosarcoma in offspring was not confirmed. However, *in utero* X-ray exposure is associated with a significant increase in risk of rhabdomyosarcoma. (CCG-E10)
- Parents' use of cocaine and marijuana significantly increased the risk of rhabdomyosarcoma in their children. (CCG-E10)
- A consistent statistically significant association was identified between reported pesticide exposure and risk of childhood AML (paternal occupation: OR = 2.7, maternal occupation: 7 cases/0 controls; and household: OR = 3.5). Risks were substantially increased for AML cases diagnosed before age 6 and for those with M4 or M5 morphology. (CCG-E05)
- Paternal occupational exposure to solvents and petroleum products was found to be associated with a statistically significant increased risk of AML. (CCG-E05)
- An 11-fold increased risk of AML was found for reported maternal use of mind-altering drugs (primarily marijuana) just prior to or during the index pregnancy. Exposed cases were significantly younger at diagnosis and were predominantly of myelomonocytic or monocytic morphology. (CCG-E05)
- Maternal alcohol consumption during the index pregnancy is associated with an increased risk of AML, particularly within the subgroup of cases with M4/M5 morphology. (CCG-E05)
- Maternal history of fetal loss was significantly associated with risk of childhood ALL. Risk increased dramatically in cases diagnosed at younger ages (i.e., cases diagnosed before 2 years of age: OR = 5.3 for any previous miscarriage; OR = 24.8 for more than one previous miscarriage). (CCG-E04)
- When assessing the potential role of parental occupation as a risk factor for Wilms' tumor, elevated odds ratios were found for paternal occupations as auto mechanic and welder. The estimated risks were highest for employment during the preconception and pregnancy periods. (CCG-E06)
- Wilms' tumor cases were significantly more likely to have fathers employed in occupations associated with solvent exposure. (CCG-E04)
- Previously reported associations between Wilms' tumor risk and parental occupational exposure to hydrocarbons and lead were not confirmed. Similarly, contrary to other reports in the literature, no associations were identified between Wilms' tumor and *a*) maternal tobacco, tea, and coffee consumption during pregnancy, *b*) maternal hypertension, hair dye use, or vaginal infection during pregnancy, *c*) *in utero* exposure to exogenous hormones, or *d*) increased birth weight. (CCG-E06)
- The hypothesis that maternal exposure to potentially hepatotoxic agents (including alcohol, chlorinated hydrocarbons, nitrosamines, viruses, or exogenous estrogens) would be associated with increased risk of hepatoblastoma was tested and rejected. (CCG-E02)
- Maternal occupational exposures to metals (OR = 8.0), hydrocarbons (OR = 3.7), and paints/pigments (OR = 3.7) and paternal occupational exposures to metals (OR = 3.0) and petroleum products (OR = 1.9) were associated with risk of hepatoblastoma. (CCG-E02)
- A multi-center/organization study designed to determine zygosity and frequency of cancer concordance of cancer in twins confirmed the view that inherited genetic factors play a minor

Table 3. Clinical and biologic data utilized in CCG epidemiology studies.

Diagnosis	Protocol	Clinical/biologic data
All diagnoses	E04	ALL immunophenotype
AML	E05	FAB morphology, cytogenetics
Retinoblastoma	E07	Cytogenetics
NHL	E08	Cytogenetics, histologic subtypes, EBV, HIV
Infant leukemia	E09	FAB morphology, cytogenetics
Soft-tissue sarcoma	E10	Histologic subtypes
Brain tumors	E12	Histologic subtypes
HD	E13	Histologic subtypes, disease, stage, EBV
AML	E14	FAB morphology, immunophenotype, cytogenetics
ALL	E15	Immunophenotype, cytogenetics
Neuroblastoma	E18	n-*myc*, stage

role in most childhood cancers. In malignancies other than retinoblastoma and leukemia, only 3 of 334 twins were concordant for cancer. Three of 197 leukemia twins were concordant, as were 5 of 19 retinoblastomas. (CCG-E11)

Current CCG Epidemiology Studies

Epidemiology of Hodgkin's Disease (CCG-E13). This is the first interview case–control study of childhood Hodgkin's disease (HD). The study is designed to fill several important gaps in knowledge by investigating environmental exposures as risk factors for childhood HD. This is a collaborative study of the Pediatric Oncology Group and CCG. The specific aims of the CCG-E13 study are *a*) to evaluate whether, on epidemiologic grounds, childhood HD is distinct from the young adult and old adult diseases; *b*) to evaluate the hypothesis that children with HD have different patterns of infectious disease than do matched controls; *c*) to assess day care of children (with its attendant increased risk of infectious diseases acquired at early ages) as a risk factor for HD; *d*) to evaluate the association between breastfeeding and risk of HD; *e*) to evaluate the association between indicators of socioeconomic status and HD; *f*) to evaluate parental occupational exposures as risk factors for HD in children; *g*) to evaluate environmental exposures to wood and chemicals as possible risk factors in children; *h*) to evaluate familial aggregation of HD (and possibly increased risk of other malignancies or multiple sclerosis); *i*) to evaluate risk factors of HD separately for each histologic subtype of the disease, and by disease stage and age at diagnosis.

Epidemiology of Acute Myeloid Leukemia (CCG-E14). This study is a followup to CCG-E05, an analytic study designed to assess specific environmental exposures as risk factors for childhood AML. Two of the strongest associations from our previous study were with maternal marijuana use and pesticide exposure (using multivariate analyses, they were found to be independently associated with an increased risk). The primary objectives of the study are *a*) to confirm the association of pesticide exposure and AML risk, and to identify the substance(s) or class of pesticide responsible for the association; *b*) to confirm the association of solvents and petroleum products and AML risk, and to determine the class of solvent responsible; *c*) to confirm the association of maternal marijuana use and AML risk; *d*) to identify subgroups, defined by age at diagnosis, FAB morphology, cytogenetic abnormality, or clinical features of the leukemia, in which associations with pesticide, solvent or marijuana exposures are strongest. Secondary aims are *e*) to further investigate identified associations of childhood AML and parental occupational exposures to paints/pigments, sawdust, metal dusts and fumes, plastics, and lead; and *f*) to assess a possible association of an extended duration of use of morning sickness medications and an increased risk for childhood AML.

Epidemiology of Acute Lymphoblastic Leukemia (CCG-E15). This study is designed to investigate the role of risk factors for acute lymphoblastic leukemia within biologically defined subgroups. Because of the availability of immunophenotypic characteristics and cytogenetics for all newly diagnosed cases, it will be possible to identify biologically distinct subgroups from all newly diagnosed children with ALL. This case–control study will investigate whether or not there are distinct risk factors within subgroups of childhood ALL. Risk factors to be investigated include those relating to demographic characteristics, preconception exposures of parents, reproductive factors including reproductive history, medical exposures during pregnancy, illnesses, events surrounding the labor and delivery, diet during pregnancy, and possible occupational exposures of mothers and fathers during the index pregnancy, postnatal exposures relating to parental occupations and general environment, as well as a family medical history. Additional objectives of this study include assessment of exposure to very low level electromagnetic fields with indirect and direct measurements, assessment of exposure to radon and gamma radiation (direct measurements), and measurement of exposure to household pesticide residues (direct measurement). Studies relating to electromagnetic field radiation, radon, and gamma radiation are being conducted in collaboration with investigators from the National Cancer Institute.

Parental Occupation and Childhood Cancer (CCG-E16). This study uses the unique data source that contains information from a self-administered questionnaire on 3549 children with cancer and 839 healthy children (E04). The cancers we will study are acute lymphoblastic leukemia, neuroblastoma, acute myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, Wilms' tumor, osteosarcoma, astrocytoma, primitive neuroectodermal tumor (PNET)/medulloblastoma, rhabdomyosarcoma, germ cell and gonadal tumor, hepatoblastoma, Ewing's sarcoma, and histiocytosis X. The following specific hypotheses will be tested: *a*) children with Wilms' tumor, brain tumor, and other cancers are more likely than controls to have parents who worked in metal-related occupations or industries; *b*) children with neuroblastoma, brain tumor, and other cancers are more likely than controls to have parents employed in the electric and electronic industry; *c*) children with brain tumor, acute myeloid leukemia, and other cancers are more likely than controls to have parents employed in agriculture or occupations with exposure to pesticides.

Epidemiology of Neuroblastoma (CCG-E18). The major purpose of the CCG-E18 study is to examine the relationships between specific environmental exposures and the occurrence of neuroblastoma. The specific aim of the study is to evaluate hypothesized risk factors, including maternal use of drugs, sex hormones, alcohol, and diuretics during pregnancy. The analysis of maternal drug use during pregnancy will include a special evaluation of the potential for these drugs to result in transplacental *N*-nitroso compound exposure. In addition, paternal employment in the electronics industry and occupational exposure to electromagnetic fields will be examined. Other risk factors previously found to be associated with neuroblastoma such as maternal age, length of gestation, birth weight, and family socioeconomic status will be evaluated. In addition, this study will collect information on additional potential risk factors that may be used to develop new etiologic hypotheses (such as family medical history, neonatal, gestational, and delivery history, and household environmental exposures); and evaluate the above potential risk factors separately for subgroups of patients defined by clinical, biologic, and genetic markers such as cytogenetic abnormality and n-*myc* oncogene amplification.

Current and Future Research Objectives

Through continued reliance on externally-funded investigations (primarily R01 grants), the CCG Epidemiology Committee plans to increase further the focus and complexity of future epidemiologic studies conducted within CCG by *a*) concentrating efforts on more detailed testing of

specific hypotheses, *b*) greater integration of biologic parameters, and *c*) including more quantitative measures of exposure.

Part of the future strategy of the CCG Epidemiology Committee is to continue to perform detailed assessments of associations identified in previous CCG epidemiologic studies. Through the series of case–control studies that have been successfully conducted within CCG, associations have been identified that require confirmation and further elucidation. For example, the CCG-E05 study found pesticide exposures and maternal drug use to be significantly associated with an increased risk of childhood AML, particularly M4 and M5 morphologies. Since the E05 study represented the first large case–control study of childhood AML, the interview included a wide range of topics, thus limiting the degree of detail that could be obtained about factors of interest. Based on the results, NIH funded a case–control study of 550 cases of childhood AML designed to test a series of hypotheses relating to pesticide exposures and maternal marijuana use. In the future, it is anticipated that followup studies will be proposed based on the results of previous CCG epidemiologic investigations to test specific hypotheses relating to childhood brain tumors, HD, non-Hodgkin's lymphoma, and ALL.

In future studies there will be more integration of direct measurements of exposure. While important associations can be identified using self-reported information obtained through interviews, it is recognized that there are limitations inherent in data collected in this manner. Accordingly, whenever possible, there will be expanded use of more direct measures of exposure. In the current leukemia studies, direct measurements are being made of electromagnetic field radiation, indoor radon, and pesticide residues, PAH, and heavy metals from house dust. While recognizing the financial and logistical issues involved in these types of measurements, experience to date clearly indicates the utility and feasibility of this approach within CCG.

When investigating etiologic hypotheses, studies of childhood cancer must be prepared to assess the potential role of biologic data, particularly in combination with exposure data. With regard to the conduct of epidemiologic studies, one of the many strengths of utilizing the cooperative clinical trials group is the availability of biologic and/or clinical information on ascertained cases. While the type of biologic information is often disease- and protocol-specific, the information generally is collected in a uniform manner at centralized resource laboratories. Previous CCG epidemiology studies have incorporated into the study design the use of data on morphology, phenotype, and cytogenetics. The current case–control study of neuroblastoma uses the information on n-*myc* amplification and ploidy. Other CCG studies have included collecting specific biologic data such as EBV. Depending on the type of biologic data available, this information can be used to stratify cases into potentially more homogeneous subgroups (i.e., morphology, phenotype, etc.) or to assess the biologic parameters as potential risk factors, either solely or in combination with other possible risk factors (i.e., EBV, p53).

Since genetics, and possible genetic-environment interactions, may be important in the etiology of childhood cancers, the CCG plans to expand the assessment of family history. While most of the previous CCG epidemiology studies have included selected information on family history, the majority have not been able to obtain a detailed family pedigree. Recognizing the potential importance of family medical history, the Epidemiology Committee plans to investigate the feasibility of systematically collecting more detailed data in future studies. One of the major deterrents to obtaining family history is the amount time required. By building upon the experience of the CCG Genetics Registry, the committee will investigate various approaches to collecting family history through self-administered and interview formats.

Because of the large proportion of childhood cancer cases that are diagnosed and treated at an institution affiliated with a clinical trials cooperative group, it is possible to investigate etiologic hypotheses in less common childhood cancers. While from a public health perspective it may be argued that these rare forms of malignancies may not warrant investigation, it is clear that rare tumors have provided some of the most important information concerning cancer etiology (i.e., retinoblastoma). In the near future the Epidemiology Committee will consider studies of rare childhood cancers including *a*) Burkitt's lymphoma to investigate environmental and genetic factors through a case-control interview study that will correlate findings with studies relating to evidence for EBV infection and occurrence of chromosomal translocations, and *b*) germ cell tumors to investigate, in a case–control study design, issues relating to congenital anomalies and *in utero* hormone exposure.

Based on information compiled on the distribution of childhood cancers registered with the pediatric cooperative groups (*11*), it has been estimated that over 95% of patients diagnosed in the United States before 10 years of age could be ascertained. Therefore, when appropriate, CCG plans to promote the conduct of intergroup epidemiologic studies to approximate a population-based sample. This possibly would allow the use of alternative methodologic approaches and promote interactions with regional cancer registries.

Lastly, the epidemiologic and biologic studies conducted by CCG and other investigators are continually providing information relating to the possible etiology of childhood cancers. It is important that this information be communicated in the most effective manner to health care professionals who interact with the population of childhood cancer patients. The CCG Epidemiology Committee, in collaboration with the CCG Nursing Committee, plans to provide a series of educational programs to facilitate the exchange of epidemiologic and etiologic information to CCG investigators, including physicians, nurses and data managers.

Summary

The experience of the CCG Epidemiology Committee demonstrates the advantages in conducting epidemiologic research within an existing clinical trials network. The detailed clinical and biologic data available on patients diagnosed within the cooperative groups facilitates the transfer of state-of-the-art technology to epidemiologic research. Discussions are underway in CCG for future studies to correlate environmental exposures with biologic parameters including 11q23 mutations in leukemia, *ras* gene mutations in childhood AML, V-D-J recombinase in leukemia and lymphoma, tyrosine kinase activity in ALL, and parent of origin of +21 in Down syndrome cases with leukemia. With the emphasis on cancer biology within CCG and other cooperative groups, the outlook for further integrating biologic measures into epidemiologic research in the future looks very promising.

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