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An Exploratory Study of Environmental and Medical Factors Potentially Related to Childhood Cancer

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To determine whether a general-purpose epidemiologic questionnaire can be used in childhood cancer hospitals to identify associations between environmental factors and the major types of childhood cancer, we report the results of the analysis of the data obtained from such a questionnaire. On admission to St. Jude Children's Research Hospital in Memphis, Tennessee, between 1979 and 1986 a questionnaire was administered to 1,270 mothers of patients diagnosed with childhood cancer. Approximately one-half of the children had acute leukemias ($n = 629$); the remainder had lymphomas ($n = 237$) or solid tumors ($n = 404$). Responses to questions regarding the patients' and parents' environmental and medical histories were compared across nine diagnostic categories. Only 5 of 232 variables remained nominally statistically significant ($P < 0.05$) after adjusting for confounding by patient or maternal age, year of birth or diagnosis, patient's race, and social class. The variables identified were length of time the patient was breast-fed ($\chi^2 = 16.1$, $P = 0.04$); having a garden with fertilizers, herbicides, and pesticides ($\chi^2 = 17.2$, $P = 0.03$); maternal use of sex hormones during the year before the patient's birth ($\chi^2 = 18.2$, $P = 0.02$); maternal cigarette consumption ($\chi^2 = 18.0$, $P = 0.02$); and patient contact with persons with cancer ($\chi^2 = 20.7$, $P = 0.01$). Despite the large number of patients studied, we identified fewer significant variables than would be expected, on the average, under the null hypothesis. We conclude that the data obtained from a general-purpose epidemiologic questionnaire do not provide a useful overview of the association between exposure to environmental factors and several types of childhood cancer.

Key words: questionnaire, epidemiology, risk factors

INTRODUCTION

Environmental factors associated with the development of one or more diagnostic categories of childhood cancer include ionizing radiation [1,2], sex hormones [3], electromagnetic fields [4], nitroso compounds [5], and maternal prenatal marijuana consumption [6]. Because any particular diagnostic category of childhood cancer is rare, the large case–control studies necessary to identify and evaluate these factors have been costly in both money and time. We wished to determine whether a general-purpose epidemiologic questionnaire administered to the mothers of all newly diagnosed patients at a childhood cancer hospital could yield useful etiologic information. The advantage of this data collecuon method is that it is more systematic than a medical record review and less costly than a case–control study. We planned to use the results to generate new hypotheses, confirm previous observations, and identify new environmental carcinogens whose effect was too small to be observed clinically. The analysis reported below was designed to summarize the salient features of the data set and to identify the most important medical or environmental variables.

MATERIALS AND METHODS

Between 1979 and 1986, 1,929 new cases of histopathologically confirmed childhood cancer were diagnosed at St. Jude in the following categories: acute lymphocytic leukemia (ALL), acute nonlymphocytic leukemia (ANLL), Hodgkin's disease, non-Hodgkin's

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lymphoma (NHL), neuroblastoma, Wilms' tumor, osteosarcoma. rhabdomyosarcoma, and Ewing's sarcoma. These nine categories represent the childhood cancers having the highest national incidence [7] except for brain and central nervous system tumors (no brain tumor program existed at St. Jude's at the time that data collection was initiated). All parents of patients with these diagnoses agreed to be interviewed. However, having a small staff precluded interviews of 659 parents, yielding a 65.8% overall participation rate. The age, sex, and race of the children whose parents were interviewed did not differ significantly from those whose parents were not. Interviews were scheduled as soon as possible after the child's diagnosis (median interval = 2.9 months) with nonsignificant differences in the intervals among the diagnostic categories. Data from admission interviews containing demographic information on patients and their families were combined with the patients' diagnoses. In addition, each patient's mother (or father in the small minority of cases when mothers were not available) was interviewed by a trained interviewer. The hour-long interview was based on a questionnaire that solicited information about the topics listed in Table I.

TABLE I. Topics In Questionnaire

Patient's history	Parent's history
Medical	Medical
Birth weight	Congenital disorders
Congenital disorders	History of cancer
Breast-fed	Illnesses
Tonsillectomy	Hospitalization
Hospitalizations	Radiation
Radiation treatment	Medication
Medication	Reproductive events
Illnesses	Contraceptive
Injuries	Illicit drug use
Residential	Occupation
Birthplace	Occupation
Residence of longest duration	during and after the pregnancy
Quality of drinking water	Occupational exposure to
Lived near factory	chemicals. dust, fumes,
Lived on farm	and x-rays
Hobbies	Tobacco and alcohol
Fertilizer, herbicides. pesticides	consumption
in garden and house	Parental and other
Chemicals in house	household members

The goal of the analysis was to summarize the data set, making as few unjustifiable assumptions as possible. We compared exposure across the nine diagnostic categories rather than arbitrarily designating one diagnostic category as cases and the others as controls. If cancer cases are used as controls and both cases and controls are associated with a common exposure, the case–control comparison will show no difference in the distribution of exposure. This lack of difference may erroneously be interpreted as no exposure effect.

To select categorical variables from the 116 created by the questionnaire, the Pearson chi-squared statistic was used to test the equality of each exposure variable among the nine diagnostic types of cancer. The categorical variables identified as differing among the diagnostic categories ($P < 0.05$) were then stratified by patient or maternal age (as substantively appropriate) and tested for equality using the Cochran-Mantel-Haenszel test of general association [8]. Sixteen continuous variables based on the questionnaire were transformed to ranks. and the Kruskal-Wallis test [9] of the equality of the median ranks over the nine diagnostic categories [10] was employed. We then adjusted these continuous variables for age using an analysis of covariance. The adjusted odds ratios for the remaining variables were estimated using polytomous logistic regression. The odds ratios were adjusted for the patient's age at diagnosis (an index of recall bias for prenatal exposures). maternal age at time of the patient's birth (for prenatal exposure). or maternal age at the time of diagnosis (for childhood exposure). year of birth (or the year of diagnosis), the patient's race. number of years of maternal education. and the father's occupation (0 = blue collar workers, such as construction workers. assembly line workers, and truck drivers; 1 = technicians. clerks, and salesmen; 2 = professionals, such as physicians, engineers, and scientists). All these potentially confounding variables were initially included in the regression equations and then removed according to the change in estimate criterion [11]. No adjustment was made for multiple testing, because this is an exploratory analysis. Thus all P values are nominal P values whose interpretation is not the usual one.

RESULTS

The patients whose parents were interviewed were representative of the St. Jude population of newly diagnosed cases between 1979 and 1986 with respect to age. sex. and race. Most of the patients were white, and 42% were female (Table II). As would be expected from the national incidence patterns of childhood cancer [7], patient sex. race. and especially age differences among the diagnostic categories were statistically significant.

The variable selection procedures described in Materials and Methods identified five statistically significant variables (Table III): 1) the number of months the patient was breast-fed: 2) parental gardening with fertilizers, herbicides, and pesticides during the period from birth to diagnosis: 3) the maternal prenatal use of sex hormones; 4) maternal cigarette consumption during the index pregnancy; and 5) the patient's contact with persons with cancer during the period from birth to diagnosis.

Rhabdomyosarcoma is used as the reference category

TABLE II. Characteristics of 1,270 Childhood Cancer Patients Whose Parents Were Interviewed

Diagnostic category	No. interviewed	Age at diagnosis[a]	White		Female	
			No.	Percent	No.	Percent
ALL	522	4.6	465	89.1	220	42.2
ANLL	107	7.4	96	89.7	41	38.3
Hodgkin's disease	133	14.6	12	90.2	54	40.6
NHL	104	10.2	90	86.5	32	30.8
Neuroblastoma	104	1.8	93	89.4	53	51.0
Wilms' tumor	101	3.3	74	73.3	55	54.5
Osteosarcoma	78	14.5	66	84.6	29	37.2
Rhabdomyosarcoma	72	7.0	63	87.5	35	48.6
Ewing's sarcoma	49	14.7	48	98.0	15	30.6
Total	1.270	6.3	1.115	87.8	534	42.1
		KW[b] = 476.2 P = 0.0001	$\chi^{2c}_{(8)}$ = 27.7 P = 0.001		$\chi^{2}_{(8)}$ = 20.6 P = 0.008	

[a] Median age in years.
[b] Kruskal-Wallis test [9] of equality of ranks of ages.
[c] Test of equality of percentages.

TABLE III. Odds Ratios* Adjusted for Confounding Variables†

Diagnostic category	Months breast-fed[a]	Gardening with pesticides[b]	Prenatal sex hormones[c]	Maternal cigarette consumption[d]	Patient contact cancer patients[e]
Rhabdomyosarcoma[f]	1.0	1.0	1.0	1.0	1.0
ALL	1.0	1.3	1.3	0.7	0.6
ANLL	0.8	0.9	0.5	1.5	0.1 (.05)[g]
Hodgkin's disease	0.4 (.02)[g]	1.4	0.5	1.1	0.9
NHL	1.1	1.3	0.8	0.6	0.9
Neuroblastoma	1.4	1.1	0.8	1.3	0.7
Wilms' tumor	0.9	0.7	1.1	0.8	0.5 (.04)[g]
Osteosarcoma	0.6	2.6 (.01)[g]	0.7	1.1	0.4 (.02)[g]
Ewing's sarcoma	2.2	1.1	1.5	1.4	1.6
Total No.	357	1.253	1.237	1.240	1.246
Average	4.0[h]	43.79	12.56	28.6%	37.96
	$\chi^{2}_{(8)}$ = 16.1[i] P = 0.042	$\chi^{2}_{(8)}$ = 17.2 P = 0.028	$\chi^{2}_{(8)}$ = 18.2 P = 0.020	$\chi^{2}_{(8)}$ = 18.2 P = 0.021	$\chi^{2}_{(8)}$ = 20.7 P = 0.008

* Ratio of exposure odds for each diagnostic category to exposure odds for rhabdomyosarcoma.
† Based on polytomous logistic regression using maternal age or age at diagnosis. year of birth or diagnosis. the patient's race. number of years of maternal education, and the father's occupation as potentially confounding variables.
[a] Above average exposure is defined as being breast-fed for 8 months or more (the third quartile); below average exposure is defined as being breast-fed for 2 months or less (the first quartile).
[b] Parents gardening with fertilizers, herbicides. and pesticides from birth to diagnosis.
[c] Maternal use of sex hormones from 1 year before the pregnancy to the time of birth.
[d] Coded as "1" if ever smoked cigarettes during the pregnancy and "0" otherwise.
[e] Contact during the period from birth to diagnosis of the patient's index cancer.
[f] Reference category.
[g] P value of less than 0.05 for chi-squared test of equality of odds ratio to 1.0.
[h] Median number of months breast-fed.
[i] Test of overall association between exposure and diagnostic category.

(odds ratio [OR] = 1.0) for the eight other diagnoses. The length of time a patient was breast-fed was reported and analyzed in months. The odds ratios for breast-feeding shown in Table 3 compare the exposure odds of breast-feeding for 8 months (the 75th percentile, relative to breast-feeding for 2 months (the 25th percentile) for each of the eight diagnostic categories separately with the exposure odds for rhabdomyosarcoma. The remaining variables in Table 3 are dichotomous (coded 1 = yes and 0 = no). Maternal cigarette consumption is considered positive if the mother reported smoking cigarettes at all during the prenatal period.

The five statistically significant variables that we identified are discussed in order of their epidemiologic plausibility based on published research. Overall, few of the odds ratios differ greatly from 1.0, and only five of the odds ratios are associated with P values of less than 0.5 (Table III).

Number of Months Breast-fed

Whether the children had been breast-fed was not related to the diagnostic categories. However, the duration of breast-feeding differed among the groups. We observed a statistically significant protective effect against Hodgkin's disease (OR = 0.4, P = 0.02) among children who were breast-fed at least 8 months compared with children who were breast-fed no more than 2 months. Breast-feeding children at least 8 months did not offer protection against NHL (OR = 1.1, P = 0.73). Because breast milk may be a vehicle for carcinogens [12,13], we assessed the modifying effect of breast-feeding on maternal cigarette consumption and use of fertilizers. herbicides. or pesticides. We found no evidence for a relationship between breast-feeding and these two variables.

Parent Gardening With Fertilizers, Herbicides, and Pesticides During the Postnatal, Prediagnostic Period

The lowest odds ratios for gardening with fertilizers. herbicides, and pesticides after the birth of the child until the date of diagnosis were reported by the parents of children with Wilms' tumor (OR = 0.7, $P = 0.30$, percentage exposed = 30.8); parents of children with osteosarcoma reported the highest exposure (OR = 2.6, $P = 0.01$, percentage exposed = 53.6). Related variables that were not statistically significant included whether pesticides were used around the house. whether the family lived on or near a farm where crops were sprayed. and whether either one or both of the parents were farmers.

Maternal Prenatal Sex Hormone Use

Of 155 mothers who reported using hormones during the year before the index birth. 8 used fertility agents. 122 used birth control pills, 26 used progesterone. and 19 used a hormone they could not identify (some women used more than one type of hormone). The odds ratios range from 0.5 ($P = 0.11$) for mothers of children with Hodgkin's disease to 1.5 ($P = 0.55$) for mothers of children with Ewing's sarcoma.

Maternal Cigarette Consumption During the Index Pregnancy

The three largest odds ratios were for mothers whose children were diagnosed with ANLL (OR = 1.5, P = 0.20), neuroblastoma (OR = 1.3. $P = 0.40$). and Ewing's sarcoma (OR = 1.4, $P = 0.39$). Despite an overall P value of 0.02. none of the nine categories individually had a P value less than 0.05 (for testing an odds ratio of 1.0). The age-adjusted proportions of mothers who smoked at least 10 cigarettes a day compared with those who smoked fewer than 10 cigarettes a day and with those who did not smoke showed little variation among the diagnostic categories.

Stjernfeldt et al. [14] found an association between maternal prenatal cigarette consumption and ALL but no relationship between maternal cigarette smoking and childhood solid tumors. To replicate their analysis, patients with solid tumors (neuroblastoma. Wilms' tumor. osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma) were used as a control group for ALL patients, and confounding variables were controlled by unconditional binomial logistic regression. Our analysis produced odds ratios of 0.8 ($P = 0.04$) for smokers of 1–9 cigarettes a day compared with those who did not smoke and of 1.1 ($P = 0.48$) for those who smoked ≥ 10 cigarettes a day compared with those who did not smoke.

Patient Contact With Persons With Cancer During the Postnatal, Prediagnostic Period

The highest odds ratios for patients who had previous contact with persons diagnosed with cancer were found among patients with Ewing's sarcoma (OR = 1.6, $P = 0.28$) and rhabdomyosarcoma (OR = 1.0. reference disease). Approximately 45% (213) of the identified contacts reportedly had the most common types of adult cancer: gastrointestinal, lung, and breast. Almost one-half of these contacts were the patients' natural grandparents. Because previous investigators [2] have identified clusters of childhood leukemia and lymphoma, the proportion of reported leukemia or lymphoma contacts of the study subjects with these diagnoses were compared with that among subjects in the other diagnostic categories. No differences were seen. with approximately 5% of the index cases of both groups reporting contact with leukemia or lymphoma patients.

DISCUSSION

In this exploratory analysis it is noteworthy that, after adjustment for confounding, few variables were found to be statistically significant. At the nominal 0.05 level, we would expect. on the average, approximately 12 (0.05×232) statistically significant variables to emerge by chance. We observed only five statistically significant variables and did not adjust for multiple testing; one interpretation is that the overall results are consistent with a global null hypothesis. This interpretation is strengthened by the fact that most of the odds ratios are near the null value (Table III). The small number of statistically significant variables after adjustment for confounding may suggest the operation of common etiologic agents

among the nine diagnostic categories of childhood cancer. Another cause could be time of exposure during the prenatal period or childhood. If time of exposure relative to the development of the fetus or child is critical in prenatal and postnatal carcinogenesis [15,16], then confounding by time could effectively remove evidence of the influence of risk factors on tumor initiation or promotion.

Although we identified fewer variables than would have been expected on the basis of chance alone. any one of the five variables (or other variables) may be a true determinant of one or more of the nine diagnostic categories of childhood cancer. Because there is no statistical method for identifying which of a group of variables are statistically significant because of alpha error (false positives) and which represent a true association, the results must be compared with those from previous studies to evaluate them. Of course, this method will not identify previously unreported associations.

Davis et al. [17] observed elevated odds ratios for all types of childhood cancer for mothers who fed their children nonhuman milk relative to mothers who breast-fed their children for at least 6 months. This odds ratio was particularly pronounced for childhood lymphoma and was probably due to an association with childhood Hodgkin's disease [18]. The association between the duration of breast-feeding and ALL. NHL. and ANLL was not observed by Magnani et al. [18]. and it was not confirmed for ALL by Van Duijn et al. [19]. McKinney et al. [20] reported no difference between the frequency with which the mothers of childhood leukemia and lymphoma cases and their controls reponed breast-feeding their children. However. they did not report the results of an analysis of the association between the duration of breast-feeding and leukemia case status. Like McKinney et al. [20], we found no association between childhood cancer and whether a mother said she breast-fed her child. However. our results are consistent with those of Davis et al. [17], who showed a protective effect of breast-feeding against Hodgkin's disease. and with the results of others [18.19] who observed no effect of breast-feeding on the childhood leukemias and NHL [18,19]. Our findings are probably not attributable to recall bias, because every mother interviewed had a child diagosed with cancer. It has been hypothesized that human milk consumption during infancy mal increase resistance to early infection. which could indirectly offer protection against the subsequent development of Hodgkin's disease [17]. In addition. the effect of breast-feeding may vary among populations depending on the environmentally determined constituents of breast milk in each population. In some populations breast-feeding could be a vehicle for postnatal exposure to carcinogens [12,13,21].

Of the several variables based or! questions designed to solicit information on pesticide use, only gardening with fertilizers. herbicides, or pesticides was statistically significant. Convincing evidence exists in the literature for an association between several types of childhood cancer and pesticide use. Buckley et al. [22] reported an association between prenatal and postnatal household and garden exposure to pesticides and childhood ANLL. Independent of this association. they also observed a relationship between parental occupational exposure to pesticides and childhood ANLL. Lowengart et al. [21] found parental use of pesticides in either the home or garden during the pregnancy and nursing period to be a predictor of childhood leukemia case status. Pesticide exposure has also been reponed in association with neuroblastoma [23]. Wilms' tumor [24], and childhood brain tumors [25]. In our study the odds ratios for the children diagnosed with leukemia (ALL [OR = 1.3. $P = 0.383$. ANL [OR= 0.9. P = 0.671). Wilms' tumor (OR = 0.7. $P = 0.30$). and neuroblastoma (OR = 1.1. $P = 0.78$) are not particularly high. However. that associated with osteosarcoma is elevated (OR = 2.6, P = 0.01). The differences between our results and those found in the literature may be explained. in part. by the association of pesticide use with more than one site of childhood cancer. Such an association could also account for the lack of statisticai significance of the other. variables designed to evaluate information on pesticide use. Although Gold et al. [25] observed an association between childhood brain tumors and household insect extermination when the– compared the brain tumor cases with nondiseased controls. they found no evidence for this association when comparing brain rumor cases with childhood cancer controls.

The evidence for an association between maternal hormone consumption and childhood cancer. other than adenocarcinoma of the vagina [3]. is inconsistent. Three relatively large. well-defined case-control studies. one of acute leukemia [26], one of neuroblastoma [27], and one of Wilms' tumor [24]. found evidence for an association between maternal hormone status or consumption and childhood cancer. In the present study. we found a relatively low odds ratio (0.8) associated with the mothers of children with neuroblastoma who reponed prenatal hormone use. Robison et al. [6]. Operskalski et al. [28]. and McKinney et al. [20] found no association between maternal prenatal hormone consumption and ANLL. osteosarcoma. and leukemia or lymphoma combined. respectively. The overall percentage of women in this stud) reponing use of sex hormones during the year before pregnancy (8.2%) was approximately the same (5%) as that observed in a similar stud!. of childhood cancer cases conducted by Li et al. [29]. Further studies that examine the time of sex hormone consumption during the pregnancy shouid be conducted.

Because no dose–response relationship was observed

for maternal cigarette consumption, the evidence for this variable in this study is weak: however, a case–control study identified a significant association between maternal prenatal cigarette consumption and childhood cancer at all sites combined and ALL [14]. Although two large childhood cancer studies found no evidence for a similar association [30,31]. further investigation would be worthwhile because of the relatively high prevalence of cigarette consumption combined with its known ability to harm the developing fetus [32] and its carcinogenicity in adults.

The three statistically significant odds ratios for patient contact with persons with cancer (Table 3) may result from the relatively high frequency with which cancer patient contact was reported by rhabdomyosarcoma cases (the reference category). Li and Fraumeni [33] and others [34–36] observed an excess of malignant neoplasms in the families of children diagnosed with both bone and soft tissue sarcomas. Although the odds ratio for Ewing's sarcoma is greater than 1.0 and consistent with these observations (OR = 1.6, $P = 0.28$), that for osteosarcoma is less than 1.0 (OR = 0.4, $P = 0.02$).

CONCLUSIONS

We conclude that of the five variables identified. further research of the association between duration of breast-feeding and development of childhood Hodgkin's diseuse is most justified. However. despite the large number of patients studied. we have identified few strong leads for further research. For conducting exploratory studies of several types of childhood cancer simultaneously the general-purpose epidemiologic questionnaire taken as a whole is unlikely to yield sufficient benefits for the: cost and effort involved. Further analyses of these data will determine whether in depth studies of particular diagnostic categories will provide useful information about the epidemiology of childhood cancer.

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