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Paternal Military Service and Risk for Childhood Leukemia in Offspring

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To assess the association between paternal military service and risk for childhood leukemia, the authors analyzed data from three case-control studies conducted by the Children's Cancer Group from 1983 to 1993. A total of 605 acute myeloid leukemia (AML, age ≤ 18 years) cases, 2,117 acute lymphoblastic leukemia (ALL, age ≤ 14 years) cases, and 3,155 individually matched controls were included in these studies. Paternal military history and other exposure data were obtained in 2,343 matched case-control sets, including 1,805 ALL and 528 AML cases. Paternal general military service was not associated with the leukemia risk. A small, but significant, increase in the risk for AML was seen, however, among offspring of veterans who had served in Vietnam or Cambodia (odds ratio (OR) = 1.7; 95% confidence interval (CI): 1.0, 2.9), after adjustment for paternal education, race, income, smoking, X-ray exposure, and marijuana use. The risk was predominantly present in children diagnosed before the age of 2 (OR = 4.6; 95% CI: 1.3, 16.1), although there were inconsistencies in the risks associated with length of time served and interval between service and diagnosis of leukemia. Military service in Vietnam or Cambodia was unrelated to the risk for ALL. The etiologic importance, if any, of these observations has yet to be determined. *Am J Epidemiol* 2000;151:231–40.

child; leukemia, lymphocytic; leukemia, myeloid; military personnel; veterans

Military service, particularly during wartime, may be associated with exposure to major health hazards, including chemicals such as solvents, herbicides, and pesticides. In addition, the prevalence of alcohol consumption and cigarette and marijuana smoking has been reported to be greater among military personnel than among the general population (1, 2). During the 1980s, questions were raised as to whether military service in Vietnam or Cambodia might have a long-term impact on the health of veterans and their offspring (2). Many studies have been conducted to address these concerns, with a main focus on the health effects of exposure to Agent Orange (2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)), an herbicide that was extensively sprayed during the Vietnam War during 1962–1971 (3–8). Some of these studies suggested an increased risk for non-Hodgkin's lymphoma, Hodgkin's disease, and soft-tissue sarcoma among Vietnam veterans exposed to high levels of Agent Orange (7, 9–11), but the results were not entirely consistent (12, 13). Exposure to Agent Orange or other chemicals used in the Vietnam War has also been linked to an excess of adverse pregnancy outcomes, such as birth defects and spontaneous abortion (7, 14).

Childhood leukemia, the leading malignancy among children under the age of 15 in the United States, has been reported in some, but not all, studies to be related to paternal occupational exposure to pesticides, ionizing radiation, and solvents and to certain parental lifestyle risk factors, such as cigarette and marijuana smoking (15–21). The effect of military service and its related exposures on the development of childhood leukemia has not been specifically assessed. In this exploratory analysis, we examined the relation between preconception paternal military service and the subsequent occurrence of childhood leukemia, using data from three case-control studies conducted by the Children's Cancer Group (CCG).

MATERIALS AND METHODS

The data evaluated in this report were obtained from interviews with fathers from three separate epidemiologic studies (protocols CCG-E09, CCG-E14, and

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Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCG, Children's Cancer Group; CI, confidence interval; OR, odds ratio.

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CCG-E15) conducted by the CCG, a cooperative clinical trials group with approximately 100 principal and affiliated institutions in the United States, Canada, and Australia. Details of these studies have been described elsewhere (18, 22). Briefly, CCG-E09 was designed to examine the association between parental exposures and acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), in children diagnosed before the age of 18 months; CCG-E14 examined parental and childhood exposures in connection with AML in children under the age of 18 years; CCG-E15 was undertaken to assess the role of parental and childhood exposures in ALL diagnosed in children under the age of 15.

Leukemia cases for all three studies were identified through the patient registration files of the CCG. Only individuals residing in the United States or Canada and diagnosed at CCG institutions were included as cases in these studies. As mentioned above, depending on the study, eligibility criteria differed with respect to age at diagnosis and type of leukemia. However, all three studies required that there be a telephone in the patient's residence and that the patient's biologic mother be available for interview and speak English. Controls for the three studies were selected using a previously described random digit telephone dialing procedure (23) and individually matched to cases on year of birth (within a year of age at diagnosis of the case for E09, within 25 percent of the age at diagnosis of the case for E14 and E15), location of residence (determined by telephone area code and exchange), sex (for E14 and E15), and race (White, non-White, for E14 and E15). If an eligible control could not be found by calling the first 150 randomly generated telephone numbers, then the matching criteria were relaxed, starting with race. The ratio of controls to cases was 2:1 for E09, 1:1 for E14 (2:1 for the rare morphologic subgroups M3, M6, M7, and MDS), and 1:1 for E15. As with cases, it was required that the biologic mothers of controls speak English and be available for interview, and that there be a telephone in the residence. Information regarding parental and childhood exposures was collected, whenever possible, by independent telephone interview of both the mother and the father, using a structured questionnaire. Table 1 summarized the participation rates, reasons for nonparticipation, and final numbers of cases and controls of the three studies included in current analysis. After excluding unmatched cases, this analysis included a total of 2,343 matched case-control sets (275 sets from E09, 450 from E14, 1,618 from E15, and a total of 2,723 controls). For those subjects included in the analysis, direct interviews with fathers were obtained for 1,968 (84 percent) cases and 1,840 (68 percent)

TABLE 1. Study samples of CCG*-E09, CCG-E14, and CCG-E15, Children's Cancer Group, United States, Canada, 1983–1993

	Eligible subjects (no.)	Telephone interviews completed with mothers		Reasons for nonparticipation: Parental refusal		Physician refusal		Other		Subjects with paternal exposure information available		Final matched case-control sets (no.)
		No.	%	No.	%	No.	%	No.	%	No.	%	
E09												
Cases	382	302	79	31	8	19	5	30	8	280	73	275
Controls	743	558	75	138	19	N/A*		47	6	511	69	
E14												
Cases	638	530	83	53	8	28	4	27	4	484	76	450
Controls	771	612	79	142	18	N/A		17	2	558	72	
E15												
Cases	2,081	1,914	92	70	3	41	2	56	3	1,800	87	1,618
Controls	2,597	1,987	77	457	18	N/A		153	6	1,814	70	

* CCG, Children's Cancer Group; N/A, not available.

controls. In the remaining instances, the father's questionnaire was completed by the mother as a surrogate for the father.

The data evaluated in this analysis were mainly derived from the paternal occupation history (providing the dates for military service) and military service history sections of the fathers' questionnaires. Information regarding potential leukemia risk factors and socioeconomic status was derived from the relevant sections of both the paternal and the maternal interview questionnaires.

We used conditional logistic regression models in the data analyses to estimate odds ratios and 95 percent confidence intervals as measures of leukemia risk associated with military service, adjusting for potential confounders. Analyses were carried out for all leukemia cases combined and for leukemia stratified by subtype (i.e., ALL and AML) and by age at diagnosis (<2 years, 2–5 years, and >5 years).

RESULTS

There were 1,805 ALL cases (2,051 matched controls) and 528 AML cases (657 matched controls) in this combined data set. The remaining cases were of other types and were not included in subgroup analysis. A total of 582 cases (25 percent) were younger than 2 years, 1,009 (43 percent) were 2–5 years, and 752 (32 percent) were more than 5 years old at diagnosis.

Selected characteristics of the study population are shown in table 2. Compared with control fathers, case fathers were less educated ($p < 0.01$) and had lower family incomes than did control fathers ($p < 0.01$). Case fathers were also more likely to be non-White (odds ratio (OR) = 2.0; $p < 0.01$), to have ever been exposed to X-rays prior to the index child's conception (OR = 1.2; $p = 0.02$), and to have ever smoked marijuana (OR = 1.5; $p < 0.01$) or cigarettes (OR = 1.2; $p = 0.04$). These factors were adjusted for their potential confounding effect in all analyses. The father's age at the birth of the index child appeared to be younger among cases than among controls, although the test for linear trend between the risk for childhood leukemia and paternal age categories was not statistically significant (linear trend, $p = 0.07$). Approximately similar proportions of case and control fathers reported a history of alcohol consumption before the index pregnancy (OR = 1.0; $p = 0.64$). Although some differences became nonsignificant in each individual study and subtype of leukemia because of decreased sample size, these patterns were seen across all three studies (table 2) and for both ALL and AML (data not shown), with the exception of paternal smoking, which was unrelated to AML (OR = 1.0; $p = 0.88$).

Characteristics of paternal general military service with their associated odds ratios and 95 percent confidence intervals for childhood leukemia, adjusted for paternal education, race, income, smoking, X-ray exposure, and marijuana use, are shown in table 3. No significant association between childhood leukemia and general paternal military service was found. Among 2,343 case fathers, there were 117 subjects (5 percent) who reported having ever served in Vietnam or Cambodia before the conception of the index child. We analyzed factors that were related to military experience in Vietnam or Cambodia, including the total number of tours, the total number of years of military service in Vietnam or Cambodia, the interval (in years) from the beginning of military service in Vietnam or Cambodia to the conception of the index child, self-reported exposure to herbicides, and history of ever taking malaria prophylaxis. The risk for AML in offspring was modestly elevated when the father reported having served in Vietnam or Cambodia (OR = 1.7; 95 percent confidence interval (CI): 1.0, 2.9), based on 40 exposed cases and 33 exposed controls (table 4). The risk was more evident for children of fathers who reported two or more tours in Vietnam or Cambodia (OR = 5.0; 95 percent CI: 1.0, 24.5), based on eight exposed cases and two exposed controls, and for children of fathers who reported an interval of >15 years from the beginning of military service in Vietnam or Cambodia to the conception of the index child (OR = 4.7; 95 percent CI: 1.2, 18.3), based on nine exposed cases and four exposed controls. Paradoxically, however, the risk was not positively correlated with the length of service in Vietnam or Cambodia. An elevated risk was found only for those offspring of fathers who served in Vietnam or Cambodia for 1 year or less (OR = 2.4; 95 percent CI: 1.1, 5.4), based on 21 exposed cases and 13 exposed controls. Military service in Vietnam or Cambodia was not related to the risk for ALL or for all leukemias combined. The reported exposure to herbicides, including Agent Orange, and to malaria prophylaxis was unrelated to the risk for ALL or for AML.

We conducted stratified analyses by age at the time of case diagnosis (<2, 2–5, >5 years) to further evaluate the association of childhood leukemia with paternal military service in Vietnam or Cambodia. The association of childhood AML and paternal military service in Vietnam or Cambodia was predominantly present in children diagnosed before the age of 2 (OR = 4.6; 95 percent CI: 1.3, 16.1), based on nine exposed cases and five exposed controls. Herbicide exposure was associated with the risk for AML subtype in the under-2 age group (Fisher's exact test, $p = 0.03$), based on four exposed cases and zero exposed controls. The risk for

TABLE 2. Odds ratios (ORs) of childhood leukemia associated with paternal characteristics, Children's Cancer Group, United States, Canada, 1983–1993

	Total			E09			E14			E15		
	Cases (%) (*n* = 2,343)†	Controls (%) (*n* = 2,723)†	OR‡	Cases (%) (*n* = 275)	Controls (%) (*n* = 478)	OR	Cases (%) (*n* = 450)	Controls (%) (*n* = 523)	OR	Cases (%) (*n* = 1,618)	Controls (%) (*n* = 1,722)	OR
Paternal age (years)												
<25	22	19	1.0	20	17	1.0	25	22	1.0	21	19	1.0
25–29	32	33	0.8*	29	33	0.7	31	33	0.8	33	33	0.9
30–34	28	29	0.9	34	32	0.8	25	26	0.8	29	30	0.9
≥35	18	18	0.8*	17	18	0.7	19	20	0.8	17	18	0.8
Paternal race												
White	84	89	1.0	86	88	1.0	82	86	1.0	85	90	1.0
Nonwhite	16	11	2.0*	14	12	1.2	18	14	2.1	15	10	2.3*
Paternal education												
≥College graduation	28	33	1.0	29	34	1.0	27	32	1.0	29	33	1.0
Some post-high school	30	30	1.2*	28	30	1.1	30	30	1.2	30	30	1.2*
≤High school	42	37	1.4*	43	36	1.5	43	38	1.4	42	37	1.4*
Family income ($)												
≥40,000	25	30	1.0	23	27	1.0	23	26	1.0	26	31	1.0
20,000–39,000	45	45	1.2*	54	54	1.2	48	44	1.3	43	43	1.2*
<20,000	30	25	1.5*	23	19	1.4	29	30	1.2	31	26	1.6*
Exposure to X-rays												
No	84	87	1.0	82	86	1.0	84	86	1.0	85	87	1.0
Yes	16	13	1.2*	18	14	1.4	16	14	1.3	15	13	1.2
Marijuana use												
No	84	88	1.0	82	90	1.0	84	87	1.0	84	89	1.0
Yes	16	12	1.5*	18	10	2.0*	16	13	1.3	16	12	1.5*
Cigarette use												
No	62	65	1.0	63	69	1.0	63	62	1.0	62	65	1.0
Yes	38	35	1.2*	37	31	1.4	37	39	1.0	38	35	1.2*
Alcohol												
No	31	32	1.0	26	30	1.0	34	33	1.0	31	32	1.0
Yes	69	68	1.0	74	70	1.3	66	67	0.9	69	68	1.1

* Statistically significant at 0.05 level.

† Frequencies were obtained for all cases and controls pooled, ignoring matching status. Subjects with missing values were excluded. In E09, cases were diagnosed before the age of 18 months, including 187 acute lymphoblastic leukemia, 78 acute myeloid leukemia, and 10 other leukemia cases in this analysis. In E14, cases were diagnosed with acute myeloid leukemia before the age of 18 years. In E15, cases were diagnosed with acute lymphoblastic leukemia before the age of 15 years.

‡ Odds ratios were derived from a conditional logistic regression model.

TABLE 3. The relation between childhood leukemia and paternal general military service, Children's Cancer Group, United States, Canada, 1983–1993

	Total				ALL*				AML*			
	Cases (*n* = 2,343)†	Controls (*n* = 2,723)†	OR*,‡	95% CI*	Cases (*n* = 1,805)	Controls (*n* = 2,051)	OR	95% CI	Cases (*n* = 528)	Controls (*n* = 657)	OR	95% CI
Ever in military service												
No	1,752	2,055	1.0		1,359	1,556	1.0		385	487	1.0	
Yes	470	547	1.0	0.9, 1.2	353	405	0.9	0.8, 1.1	115	140	1.1	0.8, 1.5
Unknown	121	121	1.1	0.8, 1.4	93	90	1.1	0.9, 1.5	28	30	1.0	0.6, 1.7
Military branch												
No military service	1,752	2,055	1.0		1,359	1,556	1.0		385	487	1.0	
Army	190	225	1.0	0.8, 1.2	142	169	0.9	0.7, 1.2	47	55	1.2	0.8, 1.9
Other	280	322	1.0	0.8, 1.2	211	236	1.0	0.8, 1.2	58	85	1.0	0.7,1.5
Total years in military service												
No military service	1,752	2,055	1.0		1,359	1,556	1.0		385	487	1.0	
≤2 years	112	123	1.1	0.8, 1.4	86	93	1.0	0.8, 1.4	24	30	1.1	0.6, 2.0
≤4 years	185	207	1.0	0.8, 1.3	141	161	1.0	0.7, 1.2	44	44	1.4	0.8, 2.2
>4 years	166	203	0.9	0.7, 1.2	120	141	0.9	0.7, 1.2	46	62	0.9	0.6, 1.4
Years since beginning military service§												
No military service	1,752	2,055	1.0		1,359	1,556	1.0		385	487	1.0	
≤5 years	71	90	0.8	0.6, 1.1	50	67	0.8	0.5, 1.1	20	23	0.9	0.5, 1.8
≤10 years	139	152	1.0	0.7, 1.3	103	105	1.0	0.7, 1.3	36	46	0.9	0.6, 1.6
>10 years	253	294	1.0	0.9, 1.3	194	225	1.0	0.8, 1.2	58	68	1.2	0.8, 1.9

* ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; OR, odds ratio; CI, confidence interval.

† Frequencies were obtained for all cases and controls pooled, ignoring matching status. Subjects with missing values were excluded.

‡ Odds ratios were derived from a conditional logistic regression model, adjusted for paternal education, paternal race, family income, ever smoking, exposure to X-rays ever, and ever taking marijuana.

§ Interval (in years) from the beginning of military service to the conception of the index child.

TABLE 4. The association of paternal military experience in Vietnam or Cambodia with childhood leukemia, Children's Cancer Group, United States, Canada, 1983–1993

	Total				ALL†				AML†			
	Cases (*n* = 2,343)‡	Controls (*n* = 2,723)‡	OR†,§	95% CI†	Cases (*n* = 1,805)	Controls (*n* = 2,051)	OR	95% CI	Cases (*n* = 528)	Controls (*n* = 657)	OR	95% CI
Ever served in Vietnam or Cambodia												
No	2,226	2,602	1.0		1,728	1,964	1.0		488	624	1.0	
Yes	117	121	1.2	0.9, 1.6	77	87	1.0	0.8, 1.4	40	33	1.7	1.0, 2.9*
Tours in Vietnam or Cambodia												
None	2,226	2,602	1.0		1,728	1,964	1.0		488	624	1.0	
Once	93	98	1.2	0.9, 1.6	61	66	1.1	0.8, 1.6	32	31	1.5	0.9, 2.6
Twice or more	24	23	1.2	0.7, 2.2	16	21	0.9	0.4, 1.7	8	2	5.0	1.0, 24.5*
Years in Vietnam or Cambodia												
Never	2,226	2,602	1.0		1,728	1,964	1.0		488	624	1.0	
≤1 year	61	56	1.4	0.9, 2.0	40	43	1.2	0.8, 1.8	21	13	2.4	1.1, 5.4*
>1 year	49	52	1.2	0.8, 1.7	33	35	1.1	0.7, 1.8	16	16	1.5	0.7, 3.2
Interval¶												
Never	2,226	2,602	1.0		1,728	1,964	1.0		488	624	1.0	
≤10 years	34	36	1.1	0.7, 1.8	16	19	1.0	0.5, 1.9	18	17	1.3	0.6, 3.0
≤15 years	41	34	1.6	1.0, 2.5	30	26	1.4	0.8, 2.4	11	8	2.1	0.8, 5.7
>15 years	37	38	1.3	0.8, 2.0	28	33	1.1	0.6, 1.8	9	4	4.7	1.2, 18.3*
Herbicide												
No	2,266	2,640	1.0		1,749	1,991	1.0		507	635	1.0	
Yes	49	45	1.3	0.9, 2.0	37	32	1.4	0.8, 2.3	12	13	1.3	0.5, 3.0
Agent orange	28	29	1.1	0.6, 1.9	22	21	1.2	0.6, 2.2	6	8	0.9	0.3, 2.9
Other	21	16	1.8	0.9, 3.5	15	11	1.8	0.8, 4.0	6	5	1.8	0.5, 6.3
Unknown	28	38	0.9	0.6, 1.5	19	28	0.8	0.4, 1.4	9	9	1.7	0.6, 4.3
Malaria prophylaxis												
No	2,251	2,629	1.0		1,743	1,986	1.0		498	629	1.0	
Yes	69	65	1.3	0.9, 1.9	44	42	1.3	0.8, 1.9	25	22	1.7	0.9, 3.2
Unknown	23	29	1.0	0.6, 1.7	18	23	0.9	0.5, 1.8	5	6	1.1	0.3, 3.6

* Statistically significant at 0.05 level.
† ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; OR, odds ratio; CI, confidence interval.
‡ Frequencies were obtained for all cases and controls pooled, ignoring matching status. Subjects with missing values were excluded.
§ Odds ratios were derived from a conditional logistic regression model, adjusted for paternal education, paternal race, family income, ever smoking, exposure to X-rays ever, and ever taking marijuana.
¶ Interval (in years) from start date served in Vietnam or Cambodia to the date of the conception of the index child.

ALL associated with military service in Vietnam or Cambodia or related exposures was not significant across all three age groups.

Paternal age may be a confounder for the association between leukemia and the interval (in years) from the beginning of military service in Vietnam or Cambodia to the conception of the index child. However, no appreciable changes in the odds ratios presented in tables 2–4 were observed after further adjustment for paternal age (data not shown).

The possibility of misclassification of exposures may be present in instances where the father's exposure history was collected by surrogate interview with the mother. To examine this possible effect, we conducted a number of analyses from which surrogate data were excluded. In these analyses, the pattern of the association between paternal military experience in Vietnam or Cambodia and childhood leukemia did not significantly change, although the point estimates of the odds ratios were no longer significant because of the reduced sample size. Adjusted estimates of AML risk from the fathers' direct interview data (OR = 1.9; 95 percent CI: 0.9, 3.8, for service in Vietnam or Cambodia; OR = 1.9; 95 percent CI: 0.7, 5.2, for service in Vietnam or Cambodia for 1 year or less; OR = 1.4; 95 percent CI: 0.5, 4.3, for service in Vietnam or Cambodia for more than 1 year) were similar to those shown in table 4.

DISCUSSION

This exploratory study, consisting of more than 2,300 leukemia cases and matched controls, specifically assessed paternal military service as a risk factor for childhood leukemia. We found no evidence of a relation between general paternal military service and the risk for leukemia among offspring. However, we did find a significantly elevated risk for AML among offspring of veterans who served in Vietnam or Cambodia, with the elevated risk confined to the small subgroup of cases with AML diagnosed before the age of 2 years.

Childhood AML and ALL have very distinct geographic distributions. AML is more common among children in Asia and developing countries, while ALL predominates in Western countries (24, 25). AML and ALL also differ biologically, suggesting that the two diseases may have distinct etiologies. In general, there appears to be more evidence for environmental risk factors in childhood AML than in childhood ALL. Early epidemiologic studies indicated that paternal exposure to cigarette smoking and marijuana, occupational exposure to solvents, metals, and pesticides, and maternal alcohol consumption during pregnancy might be associated with the risk for childhood AML (15, 19, 26). Accordingly, we felt it necessary to stratify our analysis by diagnostic categories of ALL and AML.

Military service in Vietnam or Cambodia is potentially related to a number of known or suspected carcinogens, such as cigarette and marijuana smoking and herbicide exposure (1). Over the last two decades, many studies have investigated the health effects of military experience in Vietnam or Cambodia. Significant excess risks for death and for cancers, including lymphomas, have been reported among Vietnam veterans, as has a significant risk for birth defects among their offspring (7, 9, 10, 14, 27, 28). Some studies have found exposure to Agent Orange to be associated with health consequences (5, 6), while others have failed to find any positive association (8, 29). In a recent investigation by Wolfe et al. (29), no effect of paternal exposure to Agent Orange and its dioxin contaminant was found relative to adverse reproductive outcomes after service in Southeast Asia. One study reported a nonstatistically significant elevated risk for childhood leukemia among offspring of Vietnam veterans (OR = 1.6; 95 percent CI: 0.6, 4.1) (14). In our study, we found that paternal military experience in Vietnam or Cambodia was related to a small increased risk for AML. The increased risk, however, could not be completely accounted for by self-reported paternal exposure to herbicides in the Vietnam War, including Agent Orange and other unspecified herbicides.

Cigarette smoking, alcohol consumption, and marijuana use have been reported to be more prevalent among military personnel than among the general population (1, 2). Although previous publications addressing paternal cigarette smoking and the risk for childhood leukemia are inconsistent (18, 26, 30), two recent studies found that the number of years and the amount of paternal cigarette smoking prior to conception were related to a significantly elevated risk for childhood leukemia after adjusting for the effect of maternal smoking (31, 32). We adjusted for paternal cigarette smoking status prior to pregnancy in our analysis. However, we could not adjust for the duration or the amount of paternal preconception cigarette smoking because these data were not collected. Therefore, a residual confounding effect of smoking may still exist. Several case-control studies have found a positive association between parents' marijuana use during pregnancy and the subsequent increased risk for childhood AML (33), astrocytoma (34), and rhabdomyosarcoma (35). Although we adjusted for paternal marijuana smoking status in our analyses, a residual confounding effect similar to that of cigarette smoking could remain. The consistency of the excess of childhood AML in Asian countries and the association between paternal military experience in Vietnam or Cambodia and risk for childhood AML observed in this study, particularly in children before the age of 2 years, are intriguing. Exposure to environmental factors that were more prevalent in Asia but not war related, such as some infectious diseases, could also provide a possible explanation for the observed excess risk for AML in the offspring of Vietnam veterans. Information related to such exposures, however, was not collected in our study, thus precluding a more detailed evaluation.

In the interpretation of results from this interview-based study, a general concern relates to the error in measurement of exposure and selection bias due to nonresponse, given the fact that the response rates in cases were higher that those in controls in this study. Since the Vietnam War was a significant event for most Americans, particularly for the families of Vietnam veterans, self-reported information regarding military service in Vietnam or Cambodia is considered to be quite reliable (36). Moreover, in our study, both the overall null association of childhood leukemia with paternal general military service and the absence of an association between service in Vietnam or Cambodia and risk for ALL (in contrast to the significant association between military service in Vietnam or Cambodia and childhood AML) argue against selection bias as an explanation of the findings. However, we found inconsistent results for the number of tours of duty versus the number of years spent in Vietnam or Cambodia. This apparent internal inconsistency suggests that the observed association may be due to unrecognized confounders or to random error. It is also possible that AML risk may be linked to exposures related to the frequency of moving into and out of Vietnam or Cambodia rather than to the duration of stay there. Alternatively, the increased risk might be related to paternal exposure while staying in other Southeast Asian countries, such as Laos or Thailand, during the Vietnam War. We could not evaluate this possibility, however, since we only collected information on military service in Vietnam or Cambodia but not in other Southeast Asian countries. Another unexplainable observation is that the risk for AML increased with the interval between the end of military service in Vietnam or Cambodia and the index pregnancy. Although random error might have again played a role, such a pattern might suggest an effect of some unmeasured post-war exposures.

We carefully examined parental cigarette smoking, alcohol consumption, pre- and postnatal X-ray exposure, family history of cancer, and a number of other risk factors for nine AML cases and five controls under the age of 2 years whose fathers served in Vietnam or Cambodia. None of the factors examined appeared to be particularly more prevalent among AML cases than among controls. The fathers of these nine AML cases served in four different branches of the armed forces (four in the Army, three in the Marines, one in the Navy, and one in the Air Force). Four of the five control fathers were in the Army and one was in the Marines. No information on military occupation or specialties was collected. Four of these nine AML cases were M4/M5 subtypes; the other five were other subtypes. We found that two of these nine AML cases had Down's syndrome, a genetic syndrome with a well-recognized connection to childhood AML. After the exclusion of these two subjects and their controls from the analysis, the risk for AML before the age of 2 remained elevated (OR = 4.15; 95 percent CI: 1.12, 15.36). We also adjusted for maternal drinking and smoking status in this analysis. No significant change in the estimation of AML risk was found. It should be pointed out, however, that due to the low exposure rate and the small number of Vietnam veterans, the risk estimates become unstable and the statistical power of this study for detecting a moderate risk is limited.

In summary, we found that while paternal military service in general was not related to risk for childhood leukemia, paternal military service in Vietnam or Cambodia was associated with a significantly increased risk for AML in children under the age of 2 years. Currently, there is considerable speculation regarding the role of paternal preconception exposures in childhood leukemia. If the association we found is confirmed by other studies, it would lend support to the hypothesis that paternal preconception environmental exposures are implicated in the etiology of childhood AML. The association found in our study, even if confirmed, however, would account for only a small proportion of AML in this age group (population attributable risk = 6.9 percent), because of the very low rate of exposure.

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