Is Family History of Breast Cancer a Marker of Susceptibility to Exposures in the Incidence of *de Novo* Adult Acute Leukemia?[1]

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Abstract

The risk factors for adult acute leukemia incidence have been difficult to establish. Family history of cancer might interact with environmental exposures to produce associations that are otherwise difficult to detect. In addition to family history of leukemia or other hematopoietic cancers, family history of breast cancer could be a marker of susceptibility, because leukemia and breast cancer are known to cluster in families that have specific germ-line mutations. In a population-based case control study of 779 incident adult acute leukemia patients and 625 controls, we estimated the relative risk for exposed individuals with a family history compared with unexposed individuals without a family history (RR_{11}), along with a measure of interdependence, the interaction contrast ratio. Combined with a family history of breast cancer, ever-smoking [RR_{11} = 2.4, 95% confidence interval (CI): 1.2–4.8], general solvent exposure (RR_{11} = 1.9, 95% CI: 1.1–3.4), aromatic hydrocarbon exposure (RR_{11} = 3.8, 95% CI: 1.1–14), and diagnostic ionizing radiation exposure (RR_{11} = 2.1, 95% CI: 1.2–3.8) were all associated with increased incidence. Furthermore, there was no increased incidence associated with any of these exposures in the absence of a family history of breast cancer and no increased incidence for family history of breast cancer in the absence of exposures. The pattern of relative risks strongly suggested synergy across exposures. Family history of breast cancer might be a marker of susceptibility to a range of leukemia risk factors, whose effects are generally weak or nonexistent when considered alone.

Introduction

There are ~11,000 diagnoses of adult acute leukemia each year in the United States[3] (1). The risk factors for adult acute leukemia have been difficult to establish, in part because it has been difficult to collect large, representative patient and control samples for epidemiological study and also because high case fatality complicates the collection of reliable exposure information from patients. Nonetheless, adult acute leukemia incidence has been shown to be elevated among occupational cohorts highly exposed to the aromatic hydrocarbon benzene, as well as among cohorts of atomic bomb survivors and other cohorts exposed to ionizing radiation (2–13).

These exposures do not always appear to increase risk in more common settings where exposures tend to be lower, *e.g.*, two studies of diagnostic radiation exposure found no association with leukemia incidence (14, 15). Cigarette smoke, which contains many carcinogens, including both benzene and ionizing radiation, is only weakly associated with leukemia risk (16–19).

Associations for these and other exposures might be detectable if considered in combination with a marker of genetic susceptibility, and family history of cancer might be such a marker. Breast cancer and leukemia are known to cluster together in certain family cancer syndromes (20–23), and we reported previously positive associations between family history of breast cancer and leukemia incidence in a large case control study of acute leukemia in adults (19, 24). Here, in these same data, we examined whether family history of cancer at any site, and breast cancer specifically, modified the effects of smoking, solvents, and ionizing radiation on adult acute leukemia incidence.

Materials and Methods

Patient and Control Recruitment. Patient and control recruitment and data collection procedures have been described in detail elsewhere (19). Briefly, incident cases of adult acute leukemia were recruited at the time of diagnosis through CALGB,[4] a multi-institutional cooperative cancer treatment group located throughout the United States and Canada. Approval for the study was obtained from the institutional review board at the National Institute for Environmental Health Sciences. Initial patient contact was approved by the institutional

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[4] The abbreviations used are: CALGB, cancer and leukemia group B; CI, confidence interval; ICR, interaction contrast ratio; RR, relative risk.

review board at each participating medical facility, and written informed consent was obtained from each subject. Because of requirements for ongoing CALGB clinical trials, patients were in effect excluded from the case control study (CALGB protocol 8661) if their disease was known to be secondary to chemotherapy or radiotherapy or the result of a preleukemic condition, such as myelodysplasia. From January 1986 through June 1989, 811 adult acute leukemia patients were enrolled (84% total response).

Hospitalized patients were contacted by telephone within a few days of diagnosis and either completed the interview at that time, or a later time was arranged. Next of kin participated in 34% of case interviews. The median interval between registration and completion of the interview was 8 days for self-interviewed patients and 37 days for proxy-interviewed patients.

Control subjects were selected using a two-stage random digit dialing procedure (25) with the sampling frame restricted to the area code and first three digits of the patients' telephone numbers. Controls were frequency matched to cases with respect to age (10-year intervals), sex, race (Caucasian *versus* other), and region of residence (one of six regions in the United States and Canada). Screening was completed for 792 potential controls (83%) with residential telephone numbers. Of those screened and eligible, 637 (80%) completed interviews for an overall response rate of 66%. Proxy interviews were conducted for 83 (13%) of the controls. In analyses, 779 cases and 625 controls had complete data on the study-matching factors and family history of cancer.

Family History of Cancer. Cases and controls (or their proxies) were asked to report separately for their mother, father, each sibling, and each child any history of: (*a*) aplastic anemia; (*b*) leukemia; (*c*) any other "cancer, tumor, or growth, such as lymphoma or lung cancer" and the specific sites involved; (*d*) any other blood disorder; (*e*) vital status; and (*f*) the cause of death, if deceased. Responses were written as text and later coded by site, using the International Classification of Diseases, Ninth Revision (26). Hematopoietic cancers were defined as those with International Classification of Diseases, Ninth Revision codes from 200 to 208 (first three digits), and responses such as "blood cancer" and "bone marrow cancer" were coded as leukemia, although these could potentially refer to circulating lymphoma and multiple myeloma, respectively. For 6045 case and 4774 control relatives, 260 case (4%) and 147 control relatives (3%) were missing data on cancer history. Family size was unrelated to case control status.

Smoking. An individual was defined as an ever-smoker if he or she reported smoking cigarettes for ≥6 months during his or her lifetime. Any individual who reported having started smoking within a year of their interview was defined as a never-smoker, to allow for a lag between exposure and disease onset and exclude disease onset as a cause of smoking. We created a cumulative exposure index (pack-years) based on the reported number of years of smoking and average number of cigarettes per day. We did not distinguish between current and former smokers, because we did not anticipate distinct joint effects for these two categories of smoking, especially one that could be resolved given sample size limitations.

Solvents. Individuals were asked separately about exposure to specific classes of chemicals ("Did you ever work with any of the following solvents approximately five or more times?"), products containing chemicals ("Did you use or work with any of the following products approximately five or more times?"), and items that are usually cleaned with solvents ("Did you use solvents or other chemicals approximately five or more times to clean. . . ?"). For each exposure reported from these lists, respondents were asked whether the exposure took place at work (occupational), at home (residential), or both; the brand name of the product used (as a check of validity); and if use had taken place only in the last 2 years. Exposure only in the previous 2 years was ignored to allow for lag time between exposure and leukemia onset.

We created separate categories for residential (but not occupational) exposure and occupational (regardless of residential) exposure, with the thought that individuals exposed only at home might tend to have lower exposures than those exposed at work. Solvents included all petroleum distillates, halogenated solvents, alcohols, ketones, aldehydes, and degreasers. We created a distinct variable for exposure to aromatic hydrocarbons, which included benzene, xylene, toluene, naphthalene, and any other member of this class of solvents.

Diagnostic Medical Radiation Visits. Using a list, individuals were asked if they had ever obtained diagnostic procedures involving exposure to ionizing radiation (X-rays to diagnose broken bones, chest X-rays, barium series, etc.). They were asked "how many times altogether" they had each exam listed. We identified exams associated with relatively higher exposures of ionizing radiation to the bone marrow (27, 28). These included any gastrointestinal or gallbladder series; bone, brain, liver, or other abdominal scans; kidney X-rays; or i.v. pyelograms, myelograms, and thoracic or lumbar X-rays. We summed the number of higher exposure exams for each individual, and we dichotomized the summed variable at zero *versus* one or more higher exposure exams. In separate analyses, we excluded exams within 2 and 5 years of diagnosis to allow for different lag times for exposure effects (data not shown).

Estimating Combined Effects and Interdependence. We examined the combined effects of each family history and exposure variable by estimating a RR11, comparing individuals defined as positive for both family history and exposure ("doubly exposed") to individuals defined as negative for both ("doubly unexposed"). An elevated RR11 suggested that individuals with both family history and exposure were at increased risk of leukemia, but it was not a measure of interdependence (*e.g.*, synergy). To examine if there was departure from additivity in the combined effects of family history and exposure, we constructed a measure known as the ICR, also known as the relative excess risk attributable to interaction (29–31).

In cohort studies, interdependence can be examined by comparing separate exposure rate differences for those with and without a family history of cancer. In case control studies, we can estimate only relative rates; therefore, interdependence must be examined by combining relative rates (estimated as odds ratios) in a meaningful way. The ICR is such a measure of interdependence; it estimates the difference in exposure rate differences divided by the rate in the doubly unexposed stratum. In case control studies, the ICR can be calculated as the excess relative odds in those with both family history and exposure (RR11–1) that remains after subtracting both excess relative odds for the separate effects of family history (RR10–1) and exposure (RR01–1), *e.g.*, if RR11 were equal to 2 but there was no increased incidence in either singly exposed stratum (RR01 = RR10 = 1), then the ICR would equal 1. The null value of the ICR is 0, with positive values suggesting synergy between exposure and family history. In the present study, however, only values approaching 1 were considered of sufficient size to suggest meaningful synergy.

Table 1 Distribution of exposures in adult acute leukemia cases and controls

Exposure	Cases		Controls		RR[b]	95% CI
	n[a]	(%)	n	(%)		
Ever-smoking						
No	322	41[c]	283	45	1.0	
Yes	453	58	341	55	1.2	(1.0–1.5)
Missing	4	1	1	0		
Solvent exposure						
Never	226	29	200	32	1.0	
Residential (only)	246	32	196	31	1.1	(0.8–1.5)
Occupational	296	38	225	36	1.2	(0.9–1.6)
Missing	11	1	4	1		
Aromatic hydrocarbons						
Never	630	81	526	84	1.0	
Residential (only)	57	7	52	8	0.9	(0.6–1.4)
Occupational	81	10	43	7	1.6	(1.1–2.4)
Missing	11	1	4	1		
# High radiation exams						
0	378	49	333	53	1.0	
1–2	208	27	158	25	1.2	(0.9–1.6)
3+	186	24	130	21	1.3	(1.0–1.7)
Missing	7	1	4	1		

[a] Number of cases or controls in each stratum of exposure.
[b] Adjusted for study-matching factors and estimated from odds ratios in logistic regression.
[c] Percentages do not always add exactly to 100 because of rounding.

Analyses. First, we estimated the independent effect of each exposure and family history variable on leukemia incidence, as a relative rate. Next, we modeled the joint distribution of each binary family history and binary exposure variable in logistic regression (adjusted for the study-matching factors) to estimate RR_{01}, RR_{10}, and RR_{11}. These relative rate estimates and their variance covariance matrix were then used to calculate values for ICR, along with their CIs (31, 32).

For each exposure, we estimated relative rates and ICR with family history of cancer at any site. Then, we estimated relative rates and ICR for exposures with family history breast cancer and exposures with sibling breast cancer. Finally, for family history of any cancer and family history of breast cancer, we estimated RR_{11} and ICR for each exposure separately for patients and patient proxies.

We repeated these analyses separately for both family history of leukemia and hematopoietic cancers. Data were sparse and potentially subject to both recall bias and misclassification of specific hematopoietic cancers. Therefore, these associations were not explored in detail.

Because exposures examined were not strongly associated with incidence, they were not likely to be confounders and not adjusted for in the analyses presented. In additional analyses of the combined effects of exposures with family history of any cancer and family history of breast cancer, adjusting for cumulative smoke exposure and all other exposures examined did not materially change estimates of RR_{11} and ICR (data not shown).

Results

Both cases and controls had a median age at diagnosis of 47 years (range 18–80 years); 58% of cases and 59% of controls were men. Approximately three-fourths of leukemia cases were myeloid (myeloblastic, promyelocytic, or monocytic) subtypes, and the remaining cases were a combination of lymphoblastic subtypes, mixed lineage, or other acute leukemia.

Smoking. As reported previously (19), smoking status was only weakly associated with leukemia incidence (Table 1). For older individuals (age 60+), the relative rate for ever-smoking was 2.0 (95% CI: 1.3–3), whereas in younger individuals, it was 1.0 (95% CI: 0.7–1.3).

Ever-smokers with a first-degree family history of any cancer had a 40% increased incidence compared with never-smokers without a family history ($RR_{11} = 1.4$), but there was no evidence of interdependence (ICR = −0.1, 95% CI: −0.6 to 0.4; Table 2). In combination with a family history of breast cancer, however, ever-smokers had 2.4 times the incidence compared with never-smokers without a family history (Table 2). Neither relative rate in singly exposed individuals was elevated; therefore, the estimated ICR was exactly equal to the excess relative rate in the doubly exposed (ICR = 1.4, 95% CI: −0.3, 3). In combination with a sibling history of breast cancer, ever-smokers had 3.7 times the incidence compared with never-smokers without a sibling history (Table 2).

Solvents. Residential and occupational solvent exposures were both unassociated with incidence of adult acute leukemia (Table 1). In combination with a first-degree family history of any cancer, residential and occupational solvent exposure were both associated with a modestly increased incidence when compared with unexposed individuals without a family history of cancer (Table 2). In combination with a family history of breast cancer, however, solvent-exposed individuals had a 2-fold increased incidence, and solvent-exposed individuals with a sibling breast cancer history had a ~4-fold increased incidence (Table 2). Corresponding ICR values were 1 and 2.7.

Aromatic Hydrocarbons. Occupational but not residential exposure to aromatic hydrocarbons was associated with increased incidence of adult acute leukemia (Table 1). Occupationally exposed individuals with a first-degree family history of any cancer had a 3-fold increased incidence compared with unexposed individuals without a family history, resulting in an ICR of 2 (Table 2). Combined with a family history of breast cancer, any aromatic hydrocarbon exposure (residential or occupational) was associated with a ~4-fold (although imprecise) increased incidence.

Diagnostic Radiation Exams. Higher exposure exams were weakly associated with increased incidence of adult acute leukemia (Table 1). There was no evidence of interdependence in combination with a first-degree family history of any cancer (Table 2). Combined with a family history of breast cancer, however, exposure was associated with a 2-fold increased incidence, and combined with a sibling breast cancer history, exposure was associated with a 6-fold increased incidence (Table 2). Introducing different lag times for the effect of exposure on incidence (2 and 5 years, respectively) did not materially change any of these results.

Patient *versus* Patient-proxy Reporting. Interdependence with family history of any cancer was evident only for occupational aromatic hydrocarbon exposure and both patients and patient proxies (Table 3). Interdependence with family history of breast cancer was evident across all exposures and in both patients and patient proxies (Table 3).

Family History of Leukemia and Hematopoietic Cancer. Although data were sparse, interdependence with family history of leukemia was suggested across all exposures, with RR_{11} estimates ranging from 1.6 to 3.4 and ICR estimates ranging from 0.6 to 2.1 (data not shown). Interdependence with family history of any hematopoietic cancer was suggested only in combination with aromatic hydrocarbon exposure ($RR_{11} = 2.4$, 95% CI 0.7–7.5 and ICR = 1.3).

Table 2 Interdependence between exposures and family histories of cancer on leukemia incidence

First-degree family history	Exposure	Case[a]	Control	RR[b]	95% CI	ICR	95% CI
			Smoking status				
Any site	Smoking						
No	Never	212	201	1.0			
No	Ever	255	202	1.2	(0.9, 1.6)		
Yes	Never	110	82	1.3	(0.9, 1.9)		
Yes	Ever	198	139	1.4	(1.0, 2.0)	−0.1	(−0.6, 0.4)
Breast	Smoking						
No	Never	301	263	1.0			
No	Ever	420	329	1.1	(0.9, 1.4)		
Yes	Never	21	20	0.9	(0.5, 1.8)		
Yes	Ever	33	12	2.4	(1.2, 4.8)	1.4	(−0.3, 3.0)
Sibling breast	Smoking						
No	Never	227	213	1.0			
No	Ever	313	252	1.2	(0.9, 1.6)		
Yes	Never	8	4	1.8	(0.5, 6.2)		
Yes	Ever	15	4	3.7	(1.2, 11)	1.7	(−2.4, 5.8)
			Solvent exposure				
Any site	Solvents						
No	Never	155	133	1.0			
No	Residential	125	120	0.9	(0.6, 1.3)		
No	Occupational	183	148	1.1	(0.8, 1.5)		
Yes	Never	71	67	0.9	(0.6, 1.4)		
Yes	Residential	121	76	1.4	(0.9, 2.1)	0.6	(0.0, 1.1)
Yes	Occupational	113	77	1.3	(0.9, 2.0)	0.3	(−0.3, 0.9)
Breast	Solvents						
No	Never	214	187	1.0			
No	Ever	501	402	1.1	(0.8, 1.4)		
Yes	Never	12	13	0.8	(0.3, 1.8)		
Yes	Ever	41	19	1.9	(1.1, 3.4)	1.0	(0.0, 2.1)
Sibling breast	Solvents						
No	Never	167	144	1.0			
No	Ever	369	320	1.0	(0.7, 1.3)		
Yes	Never	5	4	1.0	(0.3, 3.9)		
Yes	Ever	17	4	3.7	(1.2, 11)	2.7	(−1.4, 6.9)
			Aromatic hydrocarbon exposure				
Any site	Aromatics						
No	Never	383	337	1.0			
No	Residential	36	31	1.0	(0.6, 1.7)		
No	Occupational	44	33	1.2	(0.7, 1.9)		
Yes	Never	247	189	1.2	(0.9, 1.5)		
Yes	Residential	21	21	0.9	(0.5, 1.7)	−0.3	(−1.1, 0.5)
Yes	Occupational	37	10	3.4	(1.6, 7.0)	2.0	(−0.4, 4.5)
Breast	Aromatics						
No	Never	590	497	1.0			
No	Ever	125	92	1.2	(0.9, 1.6)		
Yes	Never	40	29	1.2	(0.7, 1.9)		
Yes	Ever	13	3	3.8	(1.1, 14)	2.5	(−2.3, 7.4)
Sibling breast	Aromatics						
No	Never	449	394	1.0			
No	Ever	87	70	1.1	(0.8, 1.6)		
Yes	Never	16	8	1.7	(0.7, 4.1)		
Yes	Ever	6	0	+++		+++	
			High exposure diagnostic radiation exams				
Any site	No. exams[c]						
No	0	259	243	1.0			
No	1+	208	161	1.3	(1.0, 1.7)		
Yes	0	120	92	1.3	(0.9, 1.8)		
Yes	1+	188	129	1.5	(1.1, 2.0)	−0.1	(−0.6, 0.4)
Breast	No. exams						
No	0	364	320	1.0			
No	1+	356	273	1.2	(0.9, 1.5)		
Yes	0	15	15	0.9	(0.4, 1.9)		
Yes	1+	40	17	2.1	(1.2, 3.9)	1.1	(−0.2, 2.3)
Sibling breast	No. exams						
No	0	275	253	1.0			
No	1+	264	211	1.2	(0.9, 1.5)		
Yes	0	4	5	0.7	(0.2, 2.8)		
Yes	1+	19	3	5.9	(1.7, 20)	5.0	(−2.2, 12)

[a] Number of cases and controls with family history and exposure data.
[b] All estimates are adjusted for study-matching factors in logistic regression.

Table 3 Interdependence between family histories and exposures, estimated separately in patients and patient-proxies

	Patients				Patient-proxies			
	N_{11}[a]	RR_{11}	95% CI	ICR	N_{11}	RR_{11}	95% CI	ICR
Family history of any cancer								
Ever-smoker	110/139	1.1	(0.8, 1.6)	−0.2	88/139	2.2	(1.4, 3.5)	0.1
Occupational solvents	70/77	1.3	(0.8, 2.1)	0.3	43/77	1.3	(0.7, 2.2)	0.2
Occupational aromatics	24/10	3.4	(1.6, 7.4)	1.9	13/10	3.6	(1.5, 8.6)	2.5
Higher-exposure exams	108/129	1.2	(0.9, 1.7)	−0.1	80/129	2.1	(1.3, 3.3)	−0.2
Family history of breast cancer								
Ever-smoker	19/12	2.1	(1.0, 4.4)	1.3	14/12	3.2	(1.4, 7.4)	1.7
Any solvents	25/19	2.0	(1.0, 3.9)	1.1	16/19	1.8	(0.8, 3.7)	1.0
Any aromatics	9/3	4.0	(1.1, 15)	2.6	4/3	3.5	(0.8, 17)	2.5
Higher exposure exams	22/17	1.8	(0.9, 3.4)	0.8	18/17	2.6	(1.3, 5.4)	1.5

[a] Number of cases and controls with both family history and exposure. All estimates are adjusted for study-matching factors in logistic regression.

Discussion

This analysis was undertaken to determine whether family history of cancer, as a marker of genetic susceptibility, might be used to detect exposure effects on adult acute leukemia incidence that might otherwise remain hidden. We found evidence of synergistic effects between exposures and first-degree family histories of breast cancer. All exposures examined, even those with little or no independent effect, were associated with at least a doubling in incidence in the presence of a family history of breast cancer, with no apparent increased incidence in the presence of either the exposure or family history alone. These results tended to be based on small numbers of individuals with both exposure and family history. The patterns of RRs, however, were strongly suggestive of synergy for all exposures, and the resulting ICR values were estimated to be >1.

Larger (although less stable) estimates of interdependence were found in combination with a sibling breast cancer history. We did not have information on the age of onset for cancer in relatives. However, at the time of the patient interview, we might reasonably assume that siblings were (on average) younger than parents, and sibling cancers were likely to have occurred (on average) at a younger age than parental cancers. Therefore, the larger effects associated with sibling breast cancer suggest the possibility that susceptibility was driven by early onset familial breast cancer.

Family history of cancer at any site may be too nonspecific a measure to aid in detecting environmental risk factors at lower exposure levels. Although those cancer sites associated with leukemia incidence might contribute to a marker of leukemia susceptibility, other positive family histories unassociated with leukemia incidence would only add noise to the measure. This may explain why family history of cancer at any site interacted only with occupational aromatic hydrocarbons, the only exposure strong enough to have a noticeable independent effect on leukemia incidence.

Although there was a suggestion of interdependence for family history of leukemia across all exposures, the number of individuals with a family history of leukemia was small, and both recall bias and confusion between leukemia and other hematopoietic cancers, or blood conditions were likely. Family history of hematopoietic cancer, in turn, is likely to be confused with other blood disorders.

Breast cancer and leukemia have been linked within families that have rare germ-line mutations in either the *p53* gene (Li-Fraumeni Syndrome) or ataxia telangiectasia gene (20–23). Although these two family cancer syndromes are very rare, other less penetrant but more prevalent defects in these same genes could also exist and account for some of the apparent specificity in joint effects between family history of breast cancer and exposures in leukemia incidence.

Proxies were involved in about one-third of patient interviews, and it is likely that they reported exposures and family histories differently than patients (32–38). Positive interactions, however, were apparent regardless of patient interview type and across the full range of exposures examined, suggesting that reporting differences did not explain these results. Furthermore, correlations and κ statistics across exposures were low (<0.2); therefore, the similarity of effects across exposures was not attributable to high correlation across exposures.

It is generally believed that benzene and related solvents are associated with acute leukemia primarily through their role in causing preleukemic conditions, such as myelodysplasia, which often lead to diagnoses of acute leukemia. In the present study, however, secondary leukemia was a reason for exclusion, and associations of exposures and family histories of cancer were with respect to *de novo* leukemia. Results from these analyses suggest that benzene and related aromatic hydrocarbons are a cause not only of secondary leukemia but of *de novo* acute leukemia as well.

In conclusion, family history of breast cancer may be a marker of susceptibility to a range of leukemia risk factors, whose effects are generally weak or nonexistent when considered alone. These synergistic effects (if real) could be attributable to genetic susceptibilities common to both cancers and represent more prevalent allele-exposure interactions.

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