

A CASE-CONTROL INQUIRY INTO THE ETIOLOGY OF HAIRY CELL LEUKEMIA

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Oleske, D. (Hematology/Oncology Section, U. of Chicago, Chicago, IL 60637). H. M. Golomb, M. D. Farber, and P. S. Levy. A case-control inquiry into the etiology of hairy cell leukemia. *Am J Epidemiol* 1985;121:675-83.

A case-control study was conducted to investigate the etiology of hairy cell leukemia. Forty-five individuals with histologically confirmed hairy cell leukemia comprised the cases. Three neighborhood controls were selected on the basis of age (± 5 years), race, sex, and residence at the time of the interview for each case. There was no association found for cigarette smoking, alcohol or coffee consumption and hairy cell leukemia. With respect to occupational risk factors, employment in woodworking or in farming was of borderline significance. Reported exposure to chemicals in the workplace was significantly greater among both sexes of the cases than among their respective matched controls (relative risk (RR) = 3.10). Other variables found to be significantly associated with hairy cell leukemia were farm birthplace (RR = 4.20), anemia (RR = 4.29), migraine (RR = 4.80), infectious mononucleosis (RR = 9.00), and routine use of aspirin (RR = 3.41) or tranquilizers (RR = 4.50). No association between radiation and hairy cell leukemia was detected.

hematologic diseases; leukemia; leukemia, hairy cell

Over the past three decades, only small strides have been made in unraveling the causal pathway of leukemia. In reviewing the extensive literature on the epidemiology of this disease, Szklo (1) states that one of the main reasons for the slow progress

in understanding the etiology of leukemia is that most studies fail to examine risk in terms of exact cell type. Indeed, when leukemia risk factors are examined by histologic type, clearer and more precise relationships have been noted (2). Thus, epidemiologic studies of leukemia would be strengthened by further investigation of its subtypes.

One histologic type for which there is little epidemiologic information is hairy cell leukemia, a rare and, typically, chronic form of leukemia. Despite the fact that it was fully described in the late 1950s, few risk factors for it are known (3). The only report of the relative frequency of the disease is by Bouroncle (4), who estimated that hairy cell leukemia comprises 2 per cent of all leukemias seen, based on the experience of a single hospital. The literature cites the age range of patients to be from the early twenties to the eighties. The

Received for publication July 6, 1984, and in final form September 11, 1984.

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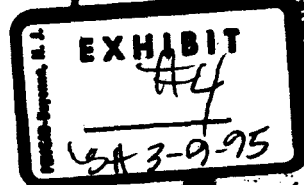
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This study was completed as part of the requirements for the Doctor of Philosophy degree, University of Illinois, School of Public Health (D. O.).

This investigation was supported in part by developmental funds from the National Cancer Institute, DHHS (CA 20071), awarded through the Illinois Cancer

The authors wish to acknowledge the assistance of Andrew Kubilius, Levis Segal, and Mary Shepherd in the programming of the data for analysis.



percentage of females in case series has been observed to range from 18 per cent to 38 per cent (5-7).

With respect to the etiology of hairy cell leukemia, only two suspect factors were discerned from a review of the literature: ionizing radiation and heritability. In a study of a cohort of individuals exposed to an atmospheric nuclear test, hairy cell leukemia was one of six histologic types of leukemia found to occur (8). Although the number of cases was greater than that expected (with all histologic types combined), only 60 per cent of the original cohort had been located at the time of publication. Stewart and Keating (9) found a higher frequency of radiation exposure among cases with hairy cell leukemia than among a control group comprised of individuals with solid tumors.

Two case reports comprise the evidence for suggesting some heritable component in the development of hairy cell leukemia. Cohen et al. (10) report the identification of hairy cell leukemia in association with a family "cluster" of lymphoproliferative disorders. In 1981, Ramseur et al. (11) published a report of a father and son who were diagnosed with hairy cell leukemia. Several aspects of the clinical history of these two individuals implicate a familial tendency.

Despite the limited amount of epidemiologic information on this disease entity, it appears from a review of the literature that hairy cell leukemia could share some risk factor characteristics common to other forms of leukemia. In an attempt to understand more about hairy cell leukemia, the strategy of this investigation was to determine which (if any) known risk factors associated with the other forms of leukemia were also associated with hairy cell leukemia. From a review of the literature, the major risk factors for the various types of leukemia, including those suggested for hairy cell leukemia, were identified. These factors served to guide in the formulation of this study. This investigation was made feasible by the existence of a hairy cell

leukemia registry which contained most of the cases in our target area.

MATERIALS AND METHODS

Cases were obtained from the Hairy Cell Tumor Registry and Treatment Center at the University of Chicago, a unique regional resource. Individuals with hairy cell leukemia come to the center's attention from physicians seeking consultation to confirm the diagnosis or for assistance with treatment and follow-up. The majority of these cases are referred from hematologists throughout Illinois.

The diagnosis of hairy cell leukemia is based upon clinical and laboratory parameters. The most common initial clinical sign is splenomegaly, frequently massive, in as many as 93 per cent of the cases reported. Lymphadenopathy and/or hepatomegaly is uncommon in this neoplasm. The onset of the disease is insidious, usually first identified as a nonspecific complaint of fatigue or weakness, with pancytopenia present in two thirds of patients (12). The diagnosis can be made from the peripheral blood, spleen, liver, bone marrow, or involved lymph node, because there are no differences in the morphologic features of the hairy cell at these sites. However, a bone core biopsy is the diagnostic procedure of choice (12). The finely diffuse network of hairy cell growth in the bone marrow is characteristic of this disease (13). In addition, pseudosinuses distended with erythrocytes in the spleen and hepatic angiomatous lesions are pathognomonic features of hairy cell leukemia (14).

Cases for this study consisted of those individuals histologically confirmed with hairy cell leukemia at the University of Chicago between January 1, 1975 and July 31, 1981. In addition, cases were limited to those who were residents of Illinois or northern Indiana, because it was determined that the majority of registry cases were referred from these areas. In an effort to identify all cases of hairy cell leukemia in the region diagnosed during this period.

an informational packet on hairy cell leukemia was developed and mailed to a total of 1,100 hematologists, pathologists, and medical oncologists in Illinois and to those located in adjacent parts of Wisconsin, Iowa, Missouri, Indiana, and Michigan. Through this mechanism, 10 additional cases were located, confirmed as having hairy cell leukemia, and added to the registry.

There were a total of 53 cases who met the eligibility criteria regarding date of diagnosis and residence at time of diagnosis. The residence distribution of these cases at the time of their diagnosis reflected the population distribution of the area. Six cases were dropped from the study because no relative could be located to respond on behalf of the case (two cases who were mentally incompetent and four deceased cases); two refused to be interviewed (one living case and a spouse of a deceased case). The remaining 45 persons comprised the study cases. Of those participating, 36 were individuals with hairy cell leukemia and nine were proxies for the cases. Proxies were either a spouse or an offspring, whoever was felt to be the most reliable respondent. The high percentage of cases reporting for themselves (80 per cent) reflects the high survival rates found among

cases receiving appropriate initial therapy (5) (table 1).

Three controls were selected on the basis of age (± 5 years), sex, and race for each case. Neighborhood controls were used in an attempt to compensate for any biases possibly operating in the referral of the cases. Controls were selected from lists constructed from city directories, produced locally (homeowner's associations, chambers of commerce), or from field listing (for rural areas). The starting point for attempting to identify eligible controls was the entry on the list representing an address consecutive to the index cases for which matched controls were sought. A phone call was made to individuals on the lists for the purpose of identifying eligible respondents. At the time of the phone call, a screening interview was conducted with any identifiable adult who answered. Individuals not at home were retelephoned up to two more times at hours and days different from the initial attempt, before the next entry was selected from the list. Of the total pool of controls found to be eligible for the study by the telephone screening interview, 18.6 per cent refused to participate in the personal interviews. An average of 14 screening phone contacts were made to obtain one eligible control who consented to participate in a personal interview.

A 196-item structured questionnaire was administered to cases and controls. In the questionnaire, the period of inquiry for exposure factors of the cases began one year before the diagnosis of hairy cell leukemia and went back in time. All variables considered lifetime exposure, with the exception of drug usage and exposure to diagnostic radiation procedures which only covered the 10-year period beginning one calendar year before the diagnosis of hairy cell leukemia. To have the cases and controls comparable with respect to any recall biases concerning drug usage or diagnostic x-ray exposure, the interviewers were given written instructions to cover the same 10-year interval for the matched controls as was

TABLE 1
Distribution of eligible cases at the Hairy Cell Tumor Registry, January 1, 1975-July 31, 1981

Cases	No.	%
Alive		
Participated in interview	36	90.0
Mentally incompetent/no next of kin available	2	5.0
Mentally incompetent/spouse interviewed	1	2.5
Refused interview	1	2.5
	40	100.0
Relative participated in interview	8	61.5
Not able to locate next of kin	4	30.8
Relative refused interview	4	7.7
	13	100.0
Total eligible cases	53	100.0

TABLE 2

Demographic characteristics among hairy cell leukemia cases and controls, 1975-1981

Characteristic	Cases (n = 45)		Controls (n = 134)	
	No.	%	No.	%
Race/sex				
White males	33	73.3	98	73.1
White females	10	22.2	30	22.4
Nonwhite males	2	4.5	6	4.5
Nonwhite females	0	0.0	0	0.0
Marital status				
Mamed	40	88.9	118	88.1
Unmamed	5	11.1	16	11.9
Religion				
Catholic	16	35.6	52	38.8
Jewish	4	8.9	4	3.0
Protestant	22	48.9	66	49.3
Other	1	2.2	3	2.2
None	2	4.4	9	6.7
Income				
≤\$9,999	9	20.0	23	17.2
\$10,000-\$19,999	13	28.9	31	23.1
\$20,000-\$29,999	10	22.2	30	22.4
≥\$30,000	11	24.4	37	27.6
Refused	2	4.4	13	9.7
Median	\$19,722		\$22,321	
Education				
High school graduate or less	22	48.9	64	47.8
Some college	9	20.0	35	26.1
College graduate	14	31.1	35	26.1
Median	13 years		12 years	
Mean age at interview (years)				
Males	56.6		56.5	
Females	53.7		53.7	
Combined	55.9		55.9	

covered for their respective cases. A complete work history was obtained from each study subject and recorded on the interview form. To be classified into an occupational category, the individual must have received payment for services or products produced and must have worked a minimum of 20 hours per week in the position for at least six months. Each employment situation meeting these criteria was assigned a code number corresponding to the appropriate job title as defined in the *Dictionary of Occupational Titles* (15).

The questionnaire used in this study was administered by the study principal investigator (D.O.) and trained interviewers. The investigator interviewed all the cases and 17.2 per cent of the controls. Ninety

seven per cent of the interviews were conducted by personal interview; 3 per cent were conducted by telephone.

The multiple logistic model for matched data as described by Breslow et al. (16) was used to obtain point estimates of and 95 per cent confidence intervals (CI) for the relative risk (RR) associated with exposure variables. Analysis was univariate, and the resulting estimates of relative risk were controlled only for the design factors (age, sex, race). Analysis was performed separately, including and excluding the proxy respondents, using two-tailed tests of significance. Since the magnitudes of the estimates of relative risks did not change appreciably when the proxy respondents were excluded, only the results for the entire study group are reported.

RESULTS

The final sample consisted of 179 in-
 cases and 134 controls. As &
 played in table 2, cases and controls were
 similar with respect to major demographic
 variables. They were also similar with re-
 spect to presence of familial consanguinity
 (thought to promote genetic predisposition
 to leukemia) and sibship size (small sibship
 size is thought to be related to greater vul-
 nerability in adulthood because of protec-
 tion from early childhood infection). As
 shown in table 3, cases and controls were
 similar in their intake of alcohol and coffee
 and in their cigarette usage. With respect
 to residence history, 17.8 per cent of all
 cases were born on a farm as opposed to
 8.2 percent of controls (RR = 4.20; 95 per
 cent CI = 1.04-16.95).

The distribution of occupational groups
 for the cases and controls of all jobs ever
 held full time is shown in table 4. In ex-
 amining the distribution, we found six oc-
 cupational categories in which the propor-
 tion of cases exceeded that of controls: ser-
 vice occupations, agricultural work, ma-
 chine trades, benchwork, structural work,
 and motor freight and transportation. Within
 each of the categories, the fre-
 quency of codes for specific job types was
 compiled. Among specific job types which
 contained at least four cases who were ever
 employed in that occupation, only the oc-
 cupations of woodworking and farming

were found to have a suggestive association
 with hairy cell leukemia (table 5).

Exposure to organic chemicals for two
 years or more was found to be significantly

associated with the disease in the study
 sample as a whole, as well as in males and
 females when analyzed separately.

Of the reported previous diseases studied,
 anemia, migraine, and infectious mononu-
 cleosis were found to be associated with
 hairy cell leukemia (table 6). Concerning
 routine medication use, aspirin (acetylsali-
 cylic acid) and tranquilizers were found to
 be associated with hairy cell leukemia (table 6).

With respect to ionizing radiation expo-
 sure, four types were evaluated diagnostic,
 military, therapeutic, and occupational. No
 differences were found between cases and
 controls in exposure to ionizing radiation
 from diagnostic procedures or from the
 three other sources combined.

DISCUSSION

This preliminary investigation into the
 etiology of hairy cell leukemia represents
 an attempt to examine the association be-
 tween this disease and factors that have
 been found in previous studies to be related
 to either hairy cell leukemia or other his-
 tologic forms of leukemia. Although the
 relatively small number of cases, use of
 proxy respondents, and the time interval
 between event and interview pose threats
 to the validity and reliability of the find-

TABLE 3

*Distribution of study subjects according to smoking status and alcohol and coffee consumption; hairy cell
 leukemia cases and control, 1975-1981*

Variable (high-/low-risk contrast)	% and NO. in high-risk category			
	Cases		Controls	
	NO.	%	NO.	%
Cigarette smoking (ever smoked 10+ cig- arettes per day/ never smoked)	21	46.7	80	59.7*
Alcohol consumption (daily consump- tion/never drank)	10	22.2	20	14.9*
Coffee consumption (4+ cups per day/ practically never)	16	35.6	55	41.0*

* $p > 0.05$.

TABLE 4

Distribution of occupations ever held full time by hairy cell leukemia cases and controls, 1975-1981*

Occupational group (DOT† codes)	Cases		Controls	
	No.	%	No.	%
Professional, technical, and managerial occupations (001-199)	15	33.3	59	44.0
Clerical and sales occupations (210-299)	16	35.6	53	39.6
Service occupations (300-389)	5	11.1	11	8.2
Agricultural, fishery, and forestry occupations (401-461)	9	20.0	17	12.7
Processing occupations (500-559)	3	6.7	20	14.9
Machine trades occupations (600-699)	8	17.8	18	13.4
Benchwork occupations (700-795)	8	17.8	18	13.4
Structural work occupations (800-899)	10	22.2	21	15.7
Motor freight and transportation occupations (900-919)	4	8.9	9	6.7
Miscellaneous occupations (920-979)	3	6.7	12	9.0

* Individuals may have held one or more different occupations.

† DOT, *Dictionary of Occupational Titles*.

TABLE 5

Distribution of select occupational factors among hairy cell leukemia cases and controls, 1975-1981

Occupational factor	Cases		Controls		Relative risk (95% confidence interval)
	No.	%	No.	%	
Occupational subcategory (DOT codes)†					
Farming (401, 410, 421)	9	25.7	16	15.4	2.94 (0.88-9.87)‡
Woodworking (660-669, 760-769, 860)	4	11.4	3	2.9	4.00 (0.90-17.87)‡
Household work (900-919)	6	16.7	12	11.3	1.50 (0.45-5.11)§

* DOT, *Dictionary of Occupational Titles*.

† Females were excluded from these analyses because there were none who reported employment in farming or woodworking.

‡ $0.05 < p < 0.10$.§ $p < 0.05$.

ings, this report represents the first attempt to examine this specific histologic form of leukemia in a study sample comprised of incident cases in a defined geographic area and of matched neighborhood controls.

Exposure to radiation, coffee drinking, smoking, and alcohol consumption have been found in previous studies to be associated with certain types of leukemia (9, 17, 18). In this study, however, there were no indications that their frequency was greater

in cases than in controls. Although acute leukemia is known to be associated with ionizing radiation (19, 20), findings from studies investigating the relationship between ionizing radiation and chronic leukemia forms, including hairy cell leukemia, have been either negative or unconvincing (9, 21, 22). This could be because of the difficulty in measuring exposure to ionizing radiation retrospectively through interviews or through review of medical charts. It may also indicate no association, or at most a weak one.

TABLE 6

Characteristic	Cases		Controls		Relative risk (95% confidence interval)
	No.	%	No.	%	
Previous disease diagnosed by a medical doctor					
Allergies	9	20.0	18	13.4	1.79 (0.67-4.77)
Anemia	13	28.9	13	9.7	4.29 (1.67-11.03)‡
Migraine	8	17.8	5	3.7	4.80 (1.57-14.67)‡
Diabetes	3	6.7	5	3.7	1.80 (0.43-7.53)
Tuberculosis	0	0.0	2	1.5	0.00
Cancer (excluding hairy cell leukemia)	0	0.0	4	3.0	0.00
Rheumatic fever	1	2.2	5	3.7	0.60 (0.07-5.14)
Hypertension	9	20.0	29	21.6	0.91 (0.39-2.14)
Cardiac disease (other than hypertension)	5	11.1	15	11.2	1.00
Stroke	2	4.4	6	4.5	1.00
Chronic gallbladder problems	6	13.3	7	5.2	2.89 (0.86-9.69)§
Stomach ulcer	3	6.7	9	6.7	1.00
Arthritis (all forms)	7	15.6	22	16.5	0.93 (0.38-2.30)
Thyroid disorder	4	8.9	10	7.5	1.25 (0.34-4.59)
Chronic skin trouble	8	17.8	10	7.5	2.63 (0.97-7.17)§
Infectious mononucleosis	6	13.3	2	1.5	9.00 (1.82-44.59)‡
Medications routinely used†					
Vitamins	8	17.8	37	27.6	0.56 (0.24-1.33)
Thyroid medicine	3	6.7	6	4.5	1.56 (0.36-6.67)
Aspirin	12	26.7	12	9.0	3.41 (1.42-8.21)‡
Other nonaspirin pain medicine	2	4.4	6	4.5	1.00
Blood pressure pills‡	8	17.8	16	11.9	1.59 (0.64-3.98)
Tranquilizers	6	13.3	4	3.0	4.50 (1.27-15.95)‡
Diet pills	3	6.7	6	4.5	1.63 (0.35-7.63)
Hormone pills	3	6.7	9	6.7	1.00

† Includes medications with a combination of pharmacologic properties.

§ $0.05 < p < 0.10$.

viewed as suspect because of small sample size (27).

[illegible]

...represent secondary ...
...linking ...
...in hairy cell leukemia.

This study also found prior infectious mononucleosis to be a significant risk factor among the cases. From a biologic perspective, certain strains of Epstein-Barr virus (the causative agent in infectious mononucleosis) are capable of in vitro transformation of lymphocytes into rapid and persistent growing cells which interact with malarial parasites to produce malignant lymphoma (31). Infectious mononucleosis has also been associated with Hodgkin's disease and acute leukemia (32, 33). Because infectious mononucleosis has been noted to occur before and after the diagnosis of a hematologic malignancy, the significance of Epstein-Barr virus-induced infection is unclear. The following are possible explanations for the association between hairy cell leukemia and infectious mononucleosis detected in this study: a 'pre-leukemic' state may promote infection; infectious mononucleosis shares some etiologic factor(s) with hairy cell leukemia such as Epstein-Barr virus; or, early hairy cell leukemia may have been misdiagnosed as infectious mononucleosis. Future study of the association between infectious mononucleosis and hairy cell leukemia would require a review of respondents' medical records to ascertain laboratory confirmation of infectious mononucleosis.

Regarding drug usage, cases reported significantly more routine use of aspirin and tranquilizers than did controls. With respect to aspirin (acetylsalicylic acid), most laboratory studies do not find this substance to be either a primary or cocarcinogen (34, 35). In fact, aspirin has been noted to delay tumor growth and metastasis (35). However, aspirin is also noted to inhibit the immune system by decreasing normal killer cell activity (36). Aspirin is also known to interfere with prostaglandin synthesis, an essential component for the maturation and differentiation of macrophage-

granulocyte progenitor cells and in the functional capabilities of leukocytes (37). Thus, aspirin ingestion may alter the body's ability to recognize and eliminate aberrant cell lines, such as hairy cell leukemia. It is also possible that the significance of aspirin among the cases may have emerged because of its use to manage symptoms precipitated by exposure to noxious insults in the work environment (viz., organic chemical exposure).

The role of tranquilizers as an etiologic factor for neoplastic growth has been previously identified. Diazepam has been found to be a tumor enhancer in laboratory animals (38). Friedman and Ury (39) reported the association of diazepam with lymphomas and leukemias. Both the major and minor tranquilizers may induce blood dyscrasia (40); thus, their role in the development of leukemia is biologically plausible. Further study of the significance of specific drugs would require each to be named by the respondents along with the condition(s) for which they were used and would require exploring the possibility of substance abuse (frequent medication use in the absence of a pathologic condition).

Some of the same disease and drug risk factors may also be indicative of a long subclinical state of hairy cell leukemia or early undiagnosed disease. For example, aspirin usage may be related to the onset of symptoms such as splenomegaly, an early sign of hairy cell leukemia, and may contribute to the development of anemia. Unfortunately, it was felt that the number of available cases at the time of the study was not sufficient to examine the significance of these subgroup associations.

An exploration into childhood lifestyle appears to be warranted in view of the significant association of hairy cell leukemia with farm birthplace detected in this study. Factors related to this agricultural environment need to be identified and isolated for future study.

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