Leukemia and Lymphoma Patients Linked by Prior Social Contact

Evaluation Using a Case-Control Approach

STEPHEN C. SCHIMPFF, M.D., F.A.C.P.; DORAH M. BRAGER; CAROL R. SCHIMPFF; GEORGE W. COMSTOCK, M.D.; and PETER H. WIERNIK, M.D., F.A.C.P.; Baltimore, Maryland

A case-control approach was used to evaluate whether patients with leukemia or lymphoma have a greater than expected tendency to have had prior close personal associations. Two census enumeration districts in different states with low population mobility were chosen, and each resident who had developed leukemia or lymphoma during a predetermined fixed interval was ascertained by review of tumor registry records. For each patient, a resident of the area was selected as a control matched for age, sex, race, and geographic location as of the time of diagnosis. Close personal associations between patients, controls, and both were determined by interviewing. In Area 1 the 8 patients had 11 social links (3 direct, 8 indirect) and the controls had 2 (both direct); $P = 0.0156$, one-tailed significance test. In Area 2, the 21 patients had 21 close links (15 direct, 6 indirect) whereas the controls had 10 (direct 8, indirect 2; $0.25 > P > 0.20$).

WE HAVE REPORTED PREVIOUSLY that 61% to 75% of all individuals with leukemia or lymphoma, residing in each of three districts and diagnosed from 1964 to 1973, could be interlinked (either directly or via an intermediary) based on their prior, close personal associations (1). To ensure that the findings of prior close personal associations among these patients in the three areas were not rare occurrences detected through unrecognized bias in the area selection, 28 patients with Hodgkin's disease, selected at random from the clinic but residing in areas not already under study, were interviewed. Ten (36%) responded that they had direct or indirect close personal contact with one or more persons with either lymphoma or leukemia.

Other investigators have previously suggested that patients with Hodgkin's disease or acute leukemia are often found to be interlinked based on prior close social contacts (not to be confused with "time-space" clusters of patients) (2-10). Many such investigations have been sharply criticized because the data were, or seemed to be, anecdotal and lacked the statistical verification of a matched controlled evaluation (11). Controlled evaluations are needed because of the potential implications associated with increased social contact prior to disease onset. The possibility exists that any resident of a rural area such as those we investigated might know nearly all other residents on a close personal basis thus negating the possible significance of previous patient interactions (11). Therefore, for the present investigation, we studied the social linkages between patients and a set of matched controls in each of two areas.

► From the Section of Medical Oncology, Baltimore Cancer Research Center, National Cancer Institute at the University of Maryland Hospital; and the Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University; Baltimore, Maryland.

Methods

A county in an eastern state was being investigated for possible prior social contacts between patients with leukemia and lymphoma. The county is well suited for this type of study because it includes urban, suburban, and rural regions all with relatively low population mobility, had previously been divided into special census enumeration districts for other epidemiologic investigations, and has a functioning tumor registry.

One enumeration district was selected for the initial evaluation. It is situated between urban and rural areas and consists of closely spaced single-family homes and is known to have a relatively stable population. The tumor registry records were reviewed to ascertain each patient with leukemia or lymphoma diagnosed while residing in this district during the 10 years ending 31 December 1973. Eight residents with leukemia or lymphoma were diagnosed from 1964 to 1973 (approximately the number expected for the population of this area).

For each of the eight patients a matched control was selected as follows. The patients were randomly ranked (to prevent any bias in selection of controls); for the first listed patient, a street within the enumeration district and then a household on that street was selected, using a table of random numbers, from the city directory for the year of that patient's diagnosis. The selected household was contacted by telephone (all of the patients had listed telephone numbers) and the individual who answered was asked if, during the year of the first patient's diagnosis, there was an individual residing in that household who was of the same sex, age (± 5 years), and race. If so, and if that individual agreed to participate, he became the control matched for age, sex, race, and geographic location as of the patient's date of diagnosis. If the household had no such individual (frequently occurred) or such person declined to cooperate (never occurred), then the selection process was repeated for both street and household. In total, more than 100 households were contacted in order to find the eight controls who were appropriately matched. Only two individuals answering the telephone declined to be interviewed to determine if

there was an appropriate control in the household. Although length of residence in the area was not considered when selecting controls, when rechecked it was found that each control had lived in this low mobility region for a time period equivalent to that of the matched patient. Nearly all patients and controls had lived in this area for more than 15 years. A special census indicated that essentially all residents were of the same socioeconomic class.

Each patient and control (or, if deceased, a surviving relative or friend) was contacted and interviewed as to whether he had any past close social associations with any of the other seven patients or the matched controls. The exact nature and timing of any close social association was determined (for example, year relation began and ended; details of relation such as dating, social groups, visits to each others' homes; and so forth).

A "surviving" relative of the control was interviewed if the control was matched to a deceased patient; that is, because a relative and not the patient himself had been interviewed it was necessary to interview a relative of the matched control whether or not the control was actually deceased. The relative interviewed was chosen to match the relative of the control whenever possible; for example, sibling of a case, and so forth. The "surviving" relative was not given an opportunity to verify his comments with the actual control, if living, thereby ensuring equivalence in interviews between patients and controls. As with the patients, each control (or "surviving" relative) was interviewed by telephone to determine the presence of any close social contacts with other controls or patients.

One Baltimore Cancer Research Center patient (B) and his wife were initially interviewed in person (three patients [B, E, F] had been treated at this Center); a repeat interview with Patient B and all interviews with other patients and controls were done by telephone by one author. Interviews began with general questions and became more specific as necessary. The patients and controls were told that the interviewer worked at the Baltimore Cancer Research Center of the National Cancer Institute and was engaged in a research project. The specific nature of the project itself, the exact reasons for the questions, or the potential significance of any answer were not revealed although many controls and patients recognized various names as those of local residents with a history of cancer.

A second area in a different state was investigated after the evaluation of the first area was completed. In choosing the new area, it was decided to select a census enumeration district of low population mobility from which the state tumor registry listed 20 to 25 patients diagnosed during the years 1960 to 1974 (the years for which registry data were available to us). The area to be selected had to be previously unstudied by us and none of the patients were to have been treated at the Baltimore Cancer Research Center. The area finally selected had 21 patients with leukemia or lymphoma.

Using the same techniques as in the first area, a group of 21 controls was selected by an interviewer who subsequently interviewed neither patients nor controls with respect to personal associations. After the controls were selected, each patient and each control (or "surviving" relative) was interviewed by one author to determine the associations between patients, controls and between patients and controls.

Close personal associations, as previously defined (1), could include direct household contacts (spouses, siblings, or other pairs or individuals residing continuously or intermittently in the same private home), social friendships (close friends which, in this study, consisted of individuals who had visited each other on multiple occasions in their own homes), or other associations that dictated close social interactions (in this study the one such interaction was between a patient and the mother of another patient who worked together in the same division of a small department store). Less well-defined associations were considered as acquaintanceships, not as close personal associations, and therefore ignored. Only associations that had existed before the onset of leukemia or lymphoma in the most recently diagnosed patient of any pair (or before the corresponding dates for matched controls) were used.

Direct close personal associations were defined as associations between two patients (two controls) or between a patient and control. Indirect associations were defined as associations in which there was one intermediary (for example, patient-intermediary-patient) who had close contacts with both individuals during the same time period. These indirect associations were ascertained from the individuals (or their surviving relatives) themselves. Indirect controls were crosschecked with the other patient (or surviving relative).

Effective contact, for the purpose of this investigation, was defined as contact occurring before the onset of disease in one member of each pair of socially linked patients or controls (12). For example, if one patient diagnosed in 1965 and another diagnosed in 1969 were close friends from 1966 to 1972, then they were effectively linked only from 1966 to 1969. However, if their friendship had not begun until 1970, that is, after the second patient's diagnosis, then they would be considered as having no effective linkage.

After determining the prior close personal associations between patients, between controls, and between patients and controls, the results were subjected to statistical analysis according to the case-control approach of Pike and Smith (12). The P values given are for a one-tailed significance test. No supposition regarding the length of a possible incubation period was formed; the evaluation was only whether patients had more close social contact with each other than expected.

Results

The close personal associations* occurring between the patients and between the controls are presented in Figure 1 for Area 1 and Figure 2 for Area 2.

In Area 1 the patients had 3 direct and 8 indirect close personal links; the controls had no direct and 2 indirect links; and there were no direct or indirect links between patients and controls.

The three direct contacts between patients is not significantly different from that expected ($P = 0.125$). Combining the direct and indirect contacts, the patients had 11 links which is significantly more than the 3.25 expected ($P = 0.0156$).

* Further details regarding these relations are available from the authors upon request.

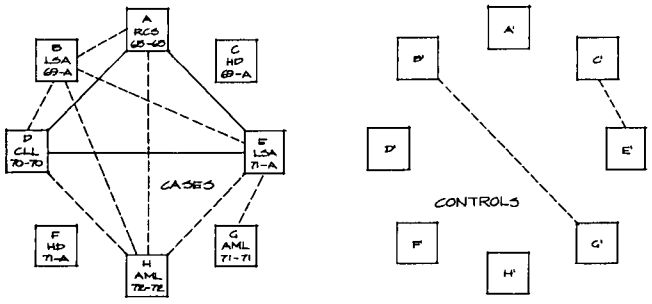

Figure 1. Area 1—close personal associations among patients (cases) with leukemia or lymphoma and their matched controls. Each box represents a patient and includes an identifying letter symbol, abbreviated diagnosis, and dates of diagnosis and death. Controls are represented by the same letter as their matched case. Solid lines between cases or controls represent direct associations (case to case); dashed lines represent indirect associations (case to intermediary to case). The figure is arranged chronologically from top to bottom by date of diagnosis. The 8 cases had 11 links (3 direct, 8 indirect) involving 6 individuals and the controls had 2 links (0 direct, 2 indirect) involving 4 individuals. RCS = reticulum cell sarcoma, LSA = lymphosarcoma, HD = Hodgkin's disease, CML = chronic myelocytic leukemia, CLL = chronic lymphocytic leukemia, AL = acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myelocytic leukemia.

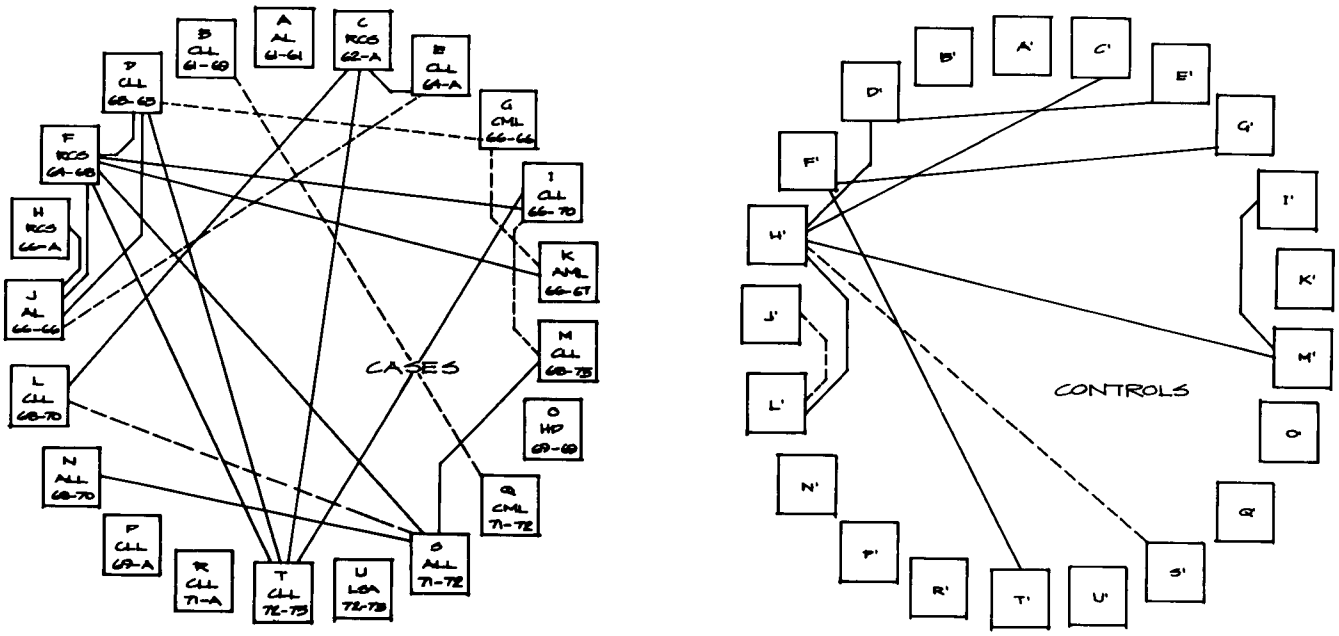

Figure 2. Area 2—close personal associations among patients (cases) with leukemia or lymphoma and their matched controls. Each box represents a patient and includes an identifying letter symbol, abbreviated diagnosis, and dates of diagnosis and death. Controls are represented by the same letter as their matched case. Solid lines between cases or controls represent direct associations (case to case); dashed lines represent indirect associations (case to intermediary to case). The figure is arranged chronologically from top to bottom by date of diagnosis. The 21 cases had 21 links (15 direct, 6 indirect) involving 16 patients; the controls had 10 links (8 direct, 2 indirect) involving 12 individuals. RCS = reticulum cell sarcoma, LSA = lymphosarcoma, HD = Hodgkin's disease, CML = chronic myelocytic leukemia, CLL = chronic lymphocytic leukemia, AL = acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myelocytic leukemia.

Two patients were blood relatives (A was a paternal aunt of D); none of the other patients are related by blood or marriage. Patients B, E, and F are patients at our center. The wife of B is a stepniece of E (and great-stepniece of A) but B and E had no personal contact either at home or at the clinic; the association is indirect via the wife of B. Patient F does not know B or E either directly or indirectly either from clinic or home. The other patients were treated at a variety of institutions in various towns and cities, therefore it does not appear that treatment at the same clinic served to remind patients of prior contacts.

In the second area, there were 21 links between cases, only 10 links between controls, and 28 links between cases and controls. None of the patients but two of the controls were blood relatives. In this second area, the 21 observed patient links when compared to the 14.75 expected links gives $\chi^2 = 1.46$, $P < 0.25$—not statistically significant.

Discussion

Numerous reports in recent years have suggested that many patients with Hodgkin's disease, acute leukemia, or other leukemias and lymphomas have a tendency to be associated on the basis of prior personal contacts (1-10). The question to be resolved is whether the associations reported are more than would have been expected among a similar group of individuals living under similar circumstances (that is, the control group).

In the investigation by Vianna and associates near Albany, New York, close personal associations interlinked 31 patients with Hodgkin's disease (2, 3). A group of seriously burned patients were matched by age, sex, race, and residence to 18 of the Hodgkin's patients as a control to determine if such a group would also have numerous prior social contacts. No contacts were found among the 18 burned patients suggesting that these matched controls were not socially interlinked in a manner similar to the patients with Hodgkin's disease. Pike and Smith, however, have criticized this evaluation because controls were picked only for the linked cases and not for each of the 208 cases of Hodgkin's disease diagnosed in the county during the study period (11).

Our recently published experience reported that 61% to 75% of all patients with either leukemia or lymphoma diagnosed over a 10-year time span while residing in any of three defined areas could be interlinked based on prior close personal associations. Thus, although evaluated on a patient-to-patient basis, all patients from each area were considered. Because each of these three areas was of low population mobility, there was presumably greater opportunity for a patient to be aware of the health status of a previous close associate than for patients from high mobility areas where they might never learn of subsequent disease among former associates. On the other hand, individuals living in areas of low population mobility such as those studied might have a high tendency to know one another as a general phenomenon. Thus, the present investigation sought to determine whether the patients had more social contacts than expected based on an analysis of social contacts among matched controls. The results are suggestive that the patients did indeed have greater contact than that expected.

We have no reason to believe that the study area controls were not appropriately chosen. Every effort was made to

ensure that the controls were interviewed as intensively as the patients. Although the controls did not necessarily have an interest in cancer research equivalent to what might be expected for the patients or their surviving relatives, we had the distinct impression that each control was attempting to cooperate fully. It is certainly likely that patients would tend to remember prior associations with other patients more readily than would controls. We attempted to adjust for this by requiring that any stated association be supported with details as to the timing and the nature of the relation; all contacts proved to be close, prolonged friendships. It seems unlikely that controls would have forgotten such close associations when specific names were mentioned repeatedly. In addition, the associations found between the patients and controls are used in the statistical evaluation. There was one blood relationship among two patients in Area 1 (A and E) and one between controls in Area 2.

The biological meaning of social controls is not entirely clear. Although the transmission of an agent(s) has been implied, an equally acceptable suggestion is that close social contact may help to define a population at greater risk of leukemia or lymphoma because of social habits (compare: cigarettes and lung cancer), unrecognized genetic background (which has influenced social patterns), or unrecognized environmental exposures (not necessarily defined by place of residence or employment). Nevertheless, our findings, in part, lend support to previous observations that patients with leukemia or lymphoma are frequently interlinked by prior close personal associations.

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► Requests for reprints should be addressed to Stephen C. Schimpff, M.D.; Baltimore Cancer Research Center; 22 South Greene Street; Baltimore, MD 21201.

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