Acute Myeloid Leukemia in Adults: A Case-Control Study in Yorkshire

R. A. Cartwright,[1] C. Darwin,[1] P. A. McKinney,[1] B. Roberts,[2] I. D. G. Richards,[3] and C. C. Bird[4]

[1]Leukaemia Research Fund, Centre for Clinical Epidemiology, Leeds; Departments of [2]Haematology and [3]Community Medicine, Leeds General Infirmary, Leeds; and [4]Department of Pathology, University of Edinburgh, U.K.

This paper reports the results of a case-control analysis of 161 cases of acute myeloid leukemia and 310 matched hospital controls. The patients were interviewed between 1982 and 1986. The study shows a weak association for cases with previous malignant disease. Furnace workers show excess risks. Urticaria and vertigo are in excess, as well as some aspects of family medical histories, including multiple sclerosis and cases of leukemia/lymphoma in blood relations.

INTRODUCTION

SEVERAL problems obscure the clear understanding of the epidemiology of the leukemias; these include difficulties of classification, particularly by cell type. Geographically based surveys attempting complete case ascertainment remain rare in this area of study. This paper examines the diagnostic subgroup of AML from a large case-control survey of leukemias and lymphomas in Yorkshire (1).

METHODS

New cases of AML in people aged 15 years or older were found as a result of visits made to hematology clinics in hospitals throughout Yorkshire. excluding South Humberside. Residents of Yorkshire who were diagnosed as having AML between October 1979 and March 1986 were eligible for the study. Dianostic details of the majority of AML cases were ascertained from the Regional Centre where subclassification of AML was achieved by morphological (FAB) (2). conventional cytochemical (peroxidase, specific and nonspecific esterases) and immunophenotypic criteria. Immunological studies undertaken included TdT and membrane CD1, CD7. and CD19 for exclusion of lymphoblastic leukemias. Myeloid leukemias were routinely examined with a panel of monoclonal reagents including HLA-Dr, CD13, CD14, and CD33 as previously described (3. 4). In this way fewer than 5% of the cases could not be satisfactorilycategorized, and these were excluded from the study. The small proportion of AML cases diagnosed at peripheral hospitals used morphological and cytochemical techniques and similarly excluded undifferentiated leukemias.

The interviewing of AML patients only commenced in 1982. For each patient interviewed, two control patients were sought from hospitals in the health dismct of residence of the patient. Such controls were of the same sex and within three years of the age of the patient at diagnosis, and were currently in hospital for reasons other than malignant disease. A wide range of conditions was used, but accidents and ''cold'' surgery cases form the bulk of the controls.

Hospital notes were perused for drug use and past medical history for both cases and controls. The general practitioners of the cases and controls were contacted and their notes were perused for further past medical and drug ingestion information. A combination.of reponed and medically verified information forms the base for analysis. Most interviews took place on wards or in outpatient clinics. Identically structured questionnaires were used for cases and controls covering many aspects of the past medical, social, and employment history, along with details of illness in the immediate family.

All the data were coded, input into the Leeds University mainframe Amdahl computer (with an anonymous format), and, following verification procedures, were analyzed using the SPSSX statistical package (5). Further statistical analyses used the methods of Rothman and Boice (6) to obtain estimated relative risks. Cornfield's exact confidence intervals were computed for the risk ratios presented in this paper, by using the algorithm of Thomas (7). The results given are those from a pooled analysis.

RESULTS

One hundred sixty-one patients and 310 controls were interviewed; 12 controls were not found in the time available for the study. During this time (October 1979 to March 1986), 529 histopathologically confirmed cases of AML occurred in the study area: 69% were not interviewed. There was an even geographic spread of non-interviewed patients, and 92% of these had died prior to an interviewer's approach. The time lapse between study start date and the beginning of AML case interviews (October 1979 to March 1982) accounts for this. However, in 1985 and 1986 special efforts were made to incorporate all cases, and here the successful interview rate was more than 65%. For the small proportion of non-interviewed live patients who were approached (8%), various reasons explained their exclusion — refusal by patient or consultant, language problems, too ill to interview.

The distribution of interviewed patients by AML subtype and age at diagnosis is given in Table 1 along with the sex ratio. Resuls are given for data pooled on age and sex, and, although FAB types were defined, the numbers were too small to stratify on this variable. Risk assessment for medical vari-

Table 1. Distribution of Interviewed AML Patients by Age and FAB Subtype.

Group	Cases[b]		Total (column %)
	<60 Years	60 Years or Over	
AML subgroup			
M1	9	13	22 (14)
M1/M2	13	12	25 (16)
M2	14	7	21 (13)
M3	8	8	16 (10)
M4	20	9	29 (18)
M4/M5	0	1	1 (<1)
M5	7	8	15 (9)
M6	1	1	2 (1)
Unclassified[c]	11	19	30 (19)
Total	83	78	

[a]See text for diagnostic criteria.
[b]Sex ratio Male:Female = 1.1:1.
[c]This category excludes undifferentiated leukemias.

Received March 3. 1988. Accepted May 9, 1988.

Abbreviations: RR. relative risk: CI, confidence interval.

Correspondence to: Dr. R. A. Cartwright, Leukaemia Research Fund Centre for Clinical Epidemiology. 17 Springfield Mount, Leeds LS2 9NG (0532-443517), U.K.

0887-6924/88/0210-0687$2.00/0
LEUKEMIA

Table 2. AML in Adults: Case-Control Study—Unassessable Results (Less than Five Case and Control Responders)

Factor	No. of Cases	No. of Controls
Past medical history		
Scarlet fever	4	3
Epilepsy	4	4
Past drug use		
Anticoagulants	2	4
Immunosuppressive drugs	3	1
Blood relatives' family history		
Carcinoma rectum	4	4
Hyperthyroidism	1	0
Hypothyroidism	0	2
Social history		
Jewish faith	0	2
Occupation		
Stationary engine driver	3	3
Administration	1	2
Industry		
Petroleum	4	3
Photographic	0	4

bles relating to past history and drug ingestion were based oth on interview and on medically recorded data.

For certain topics, responses were so infrequent that no assment could be made of their validity. These are summarized Table 2 showing topics with five responses or less, giving e exact numbers of positive responders by case or control.

The majority of the current results fail to add to our knowlge regarding putative risks for AML. These instances are tailed in Table 3, which gives numbers of "exposed" cases id controls whose comparisons showed RR less than 2. Facrs demonstrating risks either greater than 2 or having statisal significance at the 5% level are listed in Table 4. The sults are arranged by topic: past medical history, past drug istory of at least 3 months' duration, family history of disease, ocial-environmental exposures, and occupational history.

Table 4 includes aspects of past medical history, and a preious malignancy was a significant risk for both sexes. Of seven f these patients for whom sufficient records exist, four had ad radiotherapy, on average, 10 years prior to diagnosis, one ad both radiotherapy and chemotherapy (12 years prior to iagnosis), and two had had neither treatment. Of the four ontrols, two had received radiotherapy and two had neither adiotherapy nor chemotherapy. The case malignancies were:

Table 3. AML in Adults: Case Control Study—Summary of Results with Risks under 2.0 and Without Statistical Significance (certain topics excluded and appear in details in later tables)

Factor	No. of Cases	No. of Controls
Past Medical History		
Tonsillectomy	39	92
Appendectomy		
Infectious mononucleosis		
Tuberculosis	3	11
Eczema/dermatitis	18	42
Skin lesions	24	33
Asthma	8	15
Herpes zoster	9	12
Diphtheria	3	5
Malaria	2	5
Thyroid disease (all)	9	11
Diabetes	4	5
Anemias	8	9
Depression	10	32
Otitis media	6	6
Hypertension	7	18
Myocardial infarction	3	8
Angina	5	10
Bronchitis	5	11
Duodenal ulcer	3	12
Cholecystitis	5	9
Rheumatoid arthritis	2	6
Osteoarthritis	11	18
Jaundice	4	6
Radiotherapy treatment	9	10
Any diagnostic X-ray	140	287
Past drug history for at least 3 months		
Tranquilizers	31	69
Slimming tablets	1	8
Contraceptive pill	17	31
Antibiotics	7	18
Analgesics	7	28
Antihistamines	5	7
Antacids	7	28
Assorted drugs for heart disease	27	46
Anticonvulsants	6	6
Anti-inflammatory drugs	15	25
Bronchodilators	2	14
Steroids	12	24
Iron preparation[a]	11	11
Medical History of first degree blood relatives		
Any malignancy	59	113
Stomach cancer	7	12
Lung cancer	10	16
Breast cancer	9	19
Brain tumor	5	11
Tuberculosis	9	21
Diabetes	12	34
Epilepsy	2	9
Rheumatic fever	2	6
Asthma	15	42
Eczema dermatitis	6	15
Psoriasis	4	5
Rheumatoid arthritis	4	10
Social characteristics		
Single sibship	106	187
Lived on farm	17	17
Pet owner	126	260
Family sizes	(various combinations 1 child vs. more)	
Wine drinker	16	35
Spirits drinker	18	40
Occupations groups		
Agricultural workers	19	33
Miner	6	15
Chemical workers	10	17
Glass and ceramics workers	6	7
Engineering workers	41	87
Woodworkers	6	15
Leather workers	2	6
Textile workers	4	15
Clothing workers	21	43
Food processors	25	42
Printers	8	21
Construction workers	7	23
Painters and decorators	2	8
Transport workers	29	52
Warehousemen	3	6
Clerical workers	21	41
Sales workers	40	93
Service workers	42	92
Professional groups	17	30
Armed forces	31	81
Pooled Groups		
Nurses and hospital ward orderlies	9	14
Drivers	18	34
Charwoman	12	20
Those with either occupational or hobby contact		
Live animals	23	37
Dead animals	12	24
Wood dust	10	28
Solvents	42	69
Fertilizers/pesticides/herbicides	26	41
Spray paints	14	18
Epoxy glues	18	33

Certain factors excluded from this table appear in other tables.

[a]Achieves RR 2.0 but is not significant.

Table 4. AML in Adults: Case-Control Study—Risks Ratios Greater Than or Equal to 2.0 or Statistically Significant

Factor	No. of Cases	No. of Controls	RR	95% CI	Two-tailed p
Past medical history					
Previous malignancy	11	4	5.6	1.6–24.5	0.004
Vertigo	9	4	4.5	1.2–20.4	0.02
Allergy	40	109	0.6	0.4–0.95	0.02
Urticaria	6	2	6.0	1.1–60.8	0.04
Basal cell carcinoma	6	6	2.0	0.5–7.5	0.38
Family history					
Leukemia/lymphoma	11	4	5.6	1.6–24.5	0.004
Multiple sclerosis	7	5	2.8	0.7–11.2	0.14
Skin cancer	5	4	2.5	0.5–12.5	0.32
Infectious mononucleosis	5	1	9.9	1.1–469.8	0.04
Social characteristics					
Smokers	91	208	0.6	0.4–0.96	0.04
Occupation					
Electrical workers	13	11	2.4	0.95–6.0	0.06
Furnace and forge workers	8	4	4.0	1.0–18.4	0.04

three female genital tract cancers. three breast cancers, one prostate, one larynx. and two mixed parotid cancers. The four controls were malignancy of bladder. bowel. cervix. and breast. It is noteworthy that the risks for past therapeutic radiotherapy are not significant (cases = 9, controls = 10, risk ratio = 1.8, 95% CI 0.7–4.4. p = 0.2). This includes some patients who had radiotherapy for nonmalignant conditions.

The cases showing a past history of vertigo were all confirmed by perusing National Health Service records and occurred 3–25 years before diagnosis of AML. with a mean of 11 years. Four cases and one control were known to have been prescribed Stemetil: no drug treatments are recorded in the rest. The medical record of one control was incomplete.

The results for skin conditions gave a single significant excess associated with past urticaria. These cases were all confirmed by medical records and were first recorded, on average. 73 years before diagnosis of AML. No common treatment pattern emerged. nor was there any FAB type of AML in excess.

Table 4 also gives details of aspects of family history. The strongest association is with blood relatives with either lymphoma or leukemia. These are of all types. including four cases of Hodgkin's disease and four of ALL: only two cases might have been AML and neither could be properly confirmed. The multiple sclerosis family association is striking but not confined to blood relatives; of the seven cases, five were in first degree blood relations, in one case the father-in-law and sister-in-law were both affected. and in the final case a close friend of many years was affected. Skin cancer in the family achieved a pooled risk of 2.5, but this is not statistically significant.

In addition, Table 4 gives some details of occupations and the cigarette smoking risks. In the latter case there is an overall significantly negative risk which is mainly accounted for by women (RR = 0.52. 95% CI 0.29–0.91. two-tailed p = 0.02). The occupational excesses in this table are all for small groups of people. The risk for furnacemen and for forge and foundry workers is 2.5 but this is not significantly in excess. The electrical workers do represent a more substantial statistical excess, with a risk ratio of 2.5 (p = 0.03). No one clear occupational group is recorded among the electricians, although all were involved with wiring and installations, often for many years. On average the workers started their employment as electricians 31 years before diagnosis of AML. There is no preponderence of one FAB type. The excess in the chemical industry is confined to women. Of the five women, two were munitions workers, one a laboratory assistant for a dyestuff manufacturer, and one made fireworks at home.

The crude risk for solvent exposure of any type (RR = 1.24, 95% CI 0.79–1.95, two-tailed p = 0.35), the age-stratified male and female risk (male: RR = 1.45, 95% CI 0.84–2.57, two-tailed p = 0.18, female: RR = 0.76, 95% CI 0.23–2.51, two-tailed p = 0.65) and the risks by FAB types all fail to show any statistical excess. The same is true of occupational contact with ionizing irradiation, although the crude risk is higher at 2.9; this is nonsignificant (two-tailed p = 0.2).

DISCUSSION

This study is part of the larger case-control adult survey of lymphoma/leukemias in Yorkshire. This AML analysis differs somewhat in that the proportion of cases interviewed is the smallest of the groups analyzed so far. This is partly due to the later start in interviewing and partly due to the greater prevalence of rapid deaths. However, the patients interviewed were evenly distributed among the health authority areas in Yorkshire, although the study will inevitably be deficient in older cases and those subtypes resulting in rapid deaths.

The analysis itself produced large numbers of low risks less than 2.0 which were not statistically significant. The relatively few positive results are clearly shown in the accompanying tables. The two tradiational risk factors for AML: solvent exposure and ionizing irradiation are not represented directly here. Ionizing irradiation cannot account for the excess risk among people with radiotherapy for past malignancies (ca = 5, co = 2), as the situation is confused by past chemotherapy (ca = 3, co = 0). The past chemotherapy was with alkylating agents and this excess has been suggested in case reports and surveys by several authors (8, 9). Radiotherapy for cervix cancer has not produced any excess risks of leukemia (10), although the irradiation of ankylosing spondylitis is linked with a leukemia excess (11). Occupational contacts with irradiation have produced little to link them with excess AML (12, 13).

This is the first observation of a previous history of vertigo increasing the relative risk of AML, especially in men. Further studies are necessary to indicate whether this is a true relationship. One biological explanation of this finding may be an iatrogenic element. Although no significant relative risk was found for anti-nausea drugs, it may be that our exclusion of treatment spanning less than 3 months has concealed a positive risk factor. Another expianation is a possible viral link. Although vertigo is a symptom rather than a disease, and is likely to have several causes, recent indications suggest a viral etiology for Menier's disease.

Urticaria has been noted as a possible risk factor in CLL by our group (14); however, it has not been previously noted in AML as a risk factor.

There are two familial excess results: for lymphoma/leukemia and multiple sclerosis. It is noteworthy that the excess lymphomas/leukemias are in fact largely lymphomas, and not other AML cases. Reporting bias is possible here, given the diversity of lymphoid malignancies recorded, controls not being as aware of similar familial traits in their own family. These familial observations are, however, quite novel and difficult to assess until other observations are made. A link between various malignancies of the lymphoma/leukemia range already has been noted in this study series (1), and multiple sclerosis has also been noted in a familial setting with lymphoreticular malignancy (15).

Cigarette smoking was in statistical deficit among women, with risks near unity for men. This is in contrast to reports from the United States (16, 17). Comparison with hospital controls admitted for a non-smoking-related condition did not substantially alter this relationship. This negative association and, particularly, the links with women are not readily explained.

The most robust observation in the area of occupation is the link between electrical workers, as there have been several other papers also suggesting a link with "electrically related" occupations and the leukemias (18–23). Some papers have suggested a link with electromagnetic fields. In view of the variety of occupations involved, this appears to be unlikely; other hypotheses could involve fume inhalation associated with soldering, cable jointing, or even welding. This aspect is being investigated further.

Overall, because of the multiple comparisons made in this analysis, more significant factors might have been expected to emerge by chance. In general, small numbers precluded age, sex, and FAB type stratification, but a multivariate analysis of the entire Yorkshire data is in progress which may further clarify associations with AML and its subtypes.

Acknowledgments. This study could not have been accomplished without the assistance of numerous colleagues within the Yorkshire Health Region who have allowed us access to their patients. The work was funded by the Leukaemia Research Fund, and we would specifically like to acknowledge the assistance of Mary Brown, Jill Collins, Sylvia Craven, Fiona Landells, Helen Lilley, Felicity Ludolf, Anne Mainwaring, Jan Parker, Jane O'Sullivan, Bernice Pearlman, Carole Startin, and Brenda Waller, who have worked for several years with us on this project. The support of both the Department of Haematology, Cookridge Hospital, Leeds, and the Yorkshire Regional Cancer Registry is also gratefully acknowledged.

REFERENCES

1. Bernard SM, Cartwright RA, Darwin CM, Richards IDG, Roberts B, O'Brien C, Bird CC. Hodgkin's disease: case control epidemiological study in Yorkshire. Br J Cancer **1987**;5:85–89.
2. Bennett JM, Catovsky D, Daniel M-T, Flandrin G, Galton DAG, Granlick HR, Sultan C. Proposed revised criteria for the classification of acute myeloid leukaemia. Ann Intern Med **1985**;103:626–629.
3. Scott CS, Morgan M, Limbert HJ, MacKarill ID, Roberts BE. Isoenzyme studies in acute myelomonocytic leukemia: a study of 39 cases. Scand J Haematol **1985**;35:284–291.
4. Stark AN, MacKarill ID, Limbert HJ, Evans PM, Scott CS. TdT expression in acute myeloid leukaemia. Haemopoetic immaturity or maturational synchrony. Blut **1988**;56:33–38.
5. SPSS version X users guide. New York: McGraw-Hill, **1985**.
6. Rothman KH, Boice JD. Epidemiologic analysis with a programmable calculator. Boston: Epidemiology Resources Inc., **1985**.
7. Thomas DG. Exact confidence limits for the odds ratio in a 2 × 2 table. App Stat **1971**;20:105–110.
8. Cadmen EC, Capizzi RL, Bertino JR. ANLL. A delayed complication of HD therapy: analysis of 109 cases. Cancer **1977**;40:1280–1296.
9. Coleman CN, Kaplan MS, Cox R, Varghese A, Butterfield P, Rosenburg SA. Leukemias, NHL's and solid tumours in patients treated for HD. Cancer Surv **1982**;1:733–744.
10. Day NE, Boice JD. Second cancer in relation to radiation treatment for cervical cancer. World Health Organisation, IARC **1983**:No. 52.
11. Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer **1987**;55:179–190.
12. Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. Br Med J **1986**;193:845–854.
13. Beral V, Inskip H, Fraser P, Booth M, Coleman D, Rose G. Mortality of employees of UK Atomic Energy Authority 1946–1979. Br Med J **1985**;291:440–447.
14. Cartwright RA, Bernard SM, Bird CC, Darwin CM, O'Brien C, Richards IDG, Roberts B, McKinney PA. Chronic lymphocytic leukaemia: a case control epidemiological study in Yorkshire. Br J Cancer **1987**;56:79–82.
15. Grufferman S, Cohen HJ, Delzell ES, Morrison MC, Scholl SC, Moore JO. Familial aggregation of multiple myeloma and central nervous system diseases. Clin Res **1982**;30:418a.
16. Hammond EC. Smoking in relation to the death rates of one million men and women. NCI Monogr **1966**;19:127–204.
17. US Department of Health, Educatin and Welfare. Smoking and health. A report to the Surgeon General. Washington, DC: US Government Printing Office, **1979**.
18. Wright WE, Peters JM, Mack TM. Leukaemia in workers exposed to electrical and magnetic fields. [Letter.] Lancet **1982**;2:1160–1161.
19. McDowell ME. Leukaemia mortality in electrical workers in England and Wales. [Letter.] Lancet **1983**;1:246.
20. Coleman CN, Bell J, Street R. Leukaemia incidence in electrical workers. Lancet **1983**;1:982–983.
21. Pearce NE, Sheppard RA, Howard JK, Fraser J, Lilley BM. Leukaemia in electrical workers in New Zealand. Lancet **1985**;1:811–812.
22. Milham S, Jr. Mortality in workers exposed to electromagnetic fields. Environ Health Perspect **1985**;62:279–300.
23. Savitz DA, Calle EE. Leukemia and occupational exposure to electromagnetic fields: review of epidemiologic surveys. J Occup Med **1987**;29:47–51.