

Leukemia, lymphoma, and multiple myeloma following selected medical conditions

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The role of selected prior medical conditions in the etiology of hematopoietic malignancies was examined in a case-control study of members of two regional branches of the Kaiser Permanente Medical Care Program (USA). Past history of chronic infectious, autoimmune, allergic, and musculoskeletal disorders was abstracted from medical records for leukemia ($n = 299$), non-Hodgkin's lymphoma (NHL, $n = 100$), and multiple myeloma ($n = 175$) cases and matched controls ($n = 787$). Little difference was found between cases and controls for most of the chronic conditions evaluated, including sinusitis, carbuncles, urinary tract infections, pelvic infections, herpes zoster, asthma, rheumatoid arthritis, psoriasis, bursitis, and gout. Only three statistically significant elevated risks were found, *i.e.*, with combined disc disease myeloma among patients with prior eczema and disk and other musculoskeletal conditions, and NHL following tuberculosis. Only two of these associations showed consistent patterns by sex and geographic region (myeloma with eczema and with musculoskeletal conditions). While prior history of eczema and musculoskeletal conditions may slightly increase risk of myeloma, this study provided little if any support for an association of chronic infectious, autoimmune, allergic, and musculoskeletal conditions with subsequent occurrence of the leukemias or NHL. Additionally, these data did not support a role for chronic antigenic stimulation, as defined in previous epidemiologic studies, in the etiology of hematopoietic malignancies.

Key words: Allergy, autoimmune diseases, epidemiology, health maintenance organizations, infectious diseases, leukemia, lymphoma, multiple myeloma, musculoskeletal diseases, USA.

Introduction

Risk factors for leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma remain largely unknown. Relatively consistent associations have been reported for ionizing radiation, alkylating agents, and benzene with leukemia,¹ immunodeficiency states with

NHL,² and ionizing radiation, and farming and related agricultural exposures with multiple myeloma.³ Clinical reports⁴⁻⁷ and animal studies⁸⁻¹⁰ have led investigators to postulate that various chronic infectious, autoimmune, allergic, and possibly musculoskeletal

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disorders may be linked with subsequent onset of several hematopoietic malignancies.¹¹⁻¹³

Among patients with rheumatoid arthritis, risk of NHL has been found to be elevated significantly in both case-control and cohort studies.¹⁴⁻¹⁶ A few studies also have reported increased occurrence of multiple myeloma^{14,17} and leukemia¹⁴ following rheumatoid arthritis. There have been isolated reports linking multiple myeloma with urinary tract infections, rheumatic fever,¹³ scarlet fever, and tuberculosis,¹⁸ and a few studies reporting increased occurrence of myeloma following hay fever, asthma, and other allergies.^{17,19} NHL and chronic lymphatic leukemia have also been associated in one or two investigations with tuberculosis,^{20,21} herpes zoster, scarlet fever, eczema, and other skin conditions.²²⁻²⁴ Investigations exploring possible associations of specific hematopoietic malignancies with groups of related medical conditions (e.g., chronic bacterial infections, allergy-related disorders) generally have shown no relationship.^{11,12,25-28}

It has been suggested that these chronic medical conditions may induce lymphocyte hyperplasia through an unusually intense or protracted stimulation of the immune system (*i.e.*, chronic antigenic stimulation), allowing a greater opportunity for malignant transformation. Inconsistent associations among studies have been attributed to the insensitivity of interview data as an indicator of risk, to design differences among studies, and to variation in risk by subtype of hematopoietic neoplasm.^{1,21} An opportunity to evaluate the possible role of selected prior medical disorders in the etiology of several hematopoietic malignancies (testing what previous epidemiologic studies have termed the 'antigenic stimulation hypothesis') was presented by a case-control study designed to assess the relationship of diagnostic X-ray exposures with these malignancies.²⁹

Materials and methods

Population

Adult cases of leukemia, NHL, and multiple myeloma diagnosed during 1959-79 at the Kaiser Permanente Medical Care Program, Northwest Region (hereafter referred to as Northwest) in Portland, Oregon (United States), and during 1956-82 at the Kaiser Permanente Medical Care Program, Northern California Region (hereafter referred to as Northern California) were identified. Children younger than 15 years and cases treated previously with radiotherapy were not eligible. The histologic diagnoses recorded in the medical records were assumed to be accurate.

Controls were selected from members of the Kaiser

Permanente plan and individually matched to cases by region (approximately two controls per case in Northwest, one per case in Northern California), sex, age, number of years as a member in the program, and calendar year in which membership began. Because a substantial proportion of medical records in Northern California (18 percent) did not have a designation for race, it was not possible to match on this factor (Portland subjects were 99 percent Caucasian). There were no disease exclusions for controls. Ten percent had a diagnosis of cancer prior to the reference date, 54 percent of which were skin cancers.

An initial evaluation of 155 cases of leukemia and 178 with NHL in Northern California obtained X-ray report information only, after which the medical record abstraction was expanded to include information about prior medical conditions, prescription drug use, occupation, industry, exposure to hazardous substances, and family history of cancer. Some cases and controls from previous studies of leukemia and multiple myeloma were included in the present investigation.^{30,31}

Appropriately matched controls could not be found for 67 cases of leukemia, 35 cases of multiple myeloma, and six cases of NHL. An additional 111 leukemia, 33 myeloma, and 40 NHL cases who were program members for less than five years before diagnosis were excluded from the current analysis. Altogether, 299 patients with leukemia, 175 with multiple myeloma, 100 with NHL, and 787 controls were studied (Table 1).

Statistical procedures

A matched-set analysis taking into account a variable matching ratio was performed.³² The relative risks (RR) for the hematologic malignancies were estimated by the odds ratio. Assessment of past medical conditions was restricted to those with onset at least five years prior to diagnosis, and selected associations were examined further for disease onset at least 10 and up to 20 years prior to diagnosis. Risk also was evaluated separately by sex and geographic region. The overall risk is presented, except where meaningful differences by sex or region were noted. Analyses were carried out for leukemia, all types combined and separately by subtype, including acute myelocytic leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphatic leukemia (CLL), and other, mostly acute and unclassified leukemia (AUL); for NHL; and for multiple myeloma. Approximate 95 percent confidence intervals (CI) were computed by the Wald method;³² if there were zero exposed cases or controls, exact confidence limits were calculated.³³ A conditional logistic

Table 1. Characteristics of cases and controls by type^a of hematopoietic malignancy (% of cases)

Characteristics	Leukemia					Lymphoproliferative malignancies	
	Total (299,377) ^b	AML (133,162)	CML (55,72)	AUL (13,20)	CLL (98,123)	MM (175,219)	NHL (100,191) ^c
Sex							
Male	62.9	59.4	65.5	53.9	67.4	59.4	56.0
Female	37.1	40.6	34.6	46.2	32.7	40.6	44.0
Race							
White	77.3	71.4	78.2	100.0	81.6	73.1	98.0
Black	7.7	9.8	9.1	0.0	5.1	15.4	1.0
Asian	2.0	3.8	1.8	0.0	0.0	0.6	1.0
Unknown	13.0	15.0	10.9	0.0	13.3	10.3	0.0
Region							
Northern California	72.2	76.7	69.1	38.5	72.5	74.3	0.0
Northwest	27.8	23.3	30.9	61.5	27.6	25.7	100.0
Age at entry							
< 40	31.4	36.1	34.6	38.5	22.4	25.1	23.0
40-54	33.4	29.3	32.7	46.2	37.8	49.7	47.0
55 +	35.1	34.6	32.7	15.4	39.8	25.1	30.0
Calendar year of entry into health plan							
< 1955	36.8	33.1	36.4	30.8	42.9	40.6	24.0
1955-64	30.4	25.6	41.8	30.8	30.6	36.0	45.0
1965 +	32.8	41.4	21.8	38.5	26.5	23.4	31.0
No. years as a health plan member							
< 10	30.4	34.6	32.7	23.1	24.5	22.9	41.0
10-19	40.8	38.4	43.6	46.2	41.8	42.3	39.0
20 +	28.8	27.1	23.6	30.8	33.7	34.9	20.0
Age at diagnosis							
< 60	37.1	42.1	41.8	46.2	26.5	29.7	38.0
60-69	27.1	19.6	36.4	30.8	31.6	40.6	34.0
70 +	35.8	38.4	21.8	23.1	41.8	29.7	28.0
Year of diagnosis							
< 1970	10.4	4.5	20.0	0.0	14.3	10.3	19.0
1970-74	33.4	33.8	38.2	38.5	29.6	35.4	31.0
1975 +	56.2	61.7	41.8	61.5	56.2	54.3	50.0

^a AML = acute myelocytic leukemia; CML = chronic myelocytic leukemia; AUL = unclassified leukemia; CLL = chronic lymphatic leukemia; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.

^b Number of cases, number of controls.

^c Includes 23 cases of reticulum cell sarcoma, 73 cases of lymphosarcoma, and four other cases, from Northwest only.

regression model was used to explore potential confounders (e.g., medication use, X-ray exposures) and to assess the occurrence of interaction.³⁴

Results

Characteristics of cases and controls are presented in

Table 1. Over 60 percent of subjects were male, with an average age at program entry of 47, and a mean year of entry of 1959. Race was available for 91 percent of subjects overall, 82 percent in Northern California and 100 percent in Northwest. Most of the subjects were identified as being Caucasian (84 percent overall; 69 percent in Northern California; 99 percent in Northwest). Approximately 36 percent of subjects joined Kaiser

Table 2. Prior history of selected medical conditions and risk of hematopoietic malignancies

Medical condition		Leukemia					Lymphoproliferative malignancies	
		Total (299,377) ^a	AML (133,162)	CML (55,72)	AUL (13,20)	CLL (98,123)	MM (175,219)	NHL ^b (100,191)
Infectious								
Tuberculosis	OR ^c	1.3	0.7	7.4	0.0	1.1	2.0	2.3
	CI ^d	0.6-2.8	0.2-2.9	0.8-64.1	0.0-78.0 ^f	0.4-3.6	0.8-5.5	1.1-5.1
	(Ca*, Co*) ^e	(13,15)	(3,6)	(5,1)	(0,1)	(5,7)	(11,11)	(17,16)
Bronchitis	OR	0.6	0.5	0.5	∞	0.7	2.0	1.9
	CI	0.4-1.0	0.2-1.1	0.2-1.6	0.2-∞ ^f	0.3-1.6	1.0-3.9	0.9-4.0
	(Ca*, Co*)	(31,59)	(12,25)	(6,13)	(2,1)	(11,20)	(27,22)	(18,21)
Allergic								
Hay fever	OR	1.2	2.5	1.0	2.0	0.6	1.3	0.5
	CI	0.7-2.0	1.0-6.1	0.3-2.7	0.1-32.0	0.2-1.4	0.6-2.7	0.2-1.2
	(Ca*, Co*)	(34,37)	(17,8)	(7,11)	(1,1)	(9,17)	(18,18)	(6,24)
Eczema	OR	0.6	0.6	1.0	0.6	0.5	2.0	1.9
	CI	0.4-1.1	0.3-1.4	0.2-4.6	0.1-7.0	0.2-1.3	1.1-4.0	0.6-5.8
	(Ca*, Co*)	(22,36)	(9,15)	(3,4)	(1,2)	(9,15)	(25,15)	(7,7)
Rheumatic fever	OR	1.4	0.0	2.0	—	∞	1.5	0.6
	CI	0.4-5.0	0.0-1.8 ^f	0.1-32.0	—	1.0-∞ ^f	0.3-9.0	0.1-3.0
	(Ca*, Co*)	(5,5)	(0,4)	(1,1)	(0,0)	(4,0)	(3,2)	(2,6)
Musculoskeletal								
Disc disease and other ^g	OR	1.3	1.2	1.8	5.5	1.0	2.3	1.9
	CI	0.9-2.0	0.6-2.4	0.7-4.4	0.6-49.9	0.5-1.9	1.2-4.1	0.9-4.1
	(Ca*, Co*)	(53,53)	(18,19)	(13,12)	(4,1)	(18,21)	(36,27)	(17,21)
DJD ^h arthritis	OR	1.3	1.7	1.2	0.7	1.2	1.4	1.0
	CI	0.9-1.9	0.9-3.3	0.5-2.7	0.2-2.8	0.7-2.1	0.9-2.2	0.6-1.7
	(Ca*, Co*)	(123,146)	(49,51)	(22,28)	(4,8)	(48,59)	(85,96)	(43,83)

^a Number of cases, number of controls.^b NHL cases from Northwest only.^c OR = odds ratio.^d CI = 95% confidence interval.^e Ca* = number of exposed cases; Co* = number of exposed controls.^f Exact confidence limits computed using Thomas' program (1975) for matched sets.^g Includes disc disease and musculoskeletal conditions except for bursitis, gout, and DJD arthritis.^h DJD = degenerative joint disease.

prior to 1955, and nearly 30 percent were members for 20 or more years. Most cases (86 percent) were diagnosed between 1970 and 1979, with a mean age at diagnosis of 62. Northern California contributed three-quarters of the leukemia and multiple myeloma patients, while Northwest provided all the NHL cases.

Little difference was found between cases and controls for most conditions. Risk was not significantly increased or decreased for any of the hematopoietic malignancies following: rheumatoid arthritis (10 exposed cases, 13 exposed controls); sinusitis (22,21); boils or carbuncles (5,5); urinary tract infection (22,36); pelvic infection (22,18); herpes zoster (23,20); asthma (32,37); psoriasis (9,5); bursitis (34,44); or gout (16,13) (data not shown). Patients with rheumatoid arthritis did have a nonsignificantly increased risk for total leukemia (RR = 2.0), AML (3,0), AUL (1,0), CML (2,0),

multiple myeloma (RR = 1.2), and NHL (1,0), while a decreased risk was observed for CLL (RR = 0.3). Of over 100 comparisons made, there were only three that were statistically significant (Table 2). Given the number of cases available for study, however, we had less than 60 percent power to detect an RR of 2.0 for many of the conditions studied. Notable exceptions were degenerative joint disease arthritis, bursitis, disc and musculoskeletal disease, and chronic bronchitis.

Program members with eczema had a significantly increased risk of multiple myeloma, with elevated risk seen among both sexes (females, RR = 2.3, CI = 0.8-6.2; males, RR = 1.9, CI = 0.7-4.5) and in both geographic regions (Northern California, RR = 2.2, CI = 1.0-4.9; Northwest, RR = 1.6, CI = 0.4-6.0). After excluding those whose eczema was first reported within 10 years of their cancer diagnosis,

excess risk persisted for myeloma (RR = 2.2, CI = 1.0-4.8). This allergic skin condition also was associated positively with NHL, but inversely linked with total leukemia and its subtypes.

Significantly increased risk of multiple myeloma was associated separately with disc disease and with musculoskeletal conditions, not otherwise specified (NOS), although inverse patterns were noted in the two geographic regions. Myeloma risk following disc disease was high in Northern California (RR = 5.0, CI = 1.4-17.3) and low in Northwest (RR = 0.8, CI = 0.1-4.5), whereas myeloma risk following musculoskeletal disease was high in Northwest (RR = 3.0, CI = 1.1-7.6) and low in Northern California (RR = 0.9, CI = 0.3-2.3). Detailed review of medical record abstracts for cases and controls in Northwest revealed that the category 'musculoskeletal disease, NOS' consists of a variety of musculoskeletal symptoms and conditions, the vast majority (83 percent) of which represented aches and pains in the neck, back, or extremities. Since the origin of lower back pain is often unclear, symptoms may have been labelled differentially by physicians in the two regions as disc disease or musculoskeletal disease. These conditions consequently were combined into a single category, which was associated with increased risk of myeloma in both Northern California (RR = 2.1, CI = 1.0-4.7) and Northwest (RR = 2.4, CI = 1.0-4.7), and among both males (RR = 2.4, CI = 1.1-5.2) and females (RR = 2.1, CI = 0.1-5.3). For the combined category of disc and other musculoskeletal conditions, risk also was elevated for NHL and leukemia.

Since disc and other musculoskeletal conditions may represent early manifestations of myeloma, additional analyses were conducted using lag periods of 10, 15, and 20 years between onset of the condition and diagnosis of the cancer. Although based on small numbers, an elevated, almost fourfold risk was still observed at 20 years (RR = 3.9, CI = 0.8-19.4).

NHL was increased significantly among subjects with a past clinical history or radiologic evidence of tuberculosis. Risk was considerably higher among females (RR = 4.3, CI = 1.1-16.7) than males (RR = 1.6, CI = 0.6-4.3). A twofold excess risk for multiple myeloma and a 30 percent increased risk for total leukemia also were found among patients with tuberculosis. After excluding those whose TB-onset occurred within 10 years prior to diagnosis, however, risk of NHL was increased only moderately among patients with tuberculosis (RR = 1.6, CI = 0.7-4.0).

Additionally, there were a few observed associations that approached statistical significance. Kaiser members with a history of chronic bronchitis experienced an elevated risk of multiple myeloma; acute myeloid

leukemia was increased among subjects with hay fever, an elevated risk of CLL was seen in patients with a history of rheumatic fever, and subjects with bronchitis had a decreased risk of total leukemia. A positive association was found for degenerative joint disease with total leukemia (especially AML) and with myeloma.

Discussion

Overall, there was little evidence that past history of chronic infectious, autoimmune, allergic, or musculoskeletal conditions was linked to increased risk for any hematopoietic malignancy. There were three statistically significant associations, only two of which showed consistency by sex and geographic region (*i.e.*, myeloma with eczema and myeloma with disc and other musculoskeletal conditions).

Our finding of an increased risk for multiple myeloma among subjects with a prior history of eczema is consistent with results of a small Canadian case-control study.¹⁹ However, case-control studies of multiple myeloma in four geographic areas of the US,¹³ New Zealand,¹⁷ Baltimore (MD, USA),²⁷ and the United Kingdom³⁵ found no associations with this skin condition or other allergies.

There have been few reports linking any musculoskeletal disease with subsequent onset of multiple myeloma. The notable difference in the pattern of risk for myeloma associated separately with disc disease and with other musculoskeletal disorders between the two Kaiser programs is unlikely to reflect a real difference and more likely may be related to variations in terminology used by physicians to label these conditions. Difficulties in differentiating the origin of lower back pain may have contributed to this disparity. While Northwest employed spinal X-rays and myelograms slightly more often than Northern California, these diagnostic methods were used infrequently in both regions. To evaluate the disparity further, we combined the two conditions into one category and subsequently found little difference by region or sex.

Myeloma is thought to have a long prodromal period prior to diagnosis and musculoskeletal symptoms may represent early manifestations of the malignancy,³¹ but evaluation of this possibility using lag periods of 10, 15, and 20 years showed a persistence of the excess despite progressively smaller numbers of cases. Also, diagnostic X-ray exposure to the lower back was considered as a potential confounder, but no major differences occurred after adjustment for this exposure. We conclude it is unlikely that the musculoskeletal conditions reported represent a very early manifestation of multiple myeloma, although this

possibility cannot be excluded completely. Additionally, the observed association appears to be unrelated to X-ray exposure.

The elevated risk of total leukemia subsequent to degenerative joint disease and AML following both degenerative joint disease and disc and other musculoskeletal conditions consistent with the results found previously among cases in Northern California, as reported by one of us.³⁰ It should be noted, however, that there is considerable overlap between the cases included in the present study and those studied previously.^{30,31}

Reported associations between tuberculosis and NHL have been inconsistent. An excess of NHL was observed among tuberculosis patients in a hospital-based case-control study in northeast Italy,²⁰ but no increase of NHL was found in a cohort of 13,000 tuberculosis patients in Massachusetts (US),³⁶ nor in hospital-based case-control studies in Baltimore (MD)¹² and Yorkshire (UK).²³

A significant association for rheumatoid arthritis with NHL, as previously described,^{15,16,37,38} was not observed in our study, although patients with rheumatoid arthritis did have small increased risks of all hematopoietic neoplasms other than CLL. This probably reflected the low statistical power to detect any excess resulting from the low prevalence of rheumatoid arthritis in the Kaiser study population.

Results of prior studies were at odds with the other findings in this study. Although we found an increased risk of multiple myeloma among subjects with chronic bronchitis, no such associations were observed in a population-based study in four geographic areas of the US,¹³ in a hospital-based study in Baltimore,²⁷ or among subjects enrolled in the American Cancer Society study.³⁹ The finding of an increased risk of AML subsequent to hay fever in the two Kaiser programs was based on a small number of controls, and contrasts with significant protective effects observed in Yorkshire⁴⁰ and Seattle (WA, USA).⁴¹

To our knowledge, our study is only the third to evaluate simultaneously risk factors for several different hematopoietic neoplasms using a standardized data-collection method.^{40,42} Because cases and controls were members of a health maintenance organization providing comprehensive medical and routine preventive care, prior medical conditions were more likely to be ascertained more completely and in an earlier stage than usual in the US. Major advantages of medical records as a source of data include lower occurrence of false negatives and positives than with interviews, and minimization of recall bias. By restricting the study population to persons belonging to the health care program for a minimum of five years, and by excluding

first occurrence of the selected medical conditions within five years of diagnosis (and even 10 to 20 years for some conditions), the possibility of including early manifestations of hematopoietic malignancies was reduced further. Another advantage is that, while general medical practice has changed dramatically over the 30-year study period, there have been only minor changes in record-keeping within these health plans. It is unlikely, given the broad diagnostic categories utilized, that individuals would be classified differentially over time.

Although medical records are usually more complete for severe and life-threatening illnesses and major surgical procedures than interview data, relatively benign conditions such as hay fever and various allergies may not be recorded routinely.⁴³ The use of medical records as a source of information thus may share some of the same limitations as interview-derived data. It also is possible that conditions diagnosed prior to membership in the medical program may not have been fully ascertained. Some conditions found in the Kaiser medical records are obtained solely from patient reports and not confirmed by laboratory tests (*e.g.*, hay fever, musculoskeletal symptoms, chronic bronchitis, sinusitis); therefore, it is not clear that the accuracy of information about such disorders is truly greater in medical records than in interviews.⁴⁴ Finally, caution should be exercised because of the large number of comparisons made, the low statistical power to detect significant risks for many of the conditions evaluated, and the possible role of chance in the associations observed.

We believe this is the first case-control study that relies solely on medical record data to examine simultaneously a number of medical conditions in the etiology of various hematopoietic malignancies. The conditions evaluated were recorded without knowledge of future neoplasms arising among the subjects. In general, our study provides no support for the chronic antigenic stimulation hypothesis as defined by a history of specific medical conditions. Further epidemiologic studies examining a broad spectrum of prior conditions as a proxy for immune stimulation do not appear to be worthwhile given findings from the present medical record-based study and earlier interview studies. On the other hand, the literature suggests that immunologic perturbations contribute to the elevated risk of NHL following a few specific conditions (AIDS, therapeutic immunosuppression, genetic immunodeficiency syndromes, and rheumatoid arthritis)⁴⁵ and multiple myeloma among elderly subjects with benign monoclonal gammopathy.⁴⁶ Evaluation of these specific NHL and myeloma associations may require laboratory-based immunologic investi-

gation to clarify pathogenic mechanisms before additional epidemiologic studies will be useful.

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