FREQUENCY OF NEOPLASIA IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

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A patient population admitted to the hospital for either SLE or RA was surveyed for the subsequent development of neoplasms. The frequency of neoplasm in SLE patients appeared to be exaggerated, whereas the frequency of subsequent neoplasm in rheumatoid patients was unexpectedly low. A paucity of nephritis in the SLE group was noted. Further reports are encouraged so that the magnitude of the risk of malignancy developing with immunosuppressive therapy can be more precisely ascertained.

Laboratory abnormalities suggesting that autoimmune mechanisms are responsible for some of the lesions seen with several of the connective tissue diseases have led to use of immunosuppressive drugs in the management of these disorders. Concern that such agents might impair immunologic "monitoring" of neoplasia has been heightened by sporadic reports of neoplastic diseases appearing during or following such therapy (1–3). It is important to determine the natural frequency of neoplasia in these diseases in order to assess any possible drug-related increases in the frequency of neoplasm developing during the course of any one of the connective tissue diseases.

Recently eight neoplasms were reported in 70 patients with systemic lupus erythematosus (4). This communication reports the experience with neoplasia in patients hospitalized with rheumatoid arthritis and systemic lupus erythematosus in a large teaching hospital for the 20-year period, 1955–1974, and focuses on patients whose connective tissue disease clearly preceded detection of neoplasm. The frequency of neoplasm developing in a group of patients with benign essential hypertension who were seen in the same period is reported as a possible control observation.

MATERIALS AND METHODS

The patient populations to be compared were selected by computer retrieval of all medical records of hospital admissions for systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), rheumatoid arthritis (RA), and benign essential hypertension during the period 1955–1974. Patient diagnoses are coded by the ICDA and HICDA systems and stored in an IBM 370/145 computer using the Mark IV Informatic's data retrieval system. Only those hypertensive patients were included whose blood pressure abnormality was the primary diagnosis at the initial admission.

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Table 1. *Incidence of New Cancer Cases**

Year	Hospital Registrations	New Cancer Cases	Percent
1955	48,820	1,705	3.49
1956	50,073	1,735	3.46
1957	50,659	1,673	3.30
1958	49,711	1,574	3.17
1959	50,609	1,465	2.89
1960	51,947	1,280	2.47
1961	54,402	1,746	3.22
1962	56,211	1,651	2.95
1963	57,944	1,802	3.12
1964	60,049	1,835	3.05
1965	63,086	1,903	3.02
1966	64,393	1,683	2.62
1967	65,141	1,681	2.59
1968	68,280	1,849	2.71
1969	71,771	1,615	2.26
1970	75,064	1,567	2.08
1971	76,199	1,815	2.38
1972	69,315	1,742	2.51

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Patients identified in the four primary disease categories were then cross-checked against the tumor registry of the University of Michigan Hospital. This registry now includes data concerning approximately 62,000 malignant and certain benign neoplasms. Recorded data include information on the patients' sex, age, race, age at onset of neoplasm, location and histology of neoplasm, extent of disease, type of treatment, and length of survival (5). The relative frequency of neoplasm in the population visiting the University of Michigan Hospital over the study period has been approximately 2–3% of total hospital registrations (Table 1).

Patients with neoplasms included in this study met the American Rheumatism Association's criteria for SLE (6) or for definite/classic RA (7). This study attempted to focus on those patients with one of the four primary diagnoses who developed neoplasms 1 year or more after the primary diagnosis. Thus two records were excluded because the neoplasm preceded connective tissue disease, or because the diagnosis of both was established within the same year. Nineteen patients with other connective tissue diseases or with nonmalignant tumors were excluded from the present study. One hundred forty-two records from hypertensive patients were rejected either because the neoplasm preceded the hypertension or because the diagnoses were made at the same time. The age, sex, and racial characteristics of the four primary diagnostic groups at the time of initial hospital admission are summarized in Table 2.

Although there are problems inherent in a retrospective record review, it is likely that these data may help to establish the frequency (period prevalence) of occurrence of neoplasia in SLE and RA. Clearly, a study of this nature presumes that neoplasms developing in the rheumatic and hypertensive patients would be known at the University Hospital and included in the tumor registry. Because all hospital records are reviewed by a Records Completion Unit, virtually all patients are included in the tumor registry if the University of Michigan Hospital was involved in the diagnosis, management, or follow-up of their neoplasm. Although one cannot exclude the possibility that some rheumatic or hypertensive patients may have developed malignancies that were managed at other institutions, some indirect evidence suggests that the quality of follow-up of the four primary diagnostic groups is comparable. Of patients attending arthritis, hypertension, or neoplasm-related clinics during a 6-month period in 1975, 76%, 88%, and 74%, respectively, came from the adjacent twelve-county area in southeastern Michigan. Thus it is clear that patients recorded in the tumor registry come largely from the same small geographic area from which the rheumatic and hypertensive patient populations were drawn. The likelihood that rheumatic or hypertensive patients who developed a malignancy would be known to the tumor registry is a function of the practices and characteristics of the outpatient clinics providing follow-up care. Both the arthritis and hypertension clinics have had little turnover in senior staff during the period

Table 2. *Characteristics of Primary Diagnostic Groups*

Characteristic	Hypertension	RA	SLE	DLE
Total patients	3,295	2,867	484	253
Female (%)	49	64	83	68
Black (%)	18	6	14	13
White (%)	82	94	86	87
Age (mean ± SD)				
Female	44.2 ± 12.7	46.4 ± 17	33.8 ± 15.3	39.6 ± 14.7
Male	45.7 ± 13.4	47.1 ± 18.2	38.3 ± 18.4	42.6 ± 15.2

Table 3. *Types of Neoplasms Seen in Patients with RA, DLE, and SLE*

Neoplasm	RA	DLE	SLE
Carcinoma of cervix and uterus	4	1	6
Basal cell carcinoma of skin	4	0	0
Squamous cell carcinoma of lung	2	2	1
Reticulum cell sarcoma	1	0	2
Melanoma	1	0	0
Adenocarcinoma colon	1	0	1
Adenocarcinoma lung	1	0	2
Adenocarcinoma esophagus	1	0	0
Adenocarcinoma stomach	0	0	1
Adenocarcinoma breast	0	1	2
Squamous cell carcinoma of skin	0	0	1
Oat cell carcinoma of lung	1	0	0
Hodgkin's disease	1	0	1
Follicular cell carcinoma of the thyroid	0	0	1
	—	—	—
	17	4	18
Total patients	2,867	253	484

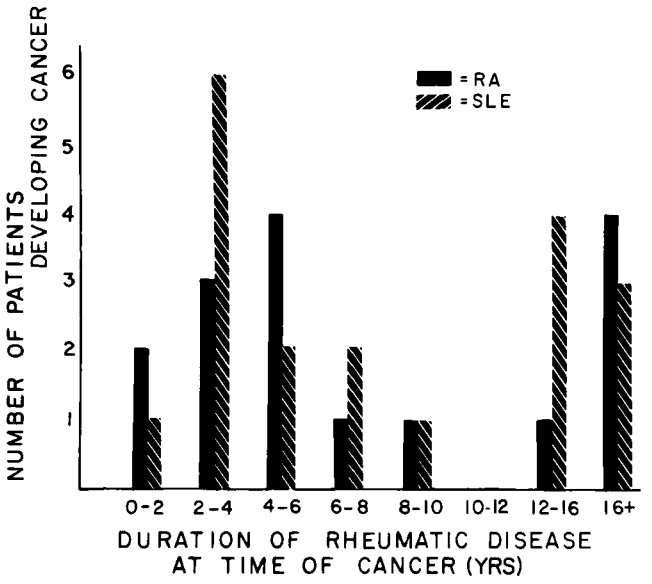

Fig 1. *Duration of rheumatoid arthritis or systemic lupus erythematosus in patients who subsequently developed neoplasms.*

1955–1974. Both clinics see 4,000–5,500 outpatients per year, over 80% of which are follow-up (return) visits.

RESULTS

Lupus Erythematosus

A total of 737 patients were admitted to the hospital with the diagnosis of lupus erythematosus during the 20-year review period. Patients with chronic discoid lupus (DLE) constituted approximately one-third of the group (253 patients) and were considered separately. Four neoplasms were found in the DLE group (Table 3). A total of 484 patients with SLE were at risk. SLE patients with neoplasms had a mean age of 42.5 years (± SD = 9.8 years; range: 32–63 years). The 18 SLE patients with neoplasms included 13 females (10 whites, 3 blacks). The mean time from diagnosis of systemic lupus to diagnosis of neoplasm was 7 years, with a range of 1–18 years (Figure 1).

The several types of malignancies found are recorded in Table 3. As noted in Table 4, nearly 4% of this particular SLE population ultimately developed some kind of malignancy. Table 5 records the frequency of the different classification criteria for SLE, and Figure 2 depicts the frequency distribution of the number of diagnostic criteria detected in individual patients. It is apparent that most patients had more than the minimum criteria (6) required for the diagnosis of SLE.

Laboratory abnormalities, shown in Table 6, were those expected with SLE. All patients were treated with adrenal corticosteroids, but only 1 received 60 mg of prednisone per day or more, and for only 1 month. The other patients generally received 20 mg of prednisone or its equivalent daily, or less. Only 1 patient, a 46-year-old woman with thrombocytopenia and hemolytic anemia, had been treated with immunosuppressive drugs. She had received cyclophosphamide, 100 mg daily for 6 days, and 1 year earlier had been treated for 2 months with 6-mercaptopurine, 50 mg daily. Her last exposure to these medications had been 18 months before the diagnosis of adenocarcinoma of the lung.

Table 4. *Statistical Summary of "Period Prevalence"*

Primary Diagnosis		Subsequent Neoplasms		
Type	No. of Patients	Number	Percent	Statistical Significance*
Benign essential hypertension	3,295	44	1.36	—
RA	2,867	17	0.59	$P < 0.005$
DLE	253	4	1.58	$P > 0.70$
SLE	484	18	3.72	$P < 0.0005$

* Computed by χ^2 analysis.

Rheumatoid Arthritis

A total of 2,867 patients were admitted to the hospital with the diagnosis of rheumatoid arthritis during the study period. Seventeen neoplasms were found in

Table 5. *Incidence of Criteria for the Classification of SLE in 18 Patients with Neoplasia*

Criteria	Patients	Percent
Nondeforming arthritis	17	94
Hematologic abnormalities*	15	81
Leukopenia—9		
Hemolytic anemia—6		
Thrombocytopenia—2		
Nervous system involvement	4	25
Renal involvement	1	6
Pleurisy	13	63
Mucocutaneous involvement		
Discoid lupus	4	25
Mucocutaneous ulcers	3	19
Facial erythemia	12	63
Alopecia	5	31
Raynaud's phenomenon	7	44
Photosensivity	5	25
False positive STS	3	19

* Some patients had more than one abnormality.

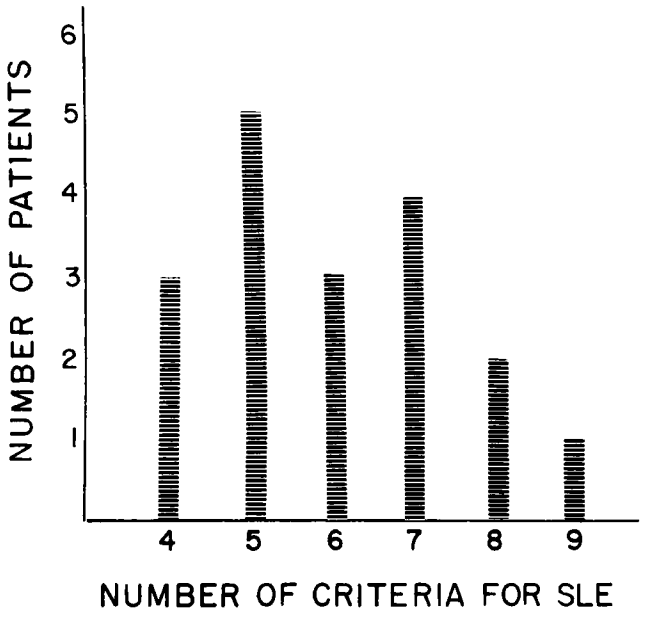

Fig 2. *All patients exhibited at least four criteria supporting the diagnosis of systemic lupus erythematosus.*

this group of patients, an overall "period prevalence" of approximately 0.6%. Patient ages ranged from 45 to 79 with a mean of 61.2 ± 8.3 years. Nine patients were males, of whom 2 were black, and all 8 females were white. At the time of diagnosis of neoplasm, these patients had had RA for a mean of 10 years (range: 1–23 years; see Figure 1). The types of malignancies found in the RA group are shown in Table 3. Table 7 records the clinical characteristics of the patients with RA. Laboratory findings in the RA patients are presented in Table 8. There were 2 patients with clinical and laboratory features compatible with Felty's syndrome. One had a melanoma and the other had a basal cell carcinoma of the skin and squamous cell carcinoma of the lung. Two patients had Sjögren's syndrome; 1 developed oat cell carcinoma of the lung and the other had adenocarcinoma of the uterus. Interestingly, 7 of the 17 patients with both RA and neoplasm had family members with neoplasms, but none was of the same type found in the proband.

Table 6. *Laboratory Characteristics of Patients with SLE and Neoplasia*

Test	Patients Positive	Percent
Positive LE preparations	17 of 18	94
Positive ANA test	11 of 16	69
Positive latex fixation	2 of 16	13
Elevated DNA binding	3 of 9	33
Decreased complement (CH_{50})	2 of 10	20

Table 7. *Clinical Criteria for the Diagnosis of 17 RA Patients with Neoplasia*

Criteria	Patients	Percent
Morning stiffness	17	100
Soft tissue swelling	17	100
Pain or tenderness of joints	17	100
Symmetric joint swelling	17	100
X-ray abnormalities	15	88
Subcutaneous nodules	14	82
Positive rheumatoid factor	17	100

Ten of 17 patients in this group had been treated with adrenal corticosteroids, 3 in "bursts" and the other 7 continuously for 1–20 years. The type of malignancy in these patients varied, but three-quarters of the patients with basal cell carcinoma had been treated with prednisone. None of the RA patients had received other forms of immunosuppressive therapy.

Benign Essential Hypertension

Among 3,295 persons admitted to the University Hospital primarily for their hypertension during the period 1955–1974, 44 (1.36%) subsequently developed neoplasms that were recorded in the tumor registry. There were 24 female patients with a mean age of 51 ± 11.3 years and 20 male patients with a mean age of 57.9 ± 9.1 years.

DISCUSSION

Studies by Penn, which led to the development of an informal tumor registry for renal transplant patients, documented an increased incidence of neoplasia in patients treated with immunosuppressive drugs for prolonged periods (3). Leibowitz and Schwartz (2) have also suggested that neoplasia can be anticipated as a complication of immunosuppressive therapy. It is important to determine the baseline frequency of neoplasia in association with the connective tissue diseases so that the potential increased occurrence of neoplasms in drug-treated cases can be recognized.

Table 8. *Laboratory Findings in Patients with RA and Neoplasia*

Lab Finding	Patients	Percent
Positive rheumatoid factor	17 of 17*	100
Positive ANA	8 of 10	80
Poor mucin clot	3 of 3	100
Consistent node histology	1 of 1	100
Felty's syndrome	3 of 17	18
Sjögren's syndrome	2 of 17	12

* Early tests (1955–1963) were considered positive at any titer. Later tests were positive in a titer of at least 1/640.

Ragan and Snyder noted the appearance of cancer in 2% of 374 patients with rheumatoid arthritis followed for 5 years (8). Owens *et al* (9) reviewed 196 patients with definite or classic RA and found 8 (4.1%) who had cancer. The types of tumors were also the same as would be expected in the general population. There have been several studies of rheumatic populations showing an apparent increase in lymphoreticular neoplasms (10–17), something not apparent in the present patients or in those reported by Ragan and Owens.

The neoplasms detected in this study comprise a general spectrum of histologic types of malignancy with no emphasis on lymphoproliferative disorders. However a referral center seeing patients with severe and complicated diseases may yield data not representative of the general population of SLE and RA patients.

Data from the SLE patients with neoplasms nevertheless deserve special comment. This group was unusual in that only 1 patient had renal disease. Canoso and Cohen noted that 50% of their patients had renal disease (4). Although this finding may mean that nephritis causes death before neoplasia can develop, more subtle mechanisms influencing susceptibility to tumor development cannot be excluded. Walker and Bole have reported an increased occurrence of lymphomas in NZB/NZW mice treated with long-term cyclophosphamide to suppress nephritis (18). In contrast to the RA patients, those with SLE developed their neoplasms at a younger mean age.

The sex distribution of SLE patients with neoplasms paralleled the usual sex ratio in this disease. However more than half the RA patients with malignancy were males. The apparent "protection" against neoplasia offered by RA (or aspirin?) is interesting. An alternative possibility might hold that benign essential hypertension, or its treatment modalities, are associated with a higher than normal frequency of malignancy. Clearly, a control study with a population group simply followed for periodic health examinations would be valuable. No special clinical characteristics, other than the decreased frequency of nephritis in SLE cases, were identified in the DLE, SLE, or RA patients that were predictive of later development of malignancies.

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