SCIENTIFIC PAPERS

Increased risk of cancer in patients with systemic lupus erythematosus

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Abstract

To evaluate the risk of cancer in patients with systemic lupus erythematosus (SLE) a series of 205 consecutive patients (182 women and 23 men) were followed up for cancer through the files of the Finnish Cancer Registry. The follow up consisted of a total of 2340 person years. Fifteen cancers were diagnosed against 5.7 expected (relative risk (RR) 2.6, 95% confidence interval (CI) 1.5 to 4.4). Among the women there were four non-Hodgkin's lymphomas against 0.09 expected (RR 44, CI 11.9 to 111) and two soft tissue sarcomas against 0.04 expected (RR 49, CI 6.0 to 177). When evaluated by a case control study previous treatment with cytostatic drugs showed no influence on the occurrence of cancer in this series of patients with SLE.

Patients with systemic lupus erythematosus (SLE) are reported to have an increased risk of cancer, especially lymphomas. This association has been documented in a number of case reports, but in only a few studies of larger series of patients.¹⁻³ We analysed the occurrence of malignant tumours in a series of 205 patients with SLE treated at a university clinic in Helsinki during a 21 year period. We also studied the possible influence of cytostatic drug treatment on the development of cancer in these patients.

Patients and methods

The study population consisted of 182 women and 23 men with SLE treated at the Fourth Department of Medicine, Helsinki University Central Hospital from 1967 to 1987. SLE was diagnosed according to the 1971 criteria of the American Rheumatism Association.⁴ In 41 patients the diagnosis of SLE had been made before the beginning of the follow up in Helsinki. Patients with discoid or drug induced lupus were excluded.

The patients were followed up for cancer through the files of the Finnish Cancer Registry and for death through the Central Statistical Office of Finland. The follow ups were carried out by using the personal identification code given to everyone residing in Finland. Calculation of person years at risk and follow up for cancer started on 1 January 1967, or at the date when the patient came to the Fourth Department of Medicine, Helsinki University Central Hospital, whichever was later, and ended at the

time of death or 31 December 1987, whichever occurred first. The follow up was complete. The total number of person years at risk was 2340.

The observed numbers of cancer were compared with those expected on the basis of the sex specific and age specific person years at risk, and the mean sex specific and age specific cancer incidence rates for the total Finnish population in 1967-87 produced by the Finnish Cancer Registry. The relative risk (RR) was defined as the ratio between the observed and expected numbers of cancers. The statistical significance of the relative risks was estimated assuming that the observed numbers followed a Poisson distribution.

To study whether the incidence of cancer was influenced by treatment with cytostatic drugs, three controls (at maximum) matched by age (± 6 years) and year of onset of SLE (± 3 years) were selected for each patient with cancer. For this analysis it was possible to also include those patients diagnosed after the closing date of the cohort analysis. The controls were followed up for cytostatic drug treatment as long as follow up was recorded for their index patient. The odds ratio and its 95% confidence interval (CI) were estimated using the exact method for stratified 2×2 tables.⁵

Results

During the follow up period 1967-87, 13 cancers were diagnosed in women against 5.2 expected (RR 2.5, 95% CI 1.3 to 4.3). There were four non-Hodgkin's lymphomas (0.09 expected; RR 44, CI 11.9 to 111), three of which were of the large cell type, two soft tissue sarcomas (0.04 expected; RR 49, CI 6.0 to 177), both of which occurred in the lower limb, and four breast cancers (1.5 expected; RR 2.7, CI 0.7 to 6.8). Two of the breast cancers were diagnosed in the same patient (1977 in the right breast and seven years later in the left), and one was a lymphoma which originated in the breast. Three other cancers (one pancreatic carcinoma, one carcinoma of the cervix uteri, and one papillary thyroid carcinoma) were observed against 3.5 expected.

One renal adenocarcinoma and one melanoma of the skin were detected in the men. The total expected number was 0.5 (RR 3.8, CI 0.5 to 14).

The RR for cancer (men and women taken together) remained unchanged during follow up. During the first five year follow up period, the RR was 2.9 (4/1.40), and after five years 2.6

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Clinical data for 17 patients with systemic lupus erythematosus (SLE) and cancer

Patient	Age ^a /sex	Duration of SLE when cancer was diagnosed (years)	Type of cancer
1	45/F	10	Non-Hodgkin's lymphoma
2	29/F	12	Non-Hodgkin's lymphoma
3	45/F	15	Non-Hodgkin's lymphoma
4	34/F	19	Non-Hodgkin's lymphoma
5	33/F	25	Non-Hodgkin's lymphoma†
6	23/F	30	Non-Hodgkin's lymphoma†
7	34/F	7	Extranodal non-Hodgkin's lymphoma in breast
8	69/F	11	Soft tissue sarcoma
9	35/F	17	Soft tissue sarcoma
10	73/F	2 and 9	Breast carcinomas
11	29/F	19	Breast carcinoma
12	57/F	8	Pancreatic carcinoma
13	36/F	3	Carcinoma of the cervix uteri
14	46/F	12	Papillary thyroid carcinoma
15	59/F	2	Hepatocellular carcinoma†
16	56/M	3	Renal carcinoma
17	67/M	8	Melanoma

^aAt diagnosis of SLE (years).

†Diagnosed after closing date 31 December 1987 of the cohort analysis.

(11/4·29). The mean duration of SLE when cancer was diagnosed was 12 (range 2–30) years. The table gives the clinical data on the patients who developed cancer during the follow up.

For the case referent part of this study it was possible to also include those patients diagnosed after the closing date of the cohort analysis. In the files of the Finnish Cancer Registry there were two women with lymphomas (patients 5 and 6, table) and one man with primary liver cancer (patient 15) diagnosed in 1988–89 (for which period the registration was not yet complete). As a result of the strict selection criteria no controls were found for the two male patients with cancer. The average number of controls for the remaining 15 patients with cancer was 2·1. Two of the patients who developed cancer (patient 1 and patient 6, table) had received treatment with cytostatic drugs (cyclophosphamide) before the diagnosis of cancer. Cyclophosphamide had been stopped eight months and 11 years, respectively, before cancer was diagnosed. Of the 34 case controls eight had received treatment with cytostatic drugs (four cyclophosphamide, three azathioprine, and one cyclophosphamide and chlorambucil) during follow up. The odds ratio related to cytostatic treatment was 0·6 (not significant, CI 0·06 to 3·5).

Discussion

There is increasing evidence to suggest a link between autoimmune diseases and cancer.^{6,7} Patients with rheumatoid arthritis have an increased risk of developing cancer of the lymphatic and haemopoietic systems,⁸ and patients with Sjögren's syndrome have an increased risk of malignant lymphoproliferative disease.⁹ Only a few studies have tried to evaluate the risk of malignant tumours in patients with SLE.

The belief that SLE is associated with lymphoma is based on several case studies, now consisting of at least 100 patients.⁶ The animal models of SLE in which malignant lymphoma and macroglobulinaemia develop spontaneously,

support this view.¹⁰ Canoso and Cohen reported eight cancers in 70 patients with SLE.¹ Two of their patients had malignant lymphoproliferative disease, but it is noteworthy that most of the malignancies in their series represented superficial non-invasive tumours. Lewis *et al* reported an increased risk of malignancy in a series of 484 patients with SLE.² The malignant tumours in their series consisted of the general spectrum of sites and histological types, with no emphasis on lymphoproliferative disorders. Black *et al* found no increased risk of malignancy in their series of 39 patients with SLE.¹¹ The study of Rubin *et al* indicates that patients with SLE have an increased occurrence of monoclonal immunoglobulins compared with the general population.¹²

Patients with SLE have defects in their cellular and humoral immune systems. The basic defect in SLE in humans is suggested to be a deficiency in suppressor T cell function, which leads to proliferation and hyperactivity of B lymphocytes.¹³ Prolonged stimulation of B lymphocytes together with a defective immune surveillance could result in autonomous B cell clones. Studies indicate that autoimmune diseases and B cell lymphoproliferative disorders may arise from similar mechanisms.¹⁴ Certain B lymphocytes (CD5+ B cells) have a strong tendency to undergo oligoclonal or monoclonal proliferation and malignant transformation.¹⁵ Moreover, increased expression of certain proto-oncogenes has been found in lymphocytes of patients with SLE.¹⁶

The results of this study show that cancer, especially lymphoma and soft tissue sarcoma, is more common in patients with SLE than in the general population. The four non-Hodgkin's lymphomas detected produced a risk ratio of 44 in women with a 95% CI of 12 to 111. Two additional lymphomas were diagnosed during the next two years of follow up. Furthermore, one of the breast cancers was an extranodal lymphoma, which is extremely rare. Hence extension of the follow up time (not yet possible) and inclusion of the extranodal lymphoma would clearly make the risk ratio higher (and the CI narrower).

The observed incidence of cancer within the cohort and the expected numbers were based on an independent data source—that is, the files of the population based countrywide cancer registry. This clearly improves their comparability.

All our patients had true clinical SLE, and none was considered to have a malignant tumour with only a lupus-like syndrome.¹⁷ There was no particular clinical or serological pattern which seemed to predispose to cancer. Patients who developed SLE later in life seemed most susceptible to cancer, which obviously reflects the higher incidence of cancer in older than in younger people.

Whether treatment with cytostatic drugs contributes to the development of cancer in patients with SLE has been a subject of concern. In our study cytostatic drugs did not seem to increase the risk of cancer; two of 15 (13·3%) of the patients with SLE who developed cancer had received cytostatic drugs, whereas

eight of 34 (23.5%) controls had received cytostatic drugs. The RR for total cancer did not increase during the time of follow up after diagnosis of SLE, which does not support the suggestion that treatment of SLE with cytostatic drugs increases the risk of cancer.

In conclusion, we observed an increased risk of cancer, particularly lymphomas and soft tissue sarcomas, in patients with SLE. Development of cancer in our patients was obviously related to SLE itself rather than to treatment with cytostatic drugs. The part played by cytostatic drugs in the development of malignancy in SLE should, however, be further addressed in a larger study.

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