Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis*

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SUMMARY The incidence of malignant neoplasms among 11 483 male and 34 618 female individuals with rheumatoid arthritis was studied using two separate nationwide data registers covering the whole Finnish population: the Social Insurance Institution's Population Data Register, which includes information on medication for certain chronic diseases, and the Finnish Cancer Registry, with data on all cancer patients diagnosed in Finland. The follow-up comprised a total of 213 911 person years. The total incidence of all malignant neoplasms was higher in males and on the level expected in females. The expected number of cases of leukemia, lymphomas, Hodgkin's disease and myeloma in both sexes was 59.6 as compared with the 130 cases observed. This difference is statistically highly significant ($p < 0.001$). The incidence of cancer of the respiratory organs was higher in males, and the incidence of cancer of the rectum and stomach lower than expected in rheumatoid females.

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Conflicting evidence has been presented on the risk of malignant neoplasms in patients with rheumatoid arthritis (RA). Moesman¹⁵¹ found cancer to be twice as common in rheumatoid patients as in the general population. On the other hand, the proportion of malignant neoplasms as a cause of death in patients with rheumatoid arthritis was lower than that in controls matched for sex and age.¹⁰² Cancer was under-represented in two autopsied series of rheumatoid arthritis.^{13 156} Lewis *et al*¹²⁶ found that cancer was less common in hospitalized RA patients than in patients with hypertension.

Special attention has been paid to the simultaneous occurrence of lymphoproliferative neoplasms and inflammatory rheumatic diseases such as RA.^{26 29 149 234} Oleinick¹⁶¹ studied the literature in English published up to December 1965. He collected a series of 951 RA patients with 9346 person

years at risk from published case reports. No support was found for the hypothesis that there is an increased risk of leukemia or lymphoma in RA patients. Miller¹⁴⁹ found the same prevalence of RA in patients with solid tumors (0.42%) or lymphoproliferative neoplasms (0.38%) as in the general American population (0.38%).

It is possible that the immunological abnormality in RA patients increases the risk of contracting leukemia, lymphoma, or myeloma. The case reports cannot, however, resolve this question. The potential significance of this hypothesis in an understanding of the pathogenesis of these malignancies warrants further investigation.¹⁶¹

In this study the incidence of cancer in a large series of patients with rheumatoid arthritis was evaluated.

Patients and methods

The incidence of malignant neoplasms in rheumatoid arthritis patients was studied by making use of two computerized nationwide data registers, the Social Insurance Institution's Population Data Register and the Finnish Cancer Registry.

The Social Insurance Institution's Population Data Register has included information since 1965 on patients with chronic diseases entitling them to reimbursable medicines. One such disease is rheumatoid arthritis. The category 'rheumatoid arthritis' in this register also includes systemic connective tissue diseases (before 1970) and ankylosing spondylitis (from 1970 onwards). In 1974, subjects with ankylosing spondylitis accounted for 2.2% of all patients and those with systemic connective tissue diseases for 1.7% of all patients in the register.¹⁷⁰

The Finnish Cancer Registry²¹³ was started in 1952, and according to established health service practice, every cancer case is reported to this registry. Reporting has been obligatory since 1961. The registry receives information from multiple sources: from hospitals (at various stages of the disease), from practitioners, and from pathological laboratories. Moreover, the registry makes an annual screening of

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all death certificates issued in the country, and thus is informed of the death of cancer patients from both cancerous and non-cancerous causes. On average, five notifications are received per case.

The patients entitled to fully reimbursable medication because of RA during the period 1967–1973 were retrieved from the Social Insurance Institution's Population Data Register. A total of 11 483 male and 34 618 female RA patients were identified.

This RA patient series was matched against the Finnish Cancer Registry. The series was followed up for new cancer cases on or after 1 January 1967, from

TABLE 1 All malignant neoplasms in males by age

Age	Number of rheumatoid patients	Person years at risk	Observed	Expected
0–4	34	38.1	0	0.0
5–9	94	234.3	1	0.0
10–14	107	384.5	0	0.0
15–19	151	575.8	0	0.1
20–24	340	1061.4	1	0.2
25–29	457	1649.8	0	0.4
30–34	611	2201.4	1	0.8
35–39	772	2948.6	2	1.8
40–44	1063	3920.3	7	4.3
45–49	1181	4997.8	11	10.1
50–54	1397	5659.7	24	21.7
55–59	1760	7301.4	60	48.7
60–64	1691	7855.0	95	85.2
65–69	998	5674.3	99	83.4
70–74	515	2883.3	50	56.2
75–79	222	1262.2	42	29.0
80–84	78	408.4	14	10.1
85–	12	74.8	0	2.1
All	11 483	49 131.0	407	354.1

The approximated Poisson confidence limits for the observed number of cases: 95%, 368.4–448.6; 99%, 356.7–461.7.

TABLE 2 Occurrence of different malignant neoplasms in rheumatoid males

Primary site	Observed	Expected	Statistical significance
Lip, oral cavity	12	13.27	NS
Esophagus	5	7.45	NS
Stomach	51	53.55	NS
Colon	11	9.88	NS
Rectum	7	10.99	NS
Liver, primary	5	3.25	NS
Gallbladder	2	2.16	NS
Pancreas	16	14.35	NS
Respiratory organs	171	132.75	p<0.01
Melanoma of the skin	4	3.20	NS
Skin other, excluding basaloma	8	6.65	NS
Prostate	30	30.43	NS
Urinary organs	14	20.88	NS
Brain	9	5.27	NS
Thyroid gland	2	1.44	NS
Hodgkin's disease	5	2.28	NS
Lymphomas	13	4.84	p<0.01
Myeloma	7	3.26	p<0.05
Leukemia	18	7.10	p<0.01
Other and unspecified sites	17	21.11	NS
All	407	354.11	p<0.01

TABLE 3 All malignant neoplasms in females by age

Age	Number of rheumatoid patients	Person years at risk	Observed	Expected
0–4	97	130.3	0	0.0
5–9	157	599.3	0	0.1
10–14	205	743.8	1	0.1
15–19	460	1336.5	0	0.2
20–24	751	2861.4	1	0.6
25–29	1079	4060.4	1	1.2
30–34	1467	6085.8	4	3.4
35–39	2007	8156.8	9	8.4
40–44	2673	11 382.0	16	18.8
45–49	3481	15 028.9	43	40.7
50–54	4570	19 083.4	58	64.6
55–59	5774	25 843.3	94	105.8
60–64	5130	27 535.3	153	151.0
65–69	3260	20 631.5	163	147.5
70–74	2065	12 123.6	114	116.5
75–79	1075	6364.5	89	79.4
80–84	290	2248.3	37	35.2
85–	77	565.5	12	10.5
All	34 618	164 780.4	795	783.8

The approximated Poisson confidence limits for the observed number of cases: 95%, 740.7–852.3; 99%, 724.0–870.3.

TABLE 4 Occurrence of different malignant neoplasms in rheumatoid females

Primary site	Observed	Expected	Statistical significance
Lip, oral cavity	10	13.32	NS
Esophagus	21	20.38	NS
Stomach	80	99.76	p<0.05
Colon	33	39.26	NS
Rectum	20	34.47	p<0.05
Liver	6	5.85	NS
Gallbladder	10	14.32	NS
Pancreas	32	30.00	NS
Respiratory organs	34	30.98	NS
Melanoma of the skin	17	10.82	NS
Skin other, excluding basaloma	18	16.58	NS
Breast	153	148.67	NS
Cervix uteri, excluding <i>in situ</i>	56	53.76	NS
Corpus uteri	50	50.01	NS
Ovary	39	46.83	NS
Other genital organs	11	10.82	NS
Urinary organs	31	27.79	NS
Brain	20	15.80	NS
Thyroid gland	7	10.92	NS
Hodgkin's disease	14	4.54	p<0.001
Lymphomas	25	9.34	p<0.001
Myeloma	21	9.49	p<0.001
Leukemia	27	18.74	NS
Other and unspecified sites	60	61.33	NS
All	795	783.78	NS

the time at which RA medication was prescribed until 31 December 1973, or the death of the patient (a total of 213 911 person years). Malignant diseases contracted before the diagnosis of RA were excluded.

The numbers of various types of neoplasms in both sexes were compared with those expected on the basis of the national cancer morbidity figures for the years 1966–1970.²¹³ The significance of the differences was tested on the assumption that the observed number of cases followed a Poisson distribution.⁵⁷

Results

A total of 407 neoplasms were observed in males, the expected number of cases being 354.1. This difference is statistically significant ($p < 0.01$, table 1). The incidence of leukemia, lymphomas, myeloma, and cancer of the respiratory organs was significantly higher in rheumatoid patients than in the general male population (table 2).

In females, the incidence of malignant neoplasms was approximately equal to that expected (table 3). An excess of leukemia was observed, but the difference was not statistically significant. The incidence of lymphomas, myeloma and Hodgkin's disease was significantly higher in females too, while the incidence of cancer of the stomach and rectum was lower than expected (table 4).

The expected number of all cancers of the lymphatic system (leukemia, lymphomas, Hodgkin's disease, and myeloma) in both sexes was 59.6 compared with the 130 cases observed. This difference is statistically highly significant ($p < 0.001$).

Discussion

Both data registers used in this study cover the whole Finnish population. This is one major advantage of a small population (4.7 million). In addition, it is possible to avoid the problems facing investigators who have used hospital registers on tumors. When a study is based on hospital patient registers, it is always possible that some rheumatoid patients have malignancies that have been treated at other institutions, and the frequency of malignant neoplasms therefore seems low.

It is probable that the drug user data of the Social Insurance Institution's Population Data Register do not include all Finnish RA patients. According to this register, the prevalence of RA among the whole population in 1971 was 0.3% in males and 1.0% in females. These figures are low compared with the prevalence of RA obtained in epidemiological studies¹⁴⁸ which, however, usually only apply to prevalence in adult populations. On the other hand, the Finnish Cancer Registry includes practically all diagnosed cancer cases in the country.²¹³

Cancer has been reported to be more common among patients with systemic lupus erythematosus than among, for example, those with RA and hypertension¹²⁶ or among the general population.²⁹ The prevalence of all systemic connective tissue diseases, including SLE, in this population was only 1.7%. It is probable that this does not significantly change the incidence of cancer in the total series. Moreover, no

cancers were found among the causes of death of 30 SLE patients in the series of Feng *et al.*⁶⁶

Many malignant neoplasms can cause rheumatic manifestations. This is especially true in children, in whom the clinical picture may suggest, e.g. juvenile rheumatoid arthritis.²⁶ Multiple myeloma may confusingly resemble RA.²³⁴ Carcinoma polyarthritis is sometimes clinically indistinguishable from RA.²⁶ If these rheumatic manifestations preceded the overt appearance of malignancy, the patient may have been registered first as RA. Such cases are, however, rare and probably have no significant influence on the results.

In general, the incidence of epithelial cancers was as expected. The higher than expected incidence of cancer of the respiratory organs in males and the lower than expected incidence of cancer of the rectum and stomach in females may be due to chance. However, Bradley *et al.*¹¹ found an association between rheumatoid factor positivity and lung cancer in a British population.

The excess risk of lymphomas, leukaemia, and myeloma in patients with RA seems indisputable. There has been discussion on whether or not continuous immunological stimulation in RA causes proliferation and malignant transformation of some clones of immunologically competent cells.²³⁵ Hyperplasia of the lymphoid system is one of the characteristics of RA, and plasmocytosis is frequently seen in this disease. Miller¹⁴⁹ discusses the theories on the etiologic relationship between immune diseases and malignant lymphomas. In his series of 17 patients, the onset of both processes occurred simultaneously in nine. He therefore concludes that the patients are susceptible to both diseases.

The excess risk of leukemia among RA patients was greater for males than for females. The series includes male patients with ankylosing spondylitis. This disease is strongly associated with HL-A antigen B27. Lawler *et al.*¹²¹ found an elevated frequency of this antigen in patients with lymphoblastic leukemia. It remains to be determined whether more cases of leukemia have accumulated among patients with ankylosing spondylitis than among rheumatoids.

The low proportion of cancer deaths in rheumatoid patients^{13 102 152} does not seem to be due to a low morbidity in cancer. Infections, cardiovascular diseases and renal diseases are more often the cause of death in rheumatoid than in non-rheumatoid subjects resulting in a lower than expected proportion of deaths due to cancer.^{33 102 152} In addition, the definition of the cause of death of an individual patient is always a matter of debate.