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Editorial

Rheumatoid Arthritis and Lymphatic Cancer

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THE PAPER by Mellemkjær and associates (pages 1753–1757) in this issue indicates a 3-fold increased risk of lymphatic cancer in patients with rheumatoid arthritis in Denmark. This finding is consistent with results of two other large cohort studies, conducted in Finland [2] and Sweden [3]. All three studies report a reduced risk of colorectal cancer and moderately increased risks of lung cancer, multiple myeloma and leukaemia, although the results in relation to these latter two malignancies are less uniform, and two studies report a reduced risk of breast cancer (Table 1). The consistency of reports and the strength of the apparent association between rheumatoid arthritis and lymphatic cancer make this aspect of the study by Mellemkjær and colleagues particularly worthy of further discussion.

Early reports of reduced risk of cancer among rheumatoid arthritis patients have, in general, been shown to be artefacts of selective follow-up and inappropriate statistical methods [4]. The study by Mellemkjær and colleagues and the other large cohort studies exploit the availability of well established disease registers and record linkage facilities in Nordic countries. These cover large populations, conferring an advantage in statistical power over studies based on single hospitals. Their complete population coverage also makes it less likely that the follow-up of rheumatoid arthritis patients was incomplete, or biased in relation to subsequent morbidity or cause of death. The end-point of interest in all three studies was the diagnosis of cancer, ascertained from a cancer registry record rather than from death certificates. Cancer registry data offer greater diagnostic precision and accuracy in this respect. The ascertainment of rheumatoid arthritis patients from health service information systems is less straightforward. While the Finnish study was based on claims for anti-rheumatic drugs from a national health insurance scheme, the Swedish and Danish studies ascertained rheumatoid arthritis patients from routine hospital discharge data. Misclassification of disease in routine data is inevitable, but none of the three studies provides information on data quality. Random misclassification of this kind leads to attenuation of relative risk estimates, so that the true relative risk of lymphatic cancer following rheumatoid arthritis is likely to be greater than estimated in these studies. There appears to be heterogeneity in the disease entities included in the studies (for example, 'systemic connective tissue diseases' and ankylosing spondilitis in Finland but not in Sweden and Denmark), but this is difficult to evaluate because of the use of 'Nordic' editions of the International Classification of Diseases, which are not well known outside the region. A delay in beginning follow-up for cancer after diagnosis with rheumatoid arthritis is important to eliminate the selective early diagnosis of cancer in patients presenting with rheumatic disease, and patients with rheumatic manifestations of cancer which may have been misdiagnosed as rheumatoid arthritis. This delay in beginning follow-up was 0, 2 and 12 months in the Finnish, Swedish and Danish studies, respectively. An important feature of the study by Mellemkjær and colleagues [1] is that they have shown persistent high risk of non-Hodgkin's lymphoma and Hodgkin's disease (and also chronic lymphocytic leukaemia) at 5–15 years following diagnosis with rheumatoid arthritis.

Despite minor differences in methodology between the three cohort studies, the consistency of results of increased risk of lymphatic cancer argues against the possibility that these are artefactual. This leaves three main possibilities:

Does the treatment of rheumatoid arthritis cause malignancy?

The possibility that treatments used for rheumatoid arthritis result in an increased risk of malignancy has been proposed, with particular concern about the use of immunosuppressive drugs such as azathioprine, cyclophosphamide and methotrexate. Azathioprine was initially used in kidney transplant patients, amongst whom a 50-fold increased risk of non-Hodgkin's lymphoma was subsequently observed [5]. A United Kingdom–Australasia collaborative study of 643 patients with rheumatoid arthritis receiving immunosuppressive therapy found a 13-fold increase in the risk of non-Hodgkin's lymphoma [6], while a register of rheumatoid arthritis patients

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Table 1. Relative risk (RR) estimates and 95% confidence intervals (CI) from three studies of cancer risk in rheumatoid arthritis patients

[Ref.]	[2]		[3]		[1]	
Location	Finland		Uppsala region, Sweden		Denmark	
Person-years at risk	213 911		101 000		144 421	
Site/morphology of cancer	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Colorectal	0.75†	(0.6–0.9)	0.66†	(0.5–0.8)	0.82	(0.7–0.9)
Lung	1.25*	(1.1–1.4)	1.31	(1.0–1.7)	1.50	(1.3–1.7)
Breast	1.03	(0.9–1.2)	0.79	(0.6–1.0)	0.81	(0.7–0.9)
Hodgkin's disease	2.79	(1.7–4.4)	2.34	(1.2–4.1)	3.40	(1.8–5.6)
Non-Hodgkin's lymphoma	2.68	(1.9–3.7)	1.88	(1.3–2.6)	2.40	(1.9–2.9)
Multiple myeloma	2.20	(1.5–3.2)	1.17	(0.7–1.9)	1.10	(0.7–1.7)
Leukaemia	1.74	(1.3–2.3)	1.43	(0.7–2.6)	1.30	(0.9–1.7)
All cancer	1.06	(1.0–1.1)	0.95	(0.9–1.0)	1.11†	(1.1–1.2)

*Includes all respiratory cancers; †Recalculated by authors.

in Canada, who had received a Disease Modifying Anti-Rheumatic drug (DMAR) (35% of whom had received azathioprine), reported an 8-fold increased risk of lymphoproliferative or leukaemic malignancies over the general population [7]. However, without a comparison group of appropriately matched rheumatoid arthritis patients not receiving such treatment it is difficult to disentangle the effects from those of the disease itself.

Information on the specific effect of azathioprine treatment on malignancy is provided by Silman and associates [8] in a study involving 202 rheumatoid arthritis patients treated with large doses of azathioprine and a similarly sized control group of rheumatoid arthritis patients matched for age, year of diagnosis and serological status who were not receiving azathioprine. A 5-fold risk of lymphoproliferative malignancy was noted in the control group while there was a 10-fold increase in risk amongst those treated with azathioprine. Studies examining the effect of cyclophosphamide on cancer risk provide inconsistent results: two studies involving 153 and 311 patients reporting no lymphomas in the treated groups [9, 10], while a study by Balthus and coworkers [11] found an excess of malignancies overall (including an excess of lymphoproliferative malignancies) amongst 81 rheumatoid arthritis patients treated with cyclophosphamide in comparison to an age and sex matched group of patients not receiving the drug.

Only recently has a possible carcinogenic effect of low-dose methotrexate been reported in patients with rheumatoid arthritis. The reported tumours have occurred in the presence of Epstein-Barr Virus (EBV) infection, and a relationship to methotrexate has been suggested by regression of the tumour on withdrawal of therapy [12].

Overall, it is difficult to be precise about the effects of immunosuppressive therapy on the risk of lymphoproliferative malignancies. Even studies which have matched cohorts of rheumatoid arthritis patients treated and not treated with immunosuppressants have not been able to match for disease severity. If severity was associated with risk of malignancy, then a relationship with treatment may be found even though none truly existed. The major conclusion to be drawn from the available data, therefore, is that the risk of lymphoproliferative malignancy associated with immunosuppressive therapy is likely to be comparatively small. It could not account, in itself, for the observed relationship with rheumatoid arthritis, given the small proportion of all rheumatoid arthritis patients receiving such therapy and the low proportion of patients with both diseases in some series who have received immunosuppressive therapy.

Is there a shared aetiological factor for the two diseases?

Another possible reason for the co-occurrence of the two diseases is a shared aetiological factor which confers increased risk of both diseases among exposed persons. The descriptive epidemiology of rheumatoid arthritis compared with that of lymphoproliferative malignancies is quite different, in terms of, for example, the age distribution of onset and the sex ratio. The aetiologies of both diseases are not well understood, and the most obvious link at present is with EBV. Persons with EBV have an increased risk of developing Hodgkin's disease, although the mechanism responsible for this is unknown. In rheumatoid arthritis, studies have shown high titres of antibody against several EBV antigens; this may represent more active EBV infection, an altered regulation of the immune response, or a true difference in exposure to infection with EBV in comparison to those without rheumatoid arthritis. Recent studies have shown a markedly higher frequency of EBV-positivity in lymphomas occurring in patients with rheumatoid arthritis in comparison to lymphomas in the general population [13], and that EBV infection is likely to have been an initial step in the development of these tumours [14].

Currently, therefore, evidence is lacking that a common aetiology between rheumatoid arthritis and the broad grouping of lymphoproliferative malignancies is the reason for their co-occurrence, although the role of EBV certainly deserves further attention.

Does lymphocyte stimulation in rheumatoid arthritis increase the risk of malignancy?

The chronic stimulation of the immune system which occurs with rheumatoid arthritis and the increased number of lymphocytes which are activated and multiplying may in itself predispose to the occurrence of lymphomas. This lymphocyte activation is also true of other autoimmune diseases such as Sjögren's syndrome (in the salivary gland) and Hashimoto's thyroiditis (in the thyroid gland) where an increased risk of lymphomas at the affected sites has also been observed. An epidemiological study of non-Hodgkin's lymphoma in the United Kingdom did relate the malignancy to several conditions involving disturbed or aberrant immunity [15], and

this may be the important mechanism relating autoimmune diseases to the development of lymphoproliferative malignancies. Further, other diseases associated with immune impairment such as AIDS have also been associated with an increased risk of non-Hodgkin's lymphoma [16].

In summary, the reported association of rheumatoid arthritis and lymphoproliferative malignancy appears to be real. A small proportion of such malignancies in rheumatoid arthritis patients may be due to immunosuppressive therapy, but this alone cannot account for the relationship. At present, the most likely explanation is that immunological defects associated with rheumatoid arthritis also predispose the individual to develop a lymphoproliferative malignancy. The recent results suggesting that EBV infection is an early step in the development of these neoplasms and may be implicated in some cases following immunosuppressive therapy provide an interesting focus for future research.

1. Mellemkjær L, Linet MS, Gridley G, *et al.* Rheumatoid arthritis and cancer risk. *Eur J Cancer* 1996, **32A**, 1753–1757.
2. Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chronic Dis* 1978, **31**, 691–696.
3. Gridley G, McLaughlin JK, Ekbom A, *et al.* Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993, **85**, 307–311.
4. Prior P. Cancer and rheumatoid arthritis: epidemiologic considerations. *Am J Med* 1985, **78**, 15–21.
5. Kinlen LJ, Sheil AGR, Peto J, *et al.* Collaborative United Kingdom–Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 1979, **2**, 1461–1466.
6. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* 1985, **78**, 44–49.
7. Matteson EL, Hickey AR, MaGuire L, Tilson HH, Urowitz MB. Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD registry. *J Rheumatol* 1991, **18**, 809–814.
8. Silman AJ, Petrie J, Hazelman B, Evans SJW. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow-up study. *Ann Rheum Dis* 1988, **47**, 988–992.
9. Lewis RB, Castor CW, Kinsley RE, *et al.* Frequency of neoplasia in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 1967, **19**, 1256–1260.
10. Farber SS, Sheon RP, Kirsner RB, *et al.* Incidence of malignant disease in patients receiving cytotoxic therapy in rheumatoid arthritis. *Arthritis Rheum* 1979, **22**, 608–611.
11. Balthus JAM, Boersma JW, Hartman AP. The occurrence of malignancies in patients with rheumatoid arthritis treated with cyclophosphamide. A controlled retrospective follow-up. *Ann Rheum Dis* 1983, **42**, 368–372.
12. Kamel OW, van de Rijn M, Weiss LM, *et al.* Reversible Epstein-Barr virus-associated lymphomas occurring in the setting of methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993, **328**, 1317–1321.
13. Kamel OW, van de Rijn M, LeBrum DP, Weiss LM, Warnke RA, Dorfman RF. Lymphoid neoplasms in patients with rheumatoid arthritis and dermatomyositis: frequency of Epstein-Barr virus and other features associated with immunosuppression. *Hum Pathol* 1994, **25**, 638–643.
14. van de Rijn M, Cleary ML, Variakojis D, Warnke RA, Chang PP, Kamel OW. Epstein-Barr virus clonality in lymphomas occurring in patients with rheumatoid arthritis. *Arthritis Rheum* 1996, **39**, 638–642.
15. Cartwright RA, McKinney PA, O'Brien C, *et al.* Non-Hodgkin's lymphoma: case–control epidemiological study in Yorkshire. *Leukaemia Res* 1988, **12**, 81–92.
16. Kinlen LJ. Malignancy in autoimmune diseases. *J Autoimmun* 1992, **5**, 363–371.