EXTENDED REPORT

Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study

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Background: Several inflammatory conditions are associated with an increased risk of lymphoma. The specific features of inflammation that mediate this risk are unknown. There are few studies on whether ankylosing spondylitis increases the risk of lymphoma. Besides inflammation-lymphoma aetiology, information on risk of lymphoma in ankylosing spondylitis is particularly important as a benchmark in the evaluation of, for example, tumour necrosis factor inhibitors.

Methods: The association between ankylosing spondylitis and malignant lymphomas overall, and separately for non-Hodgkin's lymphoma, Hodgkin's lymphoma and chronic lymphocytic leukaemia, was assessed in a nationwide, population-based case-control study of 50 615 cases of lymphoma and 92 928 matched controls by using prospectively recorded data on lymphomas from the Swedish Cancer Register (1964–2000) and data on pre-lymphoma hospitalisations for ankylosing spondylitis from the Swedish Inpatient Register (1964–2000). The odds ratios (ORs) associated with pre-lymphoma hospitalisation for ankylosing spondylitis were calculated using conditional logistic regression.

Results: 23 (0.05%) patients with lymphoma and 41 (0.05%) controls had a pre-lymphoma hospitalisation listing ankylosing spondylitis, relative risk = 1.0 (95% confidence interval (CI) 0.6 to 1.7). The number of discharges and the mean latency between ankylosing spondylitis and lymphoma were similar in patients and controls. Analyses restricted to lymphomas diagnosed during the 1990s showed similar results (OR = 1.3, 95% CI 0.6 to 2.5, number of exposed cases/controls = 14/21).

Conclusions: On average and in the absence of tumour necrosis factor inhibitors, patients hospitalised with ankylosing spondylitis do not appreciably show an increased risk of lymphoma.

Some, though not all¹, chronic inflammatory or autoimmune conditions are associated with an increased occurrence of malignant lymphomas.^{2–4} The exact mechanisms leading from inflammation or autoimmunity to lymphoma remain unclear. In the condition best studied, rheumatoid arthritis, the overall risk of lymphoma is doubled,^{5–7} and there is evidence of a strong association between markers of disease severity and risk of lymphoma.⁸ As most markers of disease severity in rheumatoid arthritis (erythrocyte sedimentation rate, swollen joint counts, joint destruction and extra-articular manifestations) are intimately correlated to each other and to the intensity of medical treatment, it has been difficult to assess whether specific aspects of inflammation are particularly linked to risk of lymphoma, and also whether anti-inflammatory or immune-suppressive treatment modifies this risk.⁹ The second uncertainty has led to particular concern in the case of tumour necrosis factor (TNF) antagonists, which have been associated with higher-than-average risks of lymphoma in rheumatoid arthritis, but are also given to those patients with the most severe disease.⁶

It follows that assessments of the risks of lymphoma in inflammatory conditions other than rheumatoid arthritis may provide important insights into the determinants and mechanism of action of inflammation-associated lymphomas. Ankylosing spondylitis is a chronic inflammatory joint disease in which the anatomical distribution of arthritis, the type of joint destruction, the extra-articular manifestations and the sex distribution (among other factors) differ from rheumatoid arthritis. Yet, information on the risk of lymphoma in ankylosing spondylitis is surprisingly limited, but signals increased risks.^{10 11}

From the perspective of pharmacovigilance, the dramatic effects of TNF inhibitors in ankylosing spondylitis^{12 13} coupled with the concern of their safety with respect to lymphomas particularly highlight the need for more data on the risk of lymphoma in patients with ankylosing spondylitis. To provide data on the risk for lymphoma in patients with ankylosing spondylitis, we carried out a population-based nationwide case-control study of malignant lymphomas in relation to history of ankylosing spondylitis, taking advantage of high-quality Swedish health registers and census registers.

SUBJECTS AND METHODS

Patients and controls

In the Swedish Cancer Register (with a nationwide and near complete coverage¹⁴), we identified all patients registered with a diagnosis of Hodgkin's lymphoma, non-Hodgkin's lymphoma or chronic lymphatic leukaemia (1964–2000), including information on dates of birth and diagnosis of lymphoma and sex. In the nationwide population register (the Swedish census register), two controls were identified for each patient, matched on sex, year of birth, marital status (unmarried, married and widowed) and county of residence in the year of lymphoma diagnosis in the patient. After exclusion of patients and controls born outside Sweden, and of controls themselves diagnosed with lymphoma before the cases, 50 615 patients and 92 928 controls remained (table 1). Through linkage with the Register of Total Population, we

Abbreviations: ICD, International Classification of Diseases; TNF, tumour necrosis factor

Table 1 Number of cases with malignant lymphoma diagnosed in Sweden (1964–2000) and their matched controls

	Cases	Controls
Overall	50 615	92 928
Sex		
Males	28 916	53 132
Females	21 699	39 796
Age at lymphoma diagnosis (years)		
<50	7 393	14 441
50–74	26 363	48 702
>75	16 312	29 783
Type of malignant lymphoma*		
Hodgkin's lymphoma	32 773	60 202
Non-Hodgkin's lymphoma	7161	13 103
Chronic lymphocytic leukaemia	10 982	20 141
Year of lymphoma diagnosis		
1964–1979	17 121	31 499
1980–1989	15 634	29 011
1990–2000	17 860	32 418
No of identified spouses	35 486	64 591

*Numbers exceed the total because of overlap.

also identified registered spouses of patients and controls until the diagnosis of lymphoma in the patients.

Ankylosing spondylitis

Information on the list of patients with ankylosing spondylitis discharged from hospital (International Classification of Diseases (ICD)7: 722.10 ICD8: 712.40 ICD9: 720A ICD10: M45), including dates of discharge, was obtained for patients and controls through linkage with the Swedish Inpatient Register (1964–2000).¹⁵ This register contains information on medical diagnoses listed on discharges from inpatient care and has a population-based (Swedish hospital care is public and population-based; referrals are independent of insurance or financial capacity) coverage that encompassed 50% of all counties in the mid-1970s and has encompassed 100% of them since 1987.¹⁵ Patients (n = 3) and controls (n = 3) who had also been discharged with rheumatoid arthritis were excluded (analyses including these patients resulted in similar estimates of relative risk (RR), data not shown).

Statistics

The RR of malignant lymphoma associated with ankylosing spondylitis was expressed as odds ratios (ORs), derived from conditional logistic regression using PROC PHREG in SAS; 95% confidence intervals (CI) excluding 1.0 were considered to be significant. Personal history was assessed for patients and controls until 1 year before (to reduce bias from misdiagnosis and reversed causality) the diagnosis of lymphoma in the index case, and stratified according to time between the first discharge listing the ankylosing spondylitis and lymphoma diagnosis (1–4, 5–9 and >10 years), age at first discharge listing ankylosing spondylitis (50–74 and >75 years), age at lymphoma diagnosis (50–74 and >75 years), decade of lymphoma diagnosis (1965–79, 1980–9 and 1990–9) and sex. To evaluate the importance of environmental factors that could confound a statistical association between personal history of ankylosing spondylitis and lymphoma, we also calculated ORs for malignant lymphoma associated with the spouse's history of ankylosing spondylitis, as spouses tend to share environmental exposures.

RESULTS

Overall, 23 (0.05%) patients and 41 (0.05%) controls had been hospitalised with ankylosing spondylitis, which

corresponded to relative risk (RR) = 1.0 (95% CI 0.6 to 1.7). The RRs for men (19 exposed cases, OR = 1.0) and women (4 exposed cases, OR = 1.0) were similar. Analyses restricted to lymphomas diagnosed during the 1990s showed similar results (OR = 1.3, 95% CI 0.6 to 2.5, number of exposed cases/controls = 14/21).

Neither the number of discharges with ankylosing spondylitis per patient nor the average latency between the first discharge with ankylosing spondylitis and lymphoma diagnosis differed between patients and controls (data not shown). Accordingly, when stratified by latency between first discharge with ankylosing spondylitis and lymphoma diagnosis, no clear trend in RR emerged, although some of the estimates were based on small numbers (OR 1–4 years = 0.9 (95% CI 0.4 to 2, n = 8/16), OR 5–9 years = 1.8 (95% CI 0.5 to 7.4, n = 4/4) and OR >10 years = 1.0 (95% CI 0.5 to 2.0, n = 11/21)). Analyses restricted to lymphoma type showed no increase in the risk of non-Hodgkin's lymphoma (OR = 0.8, 95% CI 0.4 to 1.5), but for Hodgkin's lymphoma (OR = 1.7, 95% CI 0.2 to 12) and chronic lymphocytic leukaemia (OR = 1.9, 95% CI 0.6 to 5.9), the numbers of patients or controls who were exposed were small (table 2).

To ensure that the lack of association between a personal history of ankylosing spondylitis and the risk of lymphoma was not due to any linkage-related or analysis-related failure to pick up increased risks where they were expected, we assessed the risk of lymphoma associated with a personal history of rheumatoid arthritis, only to find the expected increased risk (RR = 1.8).⁵ To assess the possibility that the lack of statistical association between personal history of ankylosing spondylitis and risk of lymphoma was due to confounding (downwards) by environmental factors somehow associated with ankylosing spondylitis and risk of lymphoma, we estimated the RR associated with having a spouse hospitalised with ankylosing spondylitis. Having a spouse hospitalised with ankylosing spondylitis was, however, not associated with any increased or decreased risk of lymphoma (OR = 0.8, 95% CI 0.4 to 1.5, n = 14/33).

DISCUSSION

The results of our study suggest that, in contrast with rheumatoid arthritis, the average risk of lymphoma is not increased in patients hospitalised with ankylosing spondylitis.

Available data on risk of lymphoma in ankylosing spondylitis are limited, but indicate the possibility of an increase in the average risk of lymphoma^{10–11} in the same range as that reported for rheumatoid arthritis. In a previous study on ankylosing spondylitis from our group, a non-significant 34% increased risk for the combined group of all haematopoietic cancers was reported.¹⁶ In comparison to that cohort study, our current study uses a case-control design to allow for adjustment also for geography and marital status and reports RRs for malignant lymphomas and major lymphoma types.

The nationwide, population-based setting of our study provided a large study population. Still, some of the stratum-specific risk estimates were based on small numbers. Our case identification permitted risk assessments for non-Hodgkin's lymphoma, Hodgkin's lymphoma and chronic lymphocytic leukaemia. Misclassification of lymphomas in the Cancer Register is $\leq 10\%$.^{17–18} In a recent case-control study on about 400 rheumatoid arthritis-associated lymphomas identified in the Swedish Cancer Register, the lymphoma diagnosis was confirmed in 98% of the reviewed specimens.¹⁹ With respect to ankylosing spondylitis, the overall diagnostic validity of the Swedish Inpatient Register is around 90%,¹⁵ and validations of the discharge diagnoses of, for example, rheumatoid arthritis and Wegener's granulomatosis indicate

Table 2 Number of cases and controls with a personal history of Ankylosing Spondylitis including corresponding odds ratios with 95% confidence intervals

Exposure	Outcome											
	All lymphomas (ca = 50 615/co = 92 928)			NHL (ca = 32 773/co = 60 202)			HL (ca = 7161/co = 13 103)			CLL (ca = 10 982/co = 20 141)		
	ca	co	OR (95% CI)	ca	co	OR (95% CI)	ca	co	OR (95% CI)	ca	co	OR (95% CI)
Personal history of AS	23	41	1.0 (0.6 to 1.7)	15	33	0.8 (0.4 to 1.5)	2	2	1.7 (0.2 to 12)	6	6	1.9 (0.6 to 5.9)

AS, ankylosing spondylitis; ca, cases; CLL, chronic lymphocytic leukaemia; co, controls; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma. Data are stratified by lymphoma type, including all lymphomas.

an overall validity close to 90% for these diagnoses.^{8, 20} Misclassification is therefore unlikely to have concealed any relevant association, and to reduce this possibility further, we excluded ankylosing spondylitis during the year before lymphoma diagnosis (inclusion of this year resulted in a non-significant OR = 1.2, data not shown). The reported population prevalence of ankylosing spondylitis ranged from 0.06% to 0.2%.²¹ The comparatively low prevalence of ankylosing spondylitis among our controls (0.05%) was because we only included ankylosing spondylitis identified through hospitalisation and during a study period limited to a few decades (rather than lifelong recruitment of all diagnosed ankylosing spondylitis). Accordingly, any estimates of ankylosing spondylitis prevalence derived from our study will only be reflective of the subset of patients hospitalised with ankylosing spondylitis. Similarly, our RRs apply to patients hospitalised with ankylosing spondylitis, whose spectrum of inflammation and treatment exposures may be different from those never hospitalised; so we cannot formally exclude the existence of increased risks of lymphoma in patients with ankylosing spondylitis who have never been hospitalised. Importantly, the incomplete ascertainment of ankylosing spondylitis (hospitalisations, and only such cases occurring after the start of the Inpatient Register) applied equally to patients and controls and did not in itself introduce detectable bias. With respect to the sex distribution, the sex ratio among our cases with ankylosing spondylitis (19/23 = 83% men) is compatible with the predominance in men normally reported in ankylosing spondylitis. Although the average RR was close to 1.0, this does not preclude the existence of a truly increased risk of lymphoma in subsets of patients with the most severe ankylosing spondylitis, but against an unelevated overall RR, such subsets either have to be small or carry moderately increased risks of lymphoma. Indeed, the apparent discrepancy between ankylosing spondylitis and rheumatoid arthritis in terms of average risk of lymphoma is probably related to the fact that the cumulative burden of systemic inflammation in rheumatoid arthritis typically exceeds that of ankylosing spondylitis. Instead, or in addition to the quantitative difference between ankylosing spondylitis and rheumatoid arthritis, the difference in risk of lymphoma may be a qualitative issue related to differences in inflammatory phenotype.

Our register-based design ruled out recall bias, but we had limited information on potential confounders. The matched design and analysis ensured adjustment for the effects of sex, age, marital status, area of residence and calendar period, and our assessment of risk associated with the spouse's ankylosing spondylitis did not suggest the presence of strong environmental confounding of the statistical association between ankylosing spondylitis and lymphoma. Our dataset and analysis also proved to be able to appropriately pick up

expected increased risks, such as that associated with rheumatoid arthritis.⁵

In conclusion, we found no evidence to suggest that the average risk of lymphoma in patients hospitalised with ankylosing spondylitis is increased, nor did we find evidence of increased risks in subsets thereof as defined by sex, time and major lymphoma types. Although these results do not preclude the existence of raised risks in yet unidentified subsets of patients with ankylosing spondylitis, our study suggests that whatever be the factors that differ between ankylosing spondylitis and rheumatoid arthritis, they may provide important information on the still unknown aetiology of rheumatoid arthritis-associated lymphomas. Moreover, our results provide a benchmark against which we may judge the occurrence of lymphoma in clinical studies of new treatments against ankylosing spondylitis.

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REFERENCES

- 1 Asking J, Brandt L, Lapidus A, Karlen P, Bjorkholm M, Lofberg R, et al. Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut* 2005;**54**:617–22.
- 2 Ekstrom K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekblom A, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. *Arthritis Rheum* 2003;**48**:963–70.
- 3 Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study. *Arthritis Rheum* 2004;**50**:1262–9.
- 4 Asking J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekblom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002;**123**:1428–35.
- 5 Asking J, Fored M, Baecklund E, Brandt L, Backlin C, Ekblom A, et al. Hematopoietic malignancies in rheumatoid arthritis. Lymphoma risk and characteristics following TNF-antagonists. *Ann Rheum Dis* 2005;**64**:1414–20.
- 6 Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004;**50**:1740–51.
- 7 Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. *Int J Cancer* 2000;**88**:497–502.
- 8 Baecklund E, Iliadou A, Asking J, Ekblom A, Backlin C, Granath F, et al. Chronic inflammation, not its treatment, increases lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:692–701.
- 9 Symmons DP, Silman AJ. Anti-tumor necrosis factor alpha therapy and the risk of lymphoma in rheumatoid arthritis: no clear answer. *Arthritis Rheum* 2004;**50**:1703–6.
- 10 Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. *Int J Cancer* 1994;**59**:327–38.

- 11 **Shibata A**, Zhao S, Makuch R, Wentworth J, Veith J, Wallis W. Lymphoma risk in ankylosing spondylitis patients is greater than that observed in the general population. *Ann Rheum Dis* 2004;**63**(Suppl 1):98.
- 12 **Heiberg MS**, Nordvag BY, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, *et al*. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum* 2005;**52**:2506–12.
- 13 **Braun J**, Brandt J, Listing J, Zink A, Alten R, Golder W, *et al*. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;**359**:1187–93.
- 14 **Socialstyrelsen**. *Cancer incidence in Sweden 1999*. Stockholm: Epidemiologiskt Centrum, Socialstyrelsen, 2001.
- 15 **Socialstyrelsen**. *Patientregistret 1987–1996 Kvalitet och innehåll*. Stockholm: Epidemiologiskt Centrum, Socialstyrelsen, 1998.
- 16 **Feltelius N**, Ekbom A, Blomqvist P. Cancer incidence among patients with ankylosing spondylitis in Sweden 1965–95: a population based cohort study. *Ann Rheum Dis* 2003;**62**:1185–8.
- 17 **Hjalgrim H**, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, *et al*. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. *N Engl J Med* 2003;**349**:1324–32.
- 18 **Ekstrom K**, Ekbom A, Hildebrand H, Glimelius B, Akerman M, Askling J. Characteristics of malignant lymphomas associated with coeliac disease. *Gut* 2005;**54**:54–9.
- 19 **Baecklund E**, Sundstrom C, Ekbom A, Catrina AI, Biberfeld P, Feltelius N, *et al*. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. *Arthritis Rheum* 2003;**48**:1543–50.
- 20 **Knight A**, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 2002;**100**:82–5.
- 21 **Olivieri I**, van Tubergen A, Salvarani C, van der Linden S. Seronegative spondyloarthritides. *Best Pract Res Clin Rheumatol* 2002;**16**:723–39.