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Association of Chronic Inflammation, Not Its Treatment, With Increased Lymphoma Risk in Rheumatoid Arthritis

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Objective. **Chronic inflammatory conditions such as rheumatoid arthritis (RA) have been associated with malignant lymphomas. This study was undertaken to investigate which patients are at highest risk, and whether antirheumatic treatment is hazardous or protective.**

Methods. **We performed a matched case–control study of 378 consecutive Swedish RA patients in whom malignant lymphoma occurred between 1964 and 1995 (from a population-based RA cohort of 74,651 RA patients), and 378 controls. Information on disease characteristics and treatment from onset of RA until lymphoma diagnosis was abstracted from medical records. Lymphoma specimens were reclassified and tested for Epstein-Barr virus (EBV). Relative risks (odds ratios [ORs]) for lymphomas (by subtype) associated with deciles of cumulative disease activity were assessed, as were ORs associated with drug treatments.**

Results. **The relative risks of lymphoma were only modestly elevated up to the seventh decile of cumulative disease activity. Thereafter, the relative risk increased dramatically (OR ninth decile 9.4 [95% confidence interval 3.1–28.0], OR tenth decile 61.6 [95% confidence interval 21.0–181.0]). Most lymphomas (48%) were of the diffuse large B cell type, but other lymphoma subtypes also displayed an association with cumulative disease activity. Standard nonbiologic treatments did not increase lymphoma risk. EBV was present in 12% of lymphomas.**

Conclusion. **Risk of lymphoma is substantially increased in a subset of patients with RA, those with very severe disease. High inflammatory activity, rather than its treatment, is a major risk determinant.**

Rheumatoid arthritis (RA) is associated with an increased occurrence of lymphomas (1–5), amounting to an average doubling of the lymphoma risk (2–5). There are, however, indications of marked variations in risk between patients (1,6,7). In a pilot study of 41 Swedish patients with RA-associated lymphoma occurring between 1965 and 1984, we observed an association between high disease activity and lymphoma risk (6). Findings in a recent cohort study whose subjects included 29 patients with RA-associated lymphoma (8) provide further indirect evidence of this association. While these findings suggest that inflammatory activity may be a driving force in lymphoma development, we are at present unable to determine what amount of inflammatory activity increases lymphoma risk. Likewise, there is very little information on the effect of antiinflammatory and immunosuppressive treatment on lymphoma risk in RA.

The basis for this uncertainty is that in several case series (9–12) as well as cohort studies (13–17) on patients treated with disease-modifying antirheumatic drugs (DMARDs) including methotrexate, information on lymphoma development (and elevated risk) in conjunction with RA was collected, but possible effects of

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treatment could not be separated from possible effects of the disease process itself. The same problem, i.e., an inability to distinguish therapy-related effects from effects of the disease, is encountered in case–control studies whose results have indicated increased lymphoma risks after treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin (18,19) and with corticosteroids (20,21). Reports based on case series and comparisons with age-matched healthy population controls have also linked tumor necrosis factor (TNF) blockade treatment to increased lymphoma risk (8,22–24). Importantly, though, none of the above studies has been able to pinpoint the specific effects of disease activity on lymphoma risk, let alone distinguish them from the effects of treatment.

Consequently, it is of clinical as well as of scientific importance to better identify which patients with RA are at high risk of developing lymphomas, and in particular to understand whether the increased lymphoma risk is disease driven and a result of suboptimal use of immunosuppressive treatment, or is an untoward effect of the very same treatment. From a drug safety point of view, knowledge of the baseline lymphoma risk is essential for the evaluation of new drugs, as illustrated by the current uncertainty of the benefits—or hazards—with respect to lymphoma risk following TNF blockade treatment in patients with RA or inflammatory bowel disease (22–24). To address this, we used data from longitudinal, population-based, high-quality registers and biobanks in Sweden, in a population-based case–control study of 378 patients with RA-associated lymphoma occurring between 1964 and 1995. We assessed the importance of RA disease activity, phenotype, and treatment on lymphoma risk overall and by lymphoma subtype.

SUBJECTS AND METHODS

Cases. From the Swedish Inpatient Register, which contains individual-based information on all patients receiving inpatient care in Sweden (25), we identified all individuals ≥16 years of age discharged with a diagnosis of RA (International Classification of Diseases, Seventh Revision [ICD-7]: 722, ICD-8: 712.38–712.39, ICD-9: 714A–C,714 W), as either the main or a secondary diagnosis, between January 1, 1964 and December 31, 1994 (n = 74,651). Through linkage with the Swedish Cancer Register, to which reporting is mandatory (26), we identified as cases all 424 individuals diagnosed with a malignant lymphoma (ICD-7: 200-202) as their first primary cancer after the first discharge listing RA, from January 1, 1964 to December 31, 1995.

Controls. For each case, we used 1 individually matched control. To achieve this and avoid having to exclude cases due to lack of a useful control, we randomly selected as potential controls 3 individuals from the underlying RA cohort. Controls had to be alive and free from any registered cancer at the time of lymphoma diagnosis of their corresponding case, and were matched by sex, year of birth, year of first RA discharge, and county of residence. From the potential controls, we included the first of the 3 (searched for as files are stored in the medical archives, i.e., by date/month/year of birth) whose medical record could be identified and who fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA (27).

Validation of RA and reclassification of lymphomas. To confirm the RA diagnosis, we reviewed the medical records of cases (n = 424) and controls. Cases whose records could not be identified (n = 11 [3%]) or who did not fulfill the ACR criteria for RA (n = 27 [6%]) were excluded. In 40 of the cases, medical records did not include enough information to evaluate whether the ACR criteria were fulfilled. These cases were kept in the study, however, because the patients had erosive/deforming polyarthritis, and all available information supported the diagnosis of RA. The same exclusion/inclusion criteria were used for the controls, i.e., of all potential controls whose files were reviewed (n = 507), 65 (13%) were excluded because the patients did not meet the ACR criteria for RA or did not have erosive/deforming polyarthritis and other typical signs of RA. To confirm the lymphoma diagnosis, paraffin-embedded lymphoma tissues were reviewed and reclassified according to the World Health Organization (WHO) classification (28), as previously described (29). We tested for Epstein-Barr virus (EBV) in the lymphomas using EBV-encoded RNA in situ hybridization (29).

Of the 386 remaining potential cases of RA-associated lymphoma, 8 were excluded because the lymphoma diagnosis could not be confirmed, and 35 could not be reviewed (specimen not located or of poor quality) although the lymphoma diagnoses were unequivocally supported by medical records. The final study thus included 378 cases (343 with reclassified lymphoma specimen) and 378 matched controls.

Information on disease characteristics and treatment. The methods for gathering data were designed to maintain blinding with regard to case versus control status. Thus, files from all medical encounters were scrutinized by investigators who were unaware of case versus control status, and files were masked with regard to results of the lymphoma reclassification from onset of RA until lymphoma diagnosis.

We used 2 approaches to assess RA disease activity, both based on swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and physician's global assessments as recorded in the medical files. The first, described in reports of our pilot study (6,29), scored *overall* disease activity for the whole RA disease period as either low, medium, or high (assessed in 376 cases/controls). The overall disease activity score was based on the estimation of a score value for each reported visit, and the final score was the mean of the total scores from all visits (Table 1). The second and principal measure, which took into account minor fluctuations in each patient's disease course, estimated the *cumulative* disease activity, as the duration (in months) of 4 different levels of disease activity (inactive, low, medium, or high) from onset of RA until lymphoma diagnosis (assessed in 372 cases/controls).

Table 1. Scoring of overall rheumatoid arthritis disease activity*

	Score at each visit		
	1	2	3
ESR, mm/hour	1–30	31–60	≥61
No. of tender and swollen joints	0–3	4–6	≥7
Physician's global assessment of disease activity	Mild	Moderate	Severe

* At each visit, the scores for erythrocyte sedimentation rate (ESR), number of tender and swollen joints, and physician's global assessment were summed to yield a total score (maximum 9) for that visit. The final score was the mean of the total scores from all visits. Disease activity was considered low if the final score was 3–4, medium if the final score was >4–8, and high if the final score was >8–9.

The definitions of the different levels of disease activity were the same in both disease activity scores.

To adapt to the ways information was typically recorded, we used a 15-point joint count, including the following joints: shoulders, elbows, knees, wrists, ankles (1 affected = 1 point, 2 affected = 2 points), metacarpophalangeal joints (1–5 affected = 1 point, 6–10 affected = 2 points), proximal interphalangeal joints (1–5 affected = 1 point, 6–10 affected = 2 points), and metatarsophalangeal joints (1–10 affected = 1 point). Joints were considered to be inflamed if reported as "tender and swollen." The joint count was categorized as inactive (0 inflamed joints), low (score of 1–3 points [of the maximum as described above]), medium (score of 4–6), or high (score of ≥7). Information on joints that were only tender or only swollen, described separately and in detail, was seldom available and therefore not included in the analyses. ESR (all recorded values until 1 year before lymphoma diagnosis) was categorized as inactive or low (≤30 mm/hour), medium (>30 mm/hour but ≤60 mm/hour), or high (>60 mm/hour). On the rare occasions when the different disease activity measures indicated different levels of activity, cumulative disease activity was categorized according to the following prioritization scheme: joint count > physician's assessments > ESR.

For each month of disease, we also abstracted information on treatment with DMARDs and other medical treatments for RA (defined as treatment with a specified drug for ≥4 consecutive weeks). Intraarticular steroid use was recorded if intraarticular steroid treatment was given within 1 month from development of signs of arthritis in ≥50% of reported flares.

Irreversible joint damage was assessed for the 15 joints/joint groups based on the definitions in the Rheumatoid Arthritis Articular Damage (RAAD) score (30).

Statistical analysis. To account for the matched design of the study, measures of relative risk (odds ratios [ORs]) were calculated using conditional logistic regression. To estimate cumulative disease activity, we integrated the monthly levels of disease activity over time and calculated the area under the curve (AUC). According to our previous findings (6), the impact of the different levels of disease activity on lymphoma risk was not linear. Therefore, we first investigated the influence of lymphoma risk associated with 1-month exposure to low, medium, or high disease activity, by conditional logistic regression. "Inactive," characterized by absence of disease activity, was assigned a score of 0, and based on the derivates from the regression analysis, low, medium, and high disease activity were assigned scores of 1, 5, and 8, respectively. Accordingly, the AUC for an individual with a total of 5 months of inactive disease, 10 months of low disease activity, and 5 months of medium disease activity would equal $(5 \times 0) + (10 \times 1) + (5 \times 5)$, or 35.

Analyses of DMARD treatment were adjusted for disease activity and the number of other DMARDs taken besides the one being analyzed. Treatment with corticosteroids, NSAIDs, and aspirin was adjusted for disease activity and DMARD use. To account for the nonlinear relationship between AUC and lymphoma risk, quartiles of AUC were used to adjust for disease activity. To assess effect modification, we stratified quartiles of AUC by median time from onset of RA, sex, and DMARD use. The Wald test and *t*-tests were used to estimate differences in duration of DMARD treatment and RA disease duration between cases and controls. SAS software (31) was used for all analyses.

RESULTS

Characteristics of cases/controls and malignant lymphomas. The mean time from RA onset until lymphoma diagnosis was 20 years (range 1–59) in cases and

Table 2. Characteristics of the Swedish patients with RA complicated by malignant lymphoma (1964–1995) and their matched controls*

	Cases (n = 378)	Controls (n = 378)
No. female/no. male	208/170	208/170
Year of RA onset	1926–1994	1915–1994
Age at RA onset, mean (range) years	50 (16–83)	53 (18–80)
Age at lymphoma diagnosis, mean (range) years	70 (32–91)	–
Duration of RA before lymphoma diagnosis, mean (range) years	20 (1–59)†	17 (1–65)
Rheumatoid factor positive‡	279/334 (84)	300/360 (83)
Confirmed Sjögren's syndrome§	7 (2)	1 (0.3)
Treatment¶		
Any DMARD	268 (71)	278 (74)
Cytotoxic drugs	19 (5)	8 (2)
Oral steroids	183 (48)	217 (57)
Intraarticular steroids	168 (44)	240 (63)
Any NSAID	334 (88)	336 (89)
Aspirin	269 (71)	225 (60)

* Except where indicated otherwise, values are the number (%).
† $P = 0.001$ versus controls.
‡ Measured by any available method from the time of onset of rheumatoid arthritis (RA) until 1 year before lymphoma diagnosis. For 44 cases and 18 controls, there was no information on rheumatoid factor status.
§ Defined according to the European Community criteria (40).
¶ Defined as regular treatment for ≥4 consecutive weeks. Disease-modifying antirheumatic drugs, (DMARDs) include antimalarial agents, auranofin, azathioprine, cyclosporine, D-penicillamine, intramuscular gold, methotrexate, podophyllotoxin, and sulfasalazine. Cytotoxic drugs include cyclophosphamide and chlorambucil. Intraarticular steroids refers to intraarticular steroids administered within 1 month from signs of arthritis in ≥50% of reported flares. NSAID = nonsteroidal antiinflammatory drug.

Table 3. Results of lymphoma reclassification in 343 patients with RA complicated by malignant lymphoma (1964–1995), and results of EBER in situ hybridization for EBV*

Lymphoma subtype, WHO classification	All reviewed lymphomas	Proportion EBV positive†
All lymphomas	343	37/304 (12)
B cell neoplasms	269 (78)	23/258 (9)
Diffuse large B cell lymphoma	165 (48)	19/160 (12)
Follicular lymphoma grade 1–3	32 (9)	0/30 (0)
Small lymphocytic lymphoma	17 (5)	0/17 (0)
Lymphoplasmacytic lymphoma	7 (2)	3/7 (43)
Mantle cell lymphoma	5 (1.5)	0/5 (0)
MALT lymphoma	3 (1)	0/3 (0)
Burkitt's lymphoma	3 (1)	0/3 (0)
Plasma cell myeloma	1 (0.3)	0/1 (0)
Splenic marginal zone lymphoma	1 (0.3)	0/1 (0)
Unspecified high-grade B cell lymphoma‡	16 (5)	1/13 (8)
Unspecified low-grade B cell lymphoma‡	10 (3)	0/9 (0)
Unspecified B cell lymphoma‡	9 (3)	0/9 (0)
T cell and NK cell neoplasms	16 (5)	2/15 (13)
Anaplastic large cell lymphoma	8 (2)	2/8 (25)
T lymphoblastic lymphoma	1 (0.3)	0/1 (0)
Mycosis fungoides	1 (0.3)	0/0
Angioimmunoblastic T cell lymphoma	1 (0.3)	0/1 (0)
Peripheral T cell lymphoma, unspecified	1 (0.3)	0/1 (0)
Unspecified high-grade T cell lymphoma‡	1 (0.3)	0/1 (0)
Unspecified low-grade T cell lymphoma‡	3 (1.0)	0/3 (0)
Hodgkin's lymphomas	21 (6)	9/19 (47)
Nodular sclerosis classic HL	9 (3)	3/9 (33)
Mixed cellularity classic HL	7 (2)	6/6 (100)
Lymphocyte-depleted classic HL	2 (0.6)	0/2 (0)
Lymphocyte-rich classic HL	1 (0.3)	0/1 (0)
Nodular lymphocyte–predominant HL	1 (0.3)	0/1 (0)
Unspecified HL	1 (0.3)	0/0
Unspecified lymphomas‡	37 (11)	3/12 (25)
Unspecified high-grade NHL‡	15 (4)	1/2 (50)
Unspecified low-grade NHL‡	8 (2)	1/2 (50)
Unspecified NHL‡	6 (2)	0/4 (0)
Unspecified malignant lymphoma‡	8 (2)	1/4 (25)

* Values are the number (%). RA = rheumatoid arthritis; EBER = Epstein-Barr virus (EBV)–encoded RNA; MALT = extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue; NK = natural killer; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma.
† Of the 343 reclassified lymphomas, 304 were examined for EBV status. Ratios describe the number of EBV-positive lymphomas of the number tested of the same subtype.
‡ Lymphoma material insufficient for diagnosis according to World Health Organization (WHO) classification.

17 years (range 1–65) in controls. Although small, this difference was significant ($P = 0.001$) (Table 2). Reclassification revealed a high number of diffuse large B cell lymphoma (DLBCLs), diagnosed in 165 of 343 reviewed lymphomas (48%) or 165 of 314 non-Hodgkin's lymphomas (NHLs) (53%) (Table 3). An additional number of high-grade NHLs, most of which were probably DLBCLs, could not be ultimately reclassified according to the WHO classification (n = 31). The distribution of other subtypes was less remarkable, as was the proportion of EBV-positive lymphomas (12%) (Table 3). As in lymphomas not associated with RA (28), EBV was most frequent in Hodgkin's lymphomas.

Lymphoma risk in relation to disease activity. Compared with low overall disease activity, medium overall disease activity was associated with an 8-fold increase, and high overall disease activity with a 70-fold increase, in lymphoma risk (Table 4). Similarly, we observed an ~70-fold gradient in lymphoma risk with increasing Steinbrocker functional class (32) (Table 4). When cumulative disease activity was assessed, we observed only modest increases (versus first decile of

Table 4. Lymphoma risk associated with overall disease activity and functional class, assessed in 376 patients with RA complicated by malignant lymphoma and their 376 matched controls

	Cases, no. (%)	Controls, no. (%)	Unadjusted OR (95% CI)*
Inflammatory activity†			
Low	94 (25)	278 (74)	1 (referent)
Medium	196 (52)	94 (25)	7.7 (4.8–12.3)
High	86 (23)	4 (1)	71.3 (24.1–211.4)
Functional class‡			
I	34 (9)	138 (37)	1 (referent)
II	185 (49)	204 (54)	3.9 (2.4–6.3)
III	105 (28)	31 (8)	13.8 (7.2–26.2)
IV	52 (14)	3 (1)	67.5 (18.9–239.8)

* OR = odds ratio; 95% CI = 95% confidence interval.
† Score reflecting the entire period from onset of rheumatoid arthritis (RA) until diagnosis of lymphoma, based on number of tender and swollen joints, erythrocyte sedimentation rate, and physician's global assessments.
‡ Defined according to the Steinbrocker criteria (32) 1 year before lymphoma diagnosis.

AUC) in the OR for lymphoma up to the seventh decile, but highly elevated ORs associated with the highest deciles: for the ninth decile, the OR was 9.4 (95% confidence interval [95% CI] 3.1–28.0), and for the tenth decile, the OR was 61.6 (95% CI 21.0–181.0) (Figure 1).

When patients with lymphoma evolving within 1 year after the first discharge for RA (n = 47) were excluded from the analyses, risk estimates decreased, but still a strong association with disease activity remained (OR for high overall disease activity 62.0 [95% CI 20.7–185.5], and OR for tenth decile of AUC for cumulative disease activity 38.0 [95% CI 12.1–119.3]).

Analyses by subtype revealed a strong association of DLBCL with disease activity (OR for third versus first tertile of AUC 93.7 [95% CI 11.8–747.3] [analyses of quartiles were precluded by small numbers in the lowest quartiles]), but also an increased risk for the combined group of all other lymphoma subtypes excluding unspecified high-grade NHLs (OR for third tertile 5.0 [95% CI 2.1–11.5]). EBV positivity was not associated with the AUC for disease activity (data not shown). When cases and controls were stratified by disease duration and sex, the influence of disease activity on lymphoma risk remained the same (data not shown).

Lymphoma risk in relation to other phenotypic aspects of RA. ESR values were documented in 362 cases and 377 controls. The mean number of ESR values recorded per patient was 23 (range 1–149) in cases and 17 (range 1–106) in controls. When the means of all documented ESRs were categorized into quartiles, the highest quartile (>45 mm/hour) was associated with an ~3-fold increased risk of lymphoma (OR 2.8 [95% CI 1.8–4.4]). We also observed increased risks associated with severe (versus partial) irreversible joint damage (RAAD score) in the hands/feet (OR 10.5 [95% CI 6.1–18.2]) and in large joints (OR 28.3 [95% CI 9.0–89.6] for severe damage in the knee) assessed in the last year before lymphoma diagnosis.

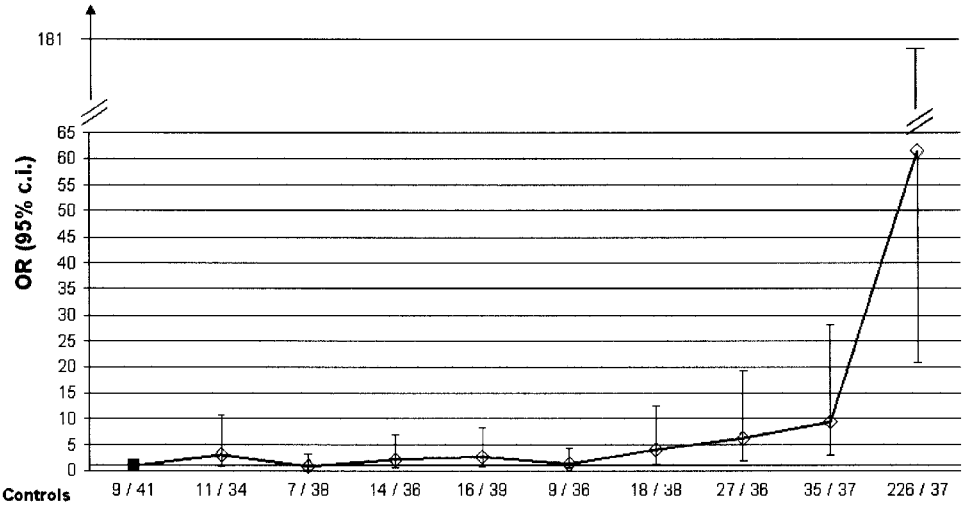

Figure 1. Risk of lymphoma in relation to cumulative disease activity, assessed in 372 patients with rheumatoid arthritis (RA) and in matched RA controls. Symbols show unadjusted odds ratios (ORs); bars show 95% confidence intervals (95% CIs). Deciles of the area under the curve for cumulative disease activity are shown on the x-axis; ORs were calculated using the first decile as the reference. A line is included where OR = 1.

Table 5. Unadjusted and adjusted odds ratios for lymphoma associated with having ever been treated with common DMARDs, steroids, NSAIDs, and aspirin, and duration of DMARD treatment, assessed in 378 patients with RA complicated by malignant lymphoma and their matched controls*

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
DMARDs				
Antimalarial agents				
No	173	152	1	1
Yes	205	226	0.8 (0.6–1.1)	0.5 (0.4–0.8)
≥4 weeks–1 year	78	83	0.8 (0.6–1.2)	0.7 (0.4–1.2)
>1–2 years	37	48	0.7 (0.4–1.1)	0.4 (0.2–0.8)
>2–5 years	49	55	0.8 (0.5–1.2)	0.5 (0.2–0.8)
>5–10 years	29	29	0.9 (0.5–1.5)	0.6 (0.3–1.3)
>10 years	12	11	0.9 (0.4–2.3)	0.3 (0.09–1.7)
Azathioprine				
No	348	364	1	1
Yes	30	14	2.3 (1.2–4.6)	4.3 (1.6–12.0)
≥4 weeks–1 year	16	6	3.0 (1.1–8.2)	2.9 (0.8–11.1)
>1–2 years	4	5	0.8 (0.2–3.4)	1.4 (0.2–9.0)
>2–5 years	5	2	2.5 (0.5–12.9)	6.3 (0.4–107.6)
>5–10 years	5	1	5.0 (0.6–42.8)	5.5 (0.4–80.2)
Intramuscular gold				
No	270	298	1	1
Yes	108	80	1.5 (1.1–2.0)	1.0 (0.6–1.6)
≥4 weeks–1 year	91	68	1.5 (1.0–2.1)	0.8 (0.5–1.2)
>1–2 years	8	7	1.4 (0.5–3.9)	1.4 (0.4–5.0)
>2–5 years	8	2	5.1 (1.1–24.5)	1.1 (0.2–6.4)
>5–10 years	1	3	0.3 (0.03–3.2)	5.5 (0.5–57.2)
Methotrexate				
No	359	354	1	1
Yes	19	24	0.8 (0.4–1.4)	0.7 (0.3–1.6)
≥4 weeks–1 year	9	9	1.0 (0.4–2.5)	0.6 (0.2–2.1)
>1–2 years	4	7	0.5 (0.1–2.0)	0.2 (0.03–1.0)
>2–5 years	6	8	0.8 (0.3–2.2)	0.9 (0.2–3.6)
Sulfasalazine				
No	335	316	1	1
Yes	43	62	0.6 (0.4–1.0)	0.6 (0.3–1.1)
≥4 weeks–1 year	22	33	0.6 (0.3–1.1)	0.4 (0.2–1.0)
>1–2 years	8	10	0.7 (0.3–1.8)	0.9 (0.3–2.8)
>2–5 years	9	14	0.6 (0.2–1.5)	0.4 (0.1–1.5)
>5–10 years	4	5	0.7 (0.2–2.6)	0.4 (0.04–3.4)
Oral steroids	183	217	0.7 (0.5–0.9)	0.6 (0.4–0.9)
Intraarticular steroids‡	168	240	0.4 (0.3–0.6)	0.4 (0.2–0.6)
NSAIDs	334	336	0.9 (0.6–1.5)	1.0 (0.5–1.9)
Aspirin	269	225	1.9 (1.3–2.6)	1.2 (0.8–1.9)

* Ever treated was defined as regular treatment for ≥4 consecutive weeks. RA = rheumatoid arthritis; OR = odds ratio; 95% CI = 95% confidence interval; NSAIDs = nonsteroidal antiinflammatory drugs.
† Adjusted for the number of other disease-modifying antirheumatic drugs (DMARDs) taken besides the one tested, and disease activity (quartiles of area under the curve). Drugs assessed, in addition to those shown, included auranofin, chlorambucil, cyclophosphamide, cyclosporine, D-penicillamine, and podophyllotoxin.
‡ Defined as injection within 1 month from signs of arthritis in ≥50% of reported flares.

Lymphoma risk in relation to RA treatment. Overall, >70% of cases and controls had received DMARD treatment (Table 2). Among those diagnosed as having RA in 1980 or later, 95% had been treated with DMARDs at some time. The mean duration of DMARD therapy was not significantly different between cases and controls; (mean 52 months [range 1–273] in cases and 44 months [range 1–222] in controls) (P = 0.13). No patients had received TNF blockade therapy. Having ever been treated with a DMARD was not associated with any increase in lymphoma risk (crude OR 0.9 [95% CI 0.6–1.2]), with or without adjustment for disease activity, and the number of DMARDs taken did not display any association with lymphoma risk (data not shown).

Based on analysis of 19 lymphoma cases treated

with methotrexate (MTX), use of this drug did not increase lymphoma risk. Two of the lymphomas occurring in MTX-treated patients were positive for EBV. While neither antimalarial agents, auranofin, chlorambucil, cyclophosphamide, cyclosporine, D-penicillamine, intramuscular gold, podophyllotoxin, nor sulfasalazine were associated with increased lymphoma risk, having ever used azathioprine (AZA) was associated with an increased risk (Table 5). Lymphoma risk linked to duration of treatment with each drug was assessed, but there were no clear time trends by duration of therapy for any of the drugs, whether adjusted for disease activity or not (Table 5).

We also assessed the interaction between DMARD therapy and AUC for cumulative disease activity. Patients in the same quartile of AUC had a tendency (nonsignificant) toward lower lymphoma risks if they had ever received DMARD treatment compared with those who had not (data not shown).

Among the 37 cases with EBV-positive lymphomas, 8 had never received DMARDs. In none of the cases with EBV-positive lymphoma did the lymphomas spontaneously regress, but among all 378 lymphomas, spontaneous regression occurred in 4. These cases included 1 patient never treated with DMARDs or corticosteroids (this patient later had a relapse of lymphoma) and 3 in whom the lymphoma regressed upon withdrawal of DMARD treatment (sulfasalazine, MTX, and AZA, respectively). The latter 3 patients had also received corticosteroid treatment for their RA.

There was a tendency toward a protective effect of oral steroids (OR 0.6 [95% CI 0.4–0.9]) and intraarticular steroids (OR 0.4 [95% CI 0.2–0.6]), calculated with adjustment for disease activity and DMARD use. Neither NSAIDs (adjusted OR 1.0 [95% CI 0.5–1.9]) nor aspirin (adjusted OR 1.2 [95% CI 0.8–1.9]) increased lymphoma risk (Table 5).

Associations were virtually unaltered when analyses were performed after exclusion of cases with lymphomas that could not be reclassified (n = 35) and cases not formally fulfilling the ACR-criteria (n = 40) (data not shown).

DISCUSSION

In this large case–control study of malignant lymphomas complicating RA, we have made a series of new observations: 1) A relatively small proportion of all patients with RA—those with the highest degree of inflammatory disease activity—have a dramatically increased lymphoma risk. 2) Treatment with most common DMARDs or antiinflammatory drugs is not in itself a risk factor for RA-associated lymphomas, nor does treatment further increase the risk associated with high inflammatory activity. 3) Although most "excess" lymphomas in RA are of the aggressive DLBCL type, the association with high disease activity also applies to other subtypes. 4) The presence of EBV in RA-associated lymphomas is low.

The strength of this study is its setting and combination of data sources. The population-based Swedish health care data combined with unique personal identifiers, high-quality, population-based health and census registers, original medical records from in- and outpatient medical care, and biobanks at pathology departments all over the country enabled us to compile detailed data on exposure (the fluctuating disease activity typical of RA, and its treatments) and outcome (reclassified and EBV-tested lymphomas). The underlying cohort of patients hospitalized with RA between 1964 and 1994 provided a well-defined source population for selection of controls and a wide range of exposure with respect to disease activity and treatments. Today, treatment of RA is not only more intensive, but also more uniform, thereby reducing the ability to dissect the collinear association between disease and treatment. Our study design also minimized recall and information bias and provided a sample size that was 10-fold higher than populations in related studies previously reported in the literature (6,7).

In our previous work (6), disease activity was linked to lymphoma risk in a nonlinear manner. Therefore, to classify each level of monthly disease activity in the cumulative disease activity score (inactive, low, medium, and high) as accurately as possible, we investigated the effect of each level of disease activity on lymphoma risk by conditional logistic regression, and used the estimates derived from this analysis for the scoring (0, 1, 5, or 8). Although this approach is not without limitations, it is an attempt to base the scoring on the actual situation rather than just using an arbitrary 0–3 score. We did, however, perform a comparison with scores of 0–3 and found somewhat different ORs, but still a striking association with cumulative disease activity (data not shown). Thus, irrespective of the measure of burden of disease activity (overall disease activity, functional class, cumulative disease activity, ESR, irreversible joint damage), the results indicate a clear association of lymphoma development with chronic inflammatory activity, thereby extending the results of our pilot study (6) to show that the risk of lymphoma among RA

patients is indeed mostly limited to those with longstanding and high disease activity.

Although cases and controls were matched both by year of birth and by calendar year of first RA discharge, review of the medical records revealed a small difference in disease duration between cases and controls (due to longer duration from onset of RA until first hospitalization in cases than in controls). To assess the impact of this difference, we stratified patients by disease duration and investigated lymphoma risk linked to AUC. We found no significant differences, which supports the notion that cumulative disease activity, rather than the time taken for it to accrue, is the major determinant of lymphoma risk.

Since our study was based on data obtained from routine medical files, there was not sufficient information to calculate repeatedly obtained data included in standard measures of disease activity, e.g., the 28-joint Disease Activity Score (DAS28) (33). Assuming that the swollen joint count is generally equivalent to the tender joint count, our definition of high disease activity would, however, broadly correspond to a DAS28 of >5.7 and low activity to a DAS28 of <4.3.

Exposure to DMARDs was less common than would be expected from current guidelines for treatment of RA, but fully reasonable considering treatment practices during the study period. Of all the medical treatments assessed, we observed increased risks associated only with AZA, which is consistent with the results of some previous studies (13,14,34) but discordant with the results of others (35). However, we noted no differences in the proportion of EBV-positive lymphomas or the distribution of lymphoma subtypes among the patients who had been treated with AZA. AZA has not been regarded as a traditional DMARD for RA and is sparsely used in RA today.

Case reports and case series have linked MTX treatment to lymphomas, often EBV positive, that are characterized by spontaneous regression once MTX is withdrawn (10,11,36,37). Investigators in France (17) recently reported on the heretofore largest number of studied RA patients who developed lymphoma and had been treated with MTX (n = 25). Although the definition of the underlying cohort hampers our ability to draw inferences from that study, no overall association between lymphoma risk and MTX treatment was observed, but 3 of the 25 lymphomas remitted after MTX was stopped (although 2 subsequently relapsed). Based on 19 cases of lymphoma occurring in MTX-treated RA patients in our well-defined population-based cohort, we did not observe any increase in lymphoma risk associated with MTX, nor did we find an increased occurrence of EBV-positive lymphomas, or any EBV-positive lymphoma that regressed spontaneously. Our results therefore suggest that although MTX might be associated with lymphomas that can regress upon treatment withdrawal, such lymphomas are likely to constitute a small minority of all lymphomas that occur in RA patients exposed to MTX, and MTX does not appear to increase overall lymphoma risk.

We found no risks linked to duration of DMARD treatment. However, for some of the individual DMARDs, analyses were based on only a few patients in each interval of treatment duration, and results should be interpreted with some caution.

By and large, our results suggest that treatment with traditional DMARDs, including MTX, is not a risk factor for malignant lymphoma in RA and does not further increase the elevated lymphoma risk in patients with high disease activity. Since DMARDs act to reduce inflammatory activity, which exhibited a strong association with lymphoma risk, and since several of the drug-specific relative risk estimates were below, rather than above, 1.0, DMARD treatment may in reality be associated with a reduction in lymphoma risk.

We found risk estimates below 1.0 to also be linked to corticosteroid use, which suggests a lymphoma-protective effect of this treatment as well. Of interest, lymphoma risk was particularly low in patients who had received frequent intraarticular corticosteroid injections in inflamed joints. A lymphoma-protective role of corticosteroids is theoretically possible; apart from being potent antiinflammatory drugs, corticosteroids are included in antilymphoma treatment and exert their effects through many mechanisms, one being apoptosis of hematologic cells (38).

Besides the association between degree of inflammatory disease and DLBCLs, we observed a 5-fold risk gradient with other lymphoma subtypes, suggesting that the lymphomagenic potential of inflammation either may be nonspecific or may exert its influence on pathways common to several lymphoma types. The fact that the proportion of lymphomas that were EBV positive (common in immunocompromised individuals [39]) was not high indirectly supports our conclusion that immunostimulation, rather than immunosuppression, is the driving force in inflammation-associated lymphomas.

The restriction of our case and control subjects to those whose RA ever required hospitalization may have led to selection of individuals with more severe RA, but does not explain the association with disease activity. The underlying cohort was population based, and we

estimate that it covers >50% of all patients with RA in Sweden during the study period, so this restriction is unlikely to have substantially affected generalizability of the results. The inclusion of patients discharged with RA as either the main or a contributory diagnosis increased the number of cases and controls who were in the hospital for reasons other than severe RA. This study spanned many years, and to avoid possible calendar period–related differences in threshold for hospitalization, register coverage, and treatment type and intensity, patients were matched for the year of first RA discharge and county of residence.

The comparatively high proportion of males in our study (45%) must be interpreted in light of the higher lymphoma incidence among males (5,28). There were, however, no significant differences in results between men and women when analyses of disease activity were stratified by sex.

We did not exclude patients with lymphoma diagnosed within the first year after the first discharge for which RA was listed. This may have led to the inclusion of some RA patients who were hospitalized due to the emerging lymphoma (confounding by indication), but allowed us to achieve a more complete study that encompassed all RA-related lymphomas that could be identified with the register-based approach. High cumulative disease activity was characteristic of the patients with lymphoma diagnosis soon after the first discharge for RA.

Given the many uncertainties regarding the link between malignant lymphomas and chronic inflammatory diseases, and the difficulties in judging the lymphoma risks associated with new therapies, the implications of the present results are substantial. The association between lymphoma risk and very high and/or longstanding disease activity indicates that most patients with RA will never have any clinically relevant increased lymphoma risk. In contrast, those who do may have highly increased risks, but can be readily identified based on their accrued inflammatory burden. Conventional medical treatment to suppress and alleviate disease activity is not by itself a risk factor for lymphoma. Rather, it is possible that aggressive treatment may reduce lymphoma risk by reducing cumulative inflammation. From a drug safety perspective, our results provide background data that should be considered essential for the evaluation of lymphoma risk following therapy with TNF blockers, for example, as well as other new drugs.

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