EXTENDED REPORT

Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers

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ABSTRACT

Background Safety data on cancer risks following tumour necrosis factor α inhibitors (TNFi) in patients with spondyloarthritis (SpA) (here defined as ankylosing spondylitis (AS), undifferentiated spondarthropathies (SpA UNS), psoriatic arthritis (PsA)) are scarce. Our objective was to assess risks for cancer overall and for common subtypes in patients with SpA treated with TNFi compared with TNFi-naive patients with SpA and to the general population.

Methods From the Swedish (Anti-Rheumatic Therapy in Sweden (ARTIS)) and Danish (DANBIO) biologics registers, we assembled 8703 ARTIS=5448, DANBIO=3255 patients with SpA initiating a first TNFI 2001–2011. From the Swedish National Patient and Population Registers we assembled a TNFI-naive SpA cohort (n=28,164) and a Swedish age-matched and sex-matched general population comparator cohort (n=131 687). We identified incident cancers by linkage with the nationwide Swedish and Danish Cancer Registers 2001–2011, and calculated age-standardised and sex-standardised incidence ratios as measures of relative risk (RR).

Results Based on 1188 cancers among the TNFI-naive patients with SpA, RR of cancer overall was 1.1 (95% CI 1.0 to 1.2). Based on 147 cancers among TNFI initiators with SpA, RR versus TNFI-naive was 0.8 (95% CI 0.7 to 1.0) and results were similar for AS and PsA when analysed separately. Site-specific cancer RRs: prostate 0.5 (95% CI 0.3 to 0.8), lung 0.6 (95% CI 0.3 to 1.3), colorectal 1.0 (95% CI 0.5 to 2.0), breast 1.3 (95% CI 0.9 to 2.0), lymphoma 0.8 (95% CI 0.4 to 1.8) and melanoma 1.4 (95% CI 0.7 to 2.6).

Conclusions In patients with SpA, treatment with TNFI was not associated with increased risks of cancer, neither overall nor for the six most common cancer types.

INTRODUCTION

Treatment with tumour necrosis factor α inhibitors (TNFi) has become a mainstay in the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA) and spondyloarthritis (SpA), here defined as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and undifferentiated spondyloarthropathies (SpA UNS). Yet, despite more than a decade of use, cancer risks with TNFi are still not completely understood. Most available data come from patients with RA, and have not demonstrated any increased overall cancer risks¹–⁷ although results are conflicting.⁸ ⁹ These risk assessments are complicated by the fact that patients with RA per se have an increased risk of certain cancer types, including malignant lymphomas and lung cancer, compared with the general population¹⁰ ¹¹ and that high RA disease activity may further modify such site-specific cancer risks.¹² Further, RA therapy is typically characterised by concomitant use of non-biological DMARDs (disease-modifying antirheumatic drugs) that alone or in combination with TNFi could lead to a possible synergistic effect on the risk of cancer. Finally, data from RA mainly pertain to patient populations typically consisting of women between 40 and 60 years of age.

In contrast to the accumulating literature on cancer risks in RA, data on cancer risks in patients with SpA, in particular those following TNFi treatment, are limited (table 1), and have so far been hampered by low power,⁶ ¹³ ¹⁴ and short follow-up.¹⁵ ¹⁶

The net effect of TNFi on cancer risk may vary across inflammatory diseases, and across populations as defined by age, sex and by exposure to different lifestyle factors or antirheumatic treatment. Thus, apart from the immediate clinical importance considering the increasing use of TNFi in SpA, the study of cancer risk in these patients may provide new insights different from RA cohorts: patients with SpA are younger, often male, have different lifestyles, frequently use biological DMARDs as monotherapy and have no intrinsic associations with, for example, malignant lymphoma.¹⁷

The aim of this study was therefore to evaluate the role of TNFi on the risk of cancer overall, and of the most common cancer types, in a large cohort of patients with SpA. To do this, we combined data from the nationwide and population-based Swedish and Danish healthcare registers including mandatory cancer reporting, and clinical registers including the nationwide Swedish (Anti-Rheumatic Therapy in Sweden (ARTIS)) and Danish (DANBIO) biologics registers.

METHODS

Study design

Population-based nationwide cohort study of patients with SpA in Sweden and Denmark, and
matched general population comparators from Sweden. The main exposure of interest was TNFi treatment. A secondary exposure was being TNFi-naïve (ie, patients with SpA who had never received TNFi). The outcome was cancer overall and six common cancer types.

**Study setting**

From an international perspective, the healthcare systems in Sweden and Denmark are similar (both are public and tax funded). Patients with SpA who are treated with DMARDs including TNFi are typically treated in public care by rheumatologists, most of whom work in hospital-based care. However, in particular, prior to the era of treatment with biological agents, a significant proportion of patients were jointly cared for by internists and primary-care physicians. Personal identification numbers in both countries permit linkage of information from national and virtually complete registers on demographics, morbidity and mortality.

Because of the register-based epidemiological design without patient contact, this study was exempt from approval by the ethical committees according to Danish law. Approval by the Danish Data Protection Board Agency was obtained. The Swedish part was approved by the Stockholm Ethics Review Board. All raw data resided with the register holders.

**Data sources used**

**Sweden**

The Swedish biologics register (ARTIS) is a subset of the Swedish Rheumatology Quality register and includes adult patients with rheumatic diseases starting any antirheumatic biological drug treatment since 1999. At start of treatment and at follow-up visits, the treating rheumatologist enters details of the disease activity and antirheumatic treatment. The coverage of biological therapies in SpA is approximately 90%. The Swedish outpatient register started in 2001 and includes information on diagnoses in specialist outpatient care (non-general practice visits) coded according to ICD-10 [international classification of diseases, 10th revision](https://www.icd-10-nci-cancer.gov/). Search terms used: Psoriatic arthritis, Ankylosing spondylitis, Spondylarthritis+Tumour Necrosis Factor (TNF) inhibitor+cancer, malignancy, co-morbidity; English, 1980–2015. *Compared with the general population.

<table>
<thead>
<tr>
<th>Type of condition</th>
<th>Author (ref) publication year</th>
<th>Type of study</th>
<th>N cancers/N study population</th>
<th>Relative risks of cancer overall (HR, OR, IRR, SIR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS/PsA</td>
<td>Burmester 2012*</td>
<td>RCT</td>
<td>N cancers not available 1684 patients with AS 837 patients with PsA</td>
<td>SIR AS 0.51 (0.16 to 1.19) PsA 0.68 (0.22 to 1.59)</td>
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<td>Meta-analysis</td>
<td>N cancer TNFi exposed; 28 Placebo group; 4 /Total 6810 patients 20% PsA, 80% Psoriasis</td>
<td>OR for entire group 1.48 (0.71 to 3.09)</td>
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<tr>
<td>AS</td>
<td>van der Heijde 2014*</td>
<td>Pooled analysis from 5 RCTs</td>
<td>N cancer 6/1074</td>
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</tr>
</tbody>
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*Compared with the general population.

AS, ankylosing spondylitis; IRR, incidence rate ratio; PsA, psoriatic arthritis; RCT, randomised clinical trial; SIR, standardised incidence ratio; TNFi, tumour necrosis factor inhibitor.

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**Clinical and epidemiological research**

**Table 1** Seminal studies on risks of cancer in patients with AS and PsA treated with TNF inhibitors (TNFi)

<table>
<thead>
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*Compared with the general population.

AS, ankylosing spondylitis; IRR, incidence rate ratio; PsA, psoriatic arthritis; RCT, randomised clinical trial; SIR, standardised incidence ratio; TNFi, tumour necrosis factor inhibitor.

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**Denmark**

The Danish biologics register (DANBIO). Danish rheumatologists have voluntarily registered rheumatologic patients treated with biologic DMARDs prospectively in the DANBIO registry since 2000. Chart reviews indicate that the positive predictive value of ICD-10 codes for AS (M45) and PsA (L40.5) is >80%. The Swedish national cancer register was established in 1958. Reporting of incident cancers is mandatory. This results in a coverage of >95%. The register contains data on date and type of cancer (ICD classification according to the WHO), ICD-O morphology and topography codes. The Swedish population register includes data on residency, dates of immigration and emigration for all people ever resident in Sweden from 1961 and onwards. Coverage is virtually complete. The Swedish cause of death register is updated annually and provides information on dates and causes of death for all deceased residents from 1952 and onwards.

**Study populations**

We identified and combined (i) two national cohorts of patients with SpA initiating TNFi, (ii) one Swedish cohort of TNFi-naïve patients with SpA and (iii) one Swedish general population comparator cohort. The study period was from 1 January 2001 through 31 December 2011.
I. **TNFi initiators** Through ARTIS and DANBIO we identified all individuals registered with a SpA diagnosis who started a TNFi treatment with any of the five TNFi (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) that were approved in Sweden and Denmark during the study period. We defined SpA as AS (ICD10=M05.9), PsA (ICD10=M06 and L40.5) and SpA UNS (ICD10=M46.8-9) as recorded by the rheumatologist in the registers. SpA UNS typically included patients with predominantly inflammatory back pain or peripheral arthritis that did not fulfil diagnosis of AS or PsA. We identified 8703 patients with SpA initiating TNFi (5448 from ARTIS and 3255 from DANBIO). Start of follow-up for individual patients began at start of their first TNFi treatment initiation.

II. **TNFi-naïve SpA** We identified all individuals who had had ≥1 visits in the Swedish outpatient register at a rheumatology or an internal medicine department with a diagnosis of SpA according to the above-mentioned ICD codes. The first visit served as start of follow-up. We excluded patients who had ever received a diagnosis of RA (ICD10 M05.9, M06), systemic lupus erythematosus (ICD10 M32) or juvenile idiopathic arthritis (ICD10 M08 and M09) in the outpatient register. We excluded individuals <16 years of age (the cut-off between paediatric and adult care in Sweden). To avoid the possibility that an underlying cancer was misclassified as SpA or constituted the reason for the visits that led to inclusion in the cohorts under study, we excluded all patient-time and all events during the first 90 days of follow-up, resulting in 28 164 TNFi-naïve patients with SpA. In a sensitivity analysis, we also applied a stricter definition of the TNFi-naïve SpA cohort, requiring ≥2 outpatient specialist visits for the patients, with the second visit as start of follow-up (n=23 175).

III. Through linkage to the Swedish population register we assembled a general population comparator cohort to the Swedish TNFi-naïve SpA cohort, matched 1:5 on age (year of birth), sex and county of residence. For a small proportion of patients (<7%), less than five comparator subjects could be identified. In total, we identified 131 687 comparator subjects. For these comparator subjects, we assigned the same date for start of follow-up as their patient with matched index SpA.

By linking all individuals in the study populations to the Cause of Death registers and to the Population Registers in Sweden and Denmark we collected information on date of emigration and date of death during the entire study period.

### Definition and assessment of outcome

We linked the study populations to the Swedish and Danish cancer registers, respectively, and identified all incident cancers in 2001–2011. Since we used first ever invasive cancer as our outcome definition, we excluded all individuals with a history of cancer at the time of entry into each cohort. Follow-up began as described above for each cohort. Follow-up ended at the earliest of any cancer diagnosis, emigration, death, start of first TNFi treatment (for the TNFi-naïve cohort) or end of study period. Patients contributed person-time and events to the TNFi-naïve patient cohort until they started a first ever TNFi. From that time point and onwards, they contributed person-time and events to the TNFi-exposed cohort.

### Statistical analyses

We calculated age-standardised and sex-standardised incidence ratios as measure of relative risk (RR), assuming a Poisson distribution among the observed cases. When we compared the TNFi-treated or the TNFi-naïve patients with SpA versus the Swedish general population comparator subjects, we used the latter as standard for the age/sex weights. When we compared TNFi-treated versus TNFi-naïve patients with SpA the TNFi-naïve served as standard.

Standardisation was performed by 5-year age groups (until 85 years, then 85+) and sex.

To confirm that Swedish TNFi-naïve patients with SpA were a reasonable comparator also for Danish TNFi-treated patients we compared separate RRs (vs the TNFi-naïve patients) in TNFi-treated patients with SpA based on DANBIO and ARTIS, respectively. We assessed RRs overall and separately for six common cancer types (prostate, lung, colorectal, breast cancer, malignant lymphoma and melanoma), separately for AS, PsA and SpA UNS, and separately for Swedish and Danish patients (see online supplementary table S1). When number of events were <5 we abstained from estimating RRs.

To reveal any potential differences in stage of cancer at time of cancer diagnosis (ie, patients with SpA could potentially be

### Table 2 Characteristics of patients with SpA from ARTIS and DANBIO treated with TNFi (n=8703), Swedish TNFi-naïve SpA patients (n=28 164) and age- and sex-matched Swedish general population comparator subjects (n=131 687) 2001 to 2011

<table>
<thead>
<tr>
<th></th>
<th>All SpA</th>
<th>AS</th>
<th>PsA</th>
<th>All SpA</th>
<th>AS</th>
<th>PsA</th>
<th>All SpA</th>
<th>AS</th>
<th>PsA</th>
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<tbody>
<tr>
<td>TNFi-treated patients</td>
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<tr>
<td>DANBIO</td>
<td>3255</td>
<td></td>
<td></td>
<td>5448</td>
<td></td>
<td></td>
<td>8703</td>
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</tr>
<tr>
<td>ARTIS</td>
<td>1491 (46)</td>
<td>1587 (29)</td>
<td>3078 (35)</td>
<td>7023 (23)*</td>
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<tr>
<td>TNFi-treated patients</td>
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<tr>
<td>DANBIO+ARTIS</td>
<td>1342 (41)</td>
<td>2491 (46)</td>
<td>3833 (44)</td>
<td>15 908 (51)*</td>
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<tr>
<td>TNFi-naïve patients</td>
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<tr>
<td>Sweden</td>
<td>422 (13)</td>
<td>1370 (25)</td>
<td>1792 (21)</td>
<td>8066 (26)*</td>
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<tr>
<td>General population</td>
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<tr>
<td>comparator cohort</td>
<td>422 (13)</td>
<td>1370 (25)</td>
<td>1792 (21)</td>
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</tbody>
</table>

*The number of patients is the sum of all unique individuals with any diagnosis of SpA; ie the total sum of the AS/PsA and SPA UNS cohorts together is bigger as, according to the definition of AS/PsA and SPA UNS, an individual can be in more than one of these cohorts. The percentage is based on the AS/PsA and SpA UNS cohorts summed together (n=30 997).

†The same applies to the general population comparator cohort; that is, the percentage is based on the total sum of all comparators=145 250.

ARTIS, Anti-Rheumatic Therapy in Sweden; AS, ankylosing spondylitis; DANBIO, Danish biologics register; PsA, psoriatic arthritis; SpA, spondyloarthritides; TNFi, tumour necrosis factor inhibitor.
diagnosed at an earlier stage of their cancer due to closer surveillance), we examined the stage distribution using the TNM-classification of solid tumours\(^\text{32}\) and compared the Swedish patients with SpA versus the general population comparators. Differences in the distribution were tested for by \(\chi^2\) test. These analyses only included individuals with a cancer diagnosis after 2003 (N cancers SpA=1097), as information on TNM classification was only available from that year.

All analyses were performed in SAS (V9).

**RESULTS**

**Overall cancer risks in TNFi-treated versus TNFi-naïve SpA**

Of the 8703 TNFi initiators in ARTIS and DANBIO, 5022 (58%) were men. The median age at start of treatment was 5.6 years (IQR 1.0–10.2 years).

During a total of 33 908 person-years of follow-up of all TNFi initiators, we observed 147 cancers (crude incidence 434 (95% CI 366 to 509) per 100 000 person-years). Compared with the TNFi-naïve patients with SpA (above), this resulted in a small and non-significantly reduced RR of cancer overall in TNFi initiators, RR=0.8 (95% CI 0.7 to 1.0). We found similar results when we analysed AS, PsA and SpA UNS separately (table 3). For male patients with SpA the RR of cancer overall in TNFi-treated versus TNFi-naïve was 0.7 (95% CI 0.5 to 0.9). Corresponding RR in female patients was 0.8 (95% CI 0.6 to 1.2).

When TNFi initiators from ARTIS and DANBIO were compared with each other, we noted a tendency towards a lower crude incidence of cancer overall in the ARTIS patients (395 (95% CI 366 to 509) compared with 510 (95% CI 387 to 659)) in DANBIO, but the RRs were largely similar (see online supplementary table S1).

When we applied a stricter exposure definition (ie, required \(\geq\) 2 outpatient visits with SpA) for the TNFi-naïve SpA comparators, results remained unchanged (RR; TNFi-treated vs TNFi-naïve 0.8 (95% CI 0.7 to 1.0) based on 758 cancers in 23 175 TNFi-naïve patients with SpA).

**Overall cancer risks in TNFi-naïve SpA versus the general population**

During 182 136 person-years in the TNFi-naïve SpA cohort, 1188 incident cancers occurred (crude incidences 598 (95% CI 581 to 614) per 100 000 person-years). Compared with the

**Table 3** Relative risk* of cancer overall in TNFi-treated patients with SpA from ARTIS and DANBIO (n=8703)† versus Swedish TNFi-naïve SpA patients (n=28 164)† and Swedish general population comparator subjects (n=131 687)† overall and in AS, PsA and SpA undifferentiated (UNS) separately 2001 to 2011

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>TNFi (DANBIO and ARTIS)-treated patients with SpA versus TNFi-naïve</th>
<th>TNFi-treated (DANBIO and ARTIS) patients with SpA versus general population</th>
<th>TNFi-naïve patients with SpA versus the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N cancers</td>
<td>TNFi-treated/TNFi-naïve</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>All SpA</td>
<td>147/1188</td>
<td>0.8 (0.7 to 1.0)</td>
<td>147/1513</td>
</tr>
<tr>
<td>AS</td>
<td>53/310</td>
<td>0.8 (0.6 to 1.1)</td>
<td>53/1296</td>
</tr>
<tr>
<td>PsA</td>
<td>71/722</td>
<td>0.9 (0.7 to 1.1)</td>
<td>71/3227</td>
</tr>
<tr>
<td>SpA UNS</td>
<td>23/200</td>
<td>0.9 (0.6 to 1.3)</td>
<td>23/979</td>
</tr>
</tbody>
</table>

*Age-standardised and sex-standardised incidence ratio (RR) with 95% CIs.

†DANBIO and ARTIS=TNFi-treated SpA, persons-years=33 908, Swedish TNFi-naïve patients with SpA, person-years=182 136, Swedish general population comparator subjects, person-years=862 380.

ARTIS, Anti-Rheumatic Therapy in Sweden; AS, ankylosing spondylitis; DANBIO, Danish biologics register; PsA, psoriatic arthritis; RR, relative risk; SpA, spondyloarthritides; TNFi, tumour necrosis factor inhibitor.
general population cohort (5153 cancers during 862,380 person-years) (crude incidence 652 (95% CI 616 to 690) per 100,000 person-years) this corresponded to an RR of cancer overall in TNFi-naïve SpA of 1.1 (95% CI 1.0 to 1.2). This risk remained largely the same when we estimated risk of cancer overall in TNFi-naïve AS, PsA and SpA UNS separately (table 3). There were no significant differences in cancer risk overall in TNFi-naïve male patients with SpA (RR=1.1, 95% CI 1.0 to 1.2) and female patients (RR=1.0; 95% CI 0.9 to 1.1) compared with their general population comparator subjects.

**Site-specific cancer risks**

Tables 4 and 5 display site-specific RRs comparing TNFi-treated to TNFi-naïve patients, and TNFi-naïve patients to the general population. We observed a decreased risk of prostate cancer, RR=0.5 (95% CI 0.3 to 0.8) in TNFi-treated versus TNFi-naïve patients with SpA, but found a small but reciprocating increased risk in TNFi-naïve patients with SpA versus the general population, RR=1.2 (95% CI 1.1 to 1.4, table 4). For the other cancer types there were no signals of increased risk associated with TNFi treatment although point estimates above 1 were noted for malignant melanoma and breast cancer (table 4). In patients with PsA-treated versus TNFi-naïve, the RR of breast cancer reached statistical significance; RR=1.8 (95% CI 1.1 to 2.9), based on 20 events (table 5).

We found no difference in the distribution of stage at cancer diagnosis (data not shown).

**DISCUSSION**

We made the following key observations: (i) there were no increased risks of cancer overall, nor of the six most common cancer types in TNFi-treated patients compared with TNFi-naïve patients with SpA, (ii) there was a decreased risk of colorectal cancer in TNFi-naïve patients with AS versus the general population.

Our observation of an unaltered cancer risk overall following treatment with TNFi in patients with SpA is consistent with the findings of previous, although relatively few and smaller studies in SpA (table 1) and with data from RA.1–7 While we noticed a tendency towards a decreased risk of cancer overall associated with TNFi treatment, mainly driven by a reduced risk of prostate cancer and a point estimate below 1 also for lung cancer, these findings may reflect pretreatment selection of patients, for example, through screening with blood test and chest X-rays, leading to earlier detection of incipient cancer. Additionally a decreased RR may also represent a chance finding as a result of the multiple significance tests performed.

Previous studies have suggested a possible increase in the melanoma risk in patients with RA treated with TNFi.13–15 In the current study we did not find any significantly increased risks of malignant melanoma in association with TNFi therapy in SpA, but note that the point estimate (RR=1.4) was of similar magnitude to that in previous studies on melanoma risk with TNFi in RA. However, apart from any biological mechanisms behind such an association, a finding of an elevated melanoma risk could also reflect increased cancer surveillance following TNFi treatment. This could likewise apply for our observed increased risk of breast cancer following TNFi treatment in patients with PsA. Alternatively, the increased risk of breast cancer may be a chance finding or due to confounding from reproductive or other risk factors.

Although data on underlying risk of cancer types in AS, in the absence of TNFi, are scarce, our findings (eg, reduced risk
for colorectal cancer) are consistent with previous observation, and may be reflective of long-term use of NSAIDs.

Our study has several strengths and limitations. Linkage of ARTIS and DANBIO enabled us to assemble large population-based cohorts that included the majority of adult patients in Sweden and in Denmark with SpA that started TNFi during the study period. The large cohort size made it possible to assess cancer risks both with respect to cancer types and in AS and PsA separately. Cancer was identified through linkage of the study population to the Swedish and Danish Cancer Registers, to which reporting is mandatory for all clinicians, which results in a very high completeness. The use of this external and independent source based on mandatory reporting for the assessment of cancer minimises the risk of bias from selective recall or reporting related to knowledge of treatment status.

Some limitations should also be mentioned. Although this study represents the so far largest assessment of cancer risk following initiation of TNFi therapy in patients with SpA, precision in some of the analyses was still limited, particularly in the assessment in subsets of patients and for specific cancer types. Although the unaltered risk of cancer overall is comforting, altered risk for cancers at less common sites may have been overlooked. Despite our comparatively long follow-up (median 5.6 years), this time span may still not be long enough to detect effects of TNfi therapy that occur many years after exposure. Although the healthcare systems, cancer registration and cancer rates were largely similar, the comparison of Danish TNFi-treated to Swedish TNFi-naïve patients with SpA may introduce elements of confounding and/or selection bias.

During our study period, the subclassification of SpA has also changed, as has clinicians’ attention to subclassifying SpA in clinical practice. Such differences may explain the somewhat different distributions of SpA in ARTIS and DANBIO (table 2), but as the RR of cancer did not differ between different SpA subgroups we do not believe that any such internal classification differences have influenced our results. Finally as a result of the register-based design we were unable to fully control for potential confounding from factors influencing treatment decisions such as comorbidity (other than a previous cancer) and disease severity when comparing patients treated or not with TNFi.

In conclusion, in this nationwide study of Swedish and Danish patients with SpA, we neither found increased risks of cancer overall nor (with one exception in a subset analysis) for six common cancer subtypes. This applied both to TNFi-naïve and TNFi-treated patients.

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Competing interests
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