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Original article

Risk of solid cancers overall and by subtypes in patients with psoriatic arthritis treated with TNF inhibitors – a Nordic cohort study

Karin Hellgren [1,2,*], Christine Ballegaard[3,4,*], Bénédicte Delcoigne[1], René Cordtz [3,4], Dan Nordström[5], Kalle Aaltonen[6], Bjorn Gudbjornsson[7], Thorvardur Jon Love[8], Sella Aarrestad Provan [9], Joe Sexton[9], Kristian Zobbe[3,4], Lars Erik Kristensen[3], Johan Askling[1,2,*] and Lene Dreyer[3,10,11,*]

Abstract

Objectives. To investigate whether TNF inhibitors (TNFi) are associated with increased risk of solid cancer in patients with psoriatic arthritis (PsA).

Methods. From the Nordic clinical rheumatology registers (CRR) here: SRQ/ARTIS (Sweden), DANBIO (Denmark), NOR-DMARD (Norway), ROB-FIN (Finland) and ICEBIO (Iceland) we identified PsA patients who started a first TNFi 2001–2017 ($n = 9655$). We identified patients with PsA not treated with biologics from (i) the CRR ($n = 14\ 809$) and (ii) the national patient registers (PR, $n = 31\ 350$). By linkage to the national cancer registers, we collected information on incident solid cancer overall and for eight cancer types. We used Cox regression to estimate hazard ratio (HR) with 95% CI of cancer (per country and pooled) in TNFi-exposed *vs* biologics-naïve, adjusting for age, sex, calendar period, comorbidities and disease activity. We also assessed standardized incidence ratios (SIR) in TNFi-exposed PsA *vs* the general population (GP).

Results. We identified 296 solid cancers among the TNFi-exposed PsA patients (55 850 person-years); the pooled adjusted HR for solid cancer overall was 1.0 (0.9–1.2) for TNFi-exposed *vs* biologics-naïve PsA from the CRR, and 0.8 (0.7–1.0) *vs* biologics-naïve PsA from the PRs. There were no significantly increased risks for any of the cancer types under study. The pooled SIR of solid cancer overall in TNFi treated PsA *vs* GP was 1.0 (0.9–1.1).

Conclusion. In this large cohort study from five Nordic countries, we found no increased risk of solid cancer in TNFi-treated PsA patients, neither for solid cancer overall nor for eight common cancer types.

CLINICAL SCIENCE

Rheumatology key messages

- Treatment with TNFi is not associated with increased risks of solid cancer overall, or eight common cancer types.
- There were no signals of different crude incidence of solid cancer overall across TNFi agents.
- The findings are of clinical importance for risk communication with patients with PsA.

[1]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, [2]Rheumatology, Theme Inflammation & Infection, Karolinska University Hospital, Stockholm, Sweden, [3]Bispebjerg and Frederiksberg, The Parker Institute, Copenhagen University Hospital, [4]Centre for Rheumatology and Spine Diseases, Rigshospitalet - Gentofte, Hellerup, Denmark, [5]Department of Medicine and Rheumatology, ROB-FIN, Helsinki University Hospital and Helsinki University, [6]ROB-FIN, Pharmaceuticals Pricing Board, Ministry of Social Affairs and Health, Helsinki, Finland, [7]Centre for Rheumatology Research, Landspitali University Hospital, and Faculty of Medicine, [8]Department of Science and Faculty of Medicine, National University Hospital of Iceland, University of Iceland, Reykjavik, Iceland, [9]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [10]Department of Rheumatology, Aalborg University Hospital, Aalborg University and [11]DANBIO Registry, Denmark

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Correspondence to: Karin Hellgren, Karolinska Institutet, Clinical Epidemiology Division, Department of Medicine, Solna, Stockholm, Sweden. E-mail: karin.hellgren@sll.se

*Karin Hellgren, Christine Ballegaard, Johan Askling and Lene Dreyer contributed equally to this study.

Introduction

TNF inhibitor (TNFi) is a mainstay in the management of several inflammatory conditions, including PsA [1, 2]. As TNF links to essentially all steps involved in carcinogenesis, there have been concerns that TNFi may lead to increased cancer incidences [3, 4]. However, most studies evaluating this association in RA or in inflammatory bowel disease (IBD) have not reported increased cancer risks overall [5–10] compared with patients not treated with TNFi.

Several inflammatory conditions are associated with excess risks of specific cancer types (e.g. lung cancer and lymphoma in RA [11], colorectal cancer in IBD [12], and lymphoma, skin- and lung cancer in psoriasis [13–15]). In PsA, this association is less well addressed. Although available studies have not indicated any increased cancer risks overall [15–20], there are reports of increased incidences of non-melanoma skin cancer and of breast cancer [15, 16, 18, 20]. The occurrence and pattern of cancer may vary across inflammatory diseases due to differences in the underlying disease mechanisms, in the use of concomitant medications, and in lifestyle factors that are frequent in patients with PsA, such as smoking, sun exposure, alcohol consumption and obesity [21, 22]. For all of these reasons, the effects of TNFi on cancer risks in PsA should not simply be extrapolated from previous studies of other, albeit closely related, inflammatory conditions [23].

Previous studies evaluating TNFi treatment in PsA have so far not reported any overall increased risk of cancer [10, 24–28]. Reports on risks for specific cancer types are, however, scarce [24, 27, 28] and limited in precision and time of follow-up. In addition, previous data have suggested that risk of cancer may differ by type of TNFi agent given their different mechanisms of action [29–31]. Risk assessments of cancer by TNFi agent in PsA are lacking.

The aim of this large collaborative Nordic study was to evaluate the association between treatment with TNFi and the risk of solid cancer, overall and for common cancer types in patients with PsA. To do this, we combined nationwide clinical and health registers from the five Nordic countries.

Subjects and methods

Cohort identification and exposure

We performed a cohort study with data from five Nordic clinical rheumatology registers (CRR): SRQ-ARTIS (Sweden), DANBIO (Denmark), NOR-DMARD (Norway), ROB-FIN (Finland) and ICEBIO (Iceland). The study period was 2001 to 2017 (Denmark to 2014). For detailed information on setting and data sources, see supplementary file and Table S1, available at *Rheumatology* online.

We identified a TNFi-treated PsA cohort by including all adult individuals (≥18 years of age) registered with PsA in the Nordic CRR who started a first TNFi treatment during the study period ($n = 9655$). This comprised any of the five TNFi (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), including their biosimilars. The diagnosis of PsA is rheumatologist-based and clinical data are collected prospectively in all CRRs [32–37].

We identified two different bDMARD-naïve PsA cohorts:

i. Disease comparator cohort 1, defined as all adults registered with PsA in the Nordic CRRs and not treated with a bDMARD ($n = 14\,809$). Start of follow-up began at the first registration with a diagnosis of PsA in the CRR during the study period. Patients could thus first contribute to the bDMARD-naïve disease comparator 1 cohort and later (after any first start of a TNFi) to the TNFi-treated cohort. As no comparator cohort could be defined for Iceland, the Danish comparator cohort served as disease comparator cohort 1 for Iceland.
ii. Disease comparator cohort 2 (Sweden and Denmark), defined as adults registered with ≥2 ICD10 codes for PsA (M07.0-3 and L40.5) in the national patient registers (PR) in Sweden [38] or Denmark [39], and not (yet, using the same time-dependent mechanism of cohort identification as in disease comparator 1) treated with bDMARD. At least one of the ICD10-codes had to be at a rheumatology or internal medicine department. For this comparator cohort, start of follow-up began at the date of the second visit with an ICD10-code of PsA in the PR during the study period ($n = 31\,350$).

To enable risk assessments of cancer in patients with PsA *vs* the general population, we used publicly available population-based national cancer incidence rates for men and women in five-year age groups and calendar time periods for each country (Denmark, Finland, Norway and Iceland), and assembled a general population comparator cohort (Sweden). For Sweden, each patient with PsA was randomly matched on age (year of birth), sex and county of residence to five general population subjects from the Swedish Population Register ($n = 129\,102$). For the Swedish general population cohort, we began follow-up at the same date as start of follow-up for their index patient with PsA in the PR. These subjects had to be alive and free from PsA at start of follow-up of their PsA index patient.

This study was approved by the Ethics Review Board Sweden (2015/1844–31/2), Finland (73/13/03/00/2014), Norway (2011/1339 and 2017/2041), and by the National Bioethics Committee, Iceland (VSNb2017010049/03.01). For Denmark, the Danish Data Protection Agency approved the study (HGH-2016–099, 04972), but no ethical approval was required according to national legislation on registry research and data protection.

For all cohorts, we linked data for each unique individual to the cause of death and the population registers in each country to assemble information on death and migration, and in Sweden also to the national prescribed

drug register (PDR) to obtain additional information on prescribed anti-rheumatic drugs [40].

Follow-up ended at the date of first cancer of any type (except non-melanoma skin cancer, NMSC), death, emigration, end of study period and, for the bDMARD-naïve PsA cohort, start of a first bDMARD (TNFi or non-TNFi bDMARD) whichever came first.

Outcomes

By linkage to the mandatory national cancer registers (NCR) in each country [41–45], we identified any first solid cancer during time of follow-up, and correspondingly so for eight common solid cancer types: colorectal-, female breast, lung-, prostate-, corpus uteri-, liver-, pancreas-, and brain cancer, for ICD10-codes see Table S1, available at *Rheumatology* online. We excluded all individuals with a history of any previous cancer (except non-melanoma skin cancer, NMSC) before start of follow-up.

Covariates

For all PsA cohorts, we collected information on sex, age (years) and calendar period (2001–2005, 2006–2010, ≥2011) at start of follow-up, selected comorbid conditions at start of follow-up. We also extracted history of hip/knee replacement, and number of hospitalizations with a diagnosis of PsA pertaining the status at start of follow-up as a proxy for PsA disease severity. For the PsA cohorts identified in the CRR, we obtained data on disease activity and lifestyle factors at start of follow-up. For detailed information see Table S1, available at *Rheumatology* online.

Statistics

For each outcome and cohort, we estimated crude incidence rates (IRs) per 100 000 person-years. We used Cox regression (attained age as time scale) to calculate hazard ratios (HRs) with 95% CI of solid cancer overall in TNFi-treated *vs* bDMARD-naïve PsA (disease comparator 1 and 2) in each country; these estimates were then pooled. We specified four types of models: (i) crude, (ii) adjusted for sex and calendar period, (iii) additionally adjusted for selected comorbidities, hip/knee replacement (yes/no), and number of hospitalizations (0,1–2, ≥3). For PsA cohorts identified in CRR (i.e. TNFi-treated PsA *vs* disease comparator 1) we (iv) further adjusted for HAQ + DAS28-CRP (continuous) at start of follow-up. We performed analyses stratified by sex, calendar period, age categories and time since start of follow-up. Due to a high proportion of missingness, we did not adjust for BMI and tobacco smoking. To avoid the possibility that an underlying cancer was misclassified as PsA or constituted the reason for the visits that lead to inclusion in the cohorts under study we performed analyses where we excluded all person-time and all events during the first year of follow-up.

To calculate relative risks (RRs) for each cancer type in TNFi *vs* bDMARD-naïve PsA, we aggregated data across countries and performed a Poisson regression estimating pooled incidence relative risks (IRR), adjusted for five-year age categories, sex, calendar period (2001–2005, 2006–2010, ≥2011) and country. If the cancer events were less than five only, frequencies with proportions, or crude IRs (events per 100 000 person-years) were presented. All analyses were based on observed data.

We further calculated RR of solid cancer overall and for site-specific cancers in TNFi-treated PsA *vs* the general population using standardized incidence ratios (SIR), i.e. the ratio between observed and expected cancer cases during follow-up. The expected number of cancer cases was calculated by multiplying the number of person-years experienced by the cohort members with the appropriate sex- and five-year age- and calendar-specific incidence rates for cancers in the general population. For the assembled Swedish general population comparator cohort, we used Cox regression (attained age as timescale) adjusted for sex and calendar period. Country-specific estimates were then pooled.

We also estimated crude IRs of solid cancer overall for each separate TNFi agent. For this we defined exposed person-time in two different ways to account for the fact that patients often are treated with more than one TNFi. Model A, 'ever exposure', i.e. from start of any TNFi until end of follow-up regardless of any discontinuation of the first TNFi or start of any second TNFi. Model B, 'most recent drug', as in ever exposure but with censoring at any start of a subsequent bDMARD drug [46]. Thus, one patient could contribute exposed person-time for ≥1 TNFi for both these exposure models.

Sensitivity analyses

In the Swedish data (i.e. the largest dataset) we (i) restricted the analyses of TNFi treated *vs* bDMARD-naïve patients with PsA that started follow-up after 2006 and after 2011, respectively, to account for the varying penetrance of TNFi during the study period and (ii) created alternative TNFi-naïve PsA disease comparator cohorts based on start and/or switch of csDMARD treatment, in order to compare with bDMARD-naïve patients that might face a similar treatment scenario as the patients that started a TNFi.

All analyses based on individual-level data were performed within each country. The country-specific results were then pooled. Data analyses were performed in R, version 3.4.0 and in SAS, version 9.4. Within this Nordic collaboration [32], patient representatives were involved in the development of the research questions and the study design.

Results

Baseline characteristics for TNFi-treated and bDMARD-naïve patients with PsA for each country are presented in Tables 1 and 2. The majority of patients were from

Table 1 Characteristics of TNFi-treated patients with PsA at start of the first TNFi

	Sweden 2001–2017	Denmark 2001–2014	Finland 2001–2017	Norway 2001– 2017	Iceland 2001–2017
All, *n*	5957	2039	597	706	356
Male, *n* (%)	2944 (49.4)	942 (46.2)	327 (54.8)	356 (50.4)	144 (40.4)
Age (years), mean (S.D.)	48.4 (12.7)	47.3 (12.1)	48.2 (11.5)	47.1 (12.0)	48.3 (12.9)
BMI (kg/m^2)	N/A	27.5 [23.9, 30.5]	27.8 [25.0, 31.2]	N/A	29.6 [26.3, 33.3]
BMI missing (*n*, %)	5957 (100)	1737 (85.2)	148 (24.8)	706 (100)	203 (57.0)
Smoking status, *n* (%)					
Current	197 (3.3)	133 (6.5)	12 (2.0)	180 (25.5)	39 (11.0)
Previous	590 (9.9)	125 (6.1)	N/A	236 (33.4)	64 (18.0)
Never	624 (10.5)	178 (8.7)	88 (14.7)	247 (35.0)	110 (30.9)
Missing	4546 (76.3)	1603 (78.6)	497 (83.2)	43 (6.1)	143 (40.2)
Disease related characteristics at start of first TNFi					
Tender joint count (0–28)	5.0 [2.0, 9.0]	5.0 [2.0, 11.0]	1.0 [0.0, 4.0]	3.0 [1.0, 7.0]	5.00 [2.0, 8.0]
Swollen joint count (0–28)	3.0 [1.0, 6.0]	2.0 [0.0, 5.0]	1.0 [0.0, 4.0]	1.0 [0.0, 4.0]	4.0 [2.0, 6.0]
HAQ score (0–3)	0.9 [0.5, 1.3]	1.0 [0.5, 1.5]	0.9 [0.4, 1.4]	1.2 [0.7, 1.7]	1.1 [0.6, 1.6]
Missing *n* (%)	1943 (33.0)	655 (32.0)	110 (18.4)	27 (3.8)	209 (58.7)
DAS28-CRP (0–10)	4.2 [3.5, 5.0]	4.4 [3.5, 5.3]	3.7 [2.7, 4.5]	3.7 [2.9, 4.6]	4.4 [3.9, 5.0]
Missing *n* (%)	2130 (36.0)	775 (38.0)	172 (28.8)	55 (7.8)	207 (58.1)
CRP (mg/liter)	6.3 [3.0, 16.0]	7.00 [3.0, 17.0]	8.0 [3.0, 18.0]	6.0 [3.0, 16.0]	N/A
First TNFi, *n* (%)					
Adalimumab	1549 (26.0)	861 (42.2)	198 (33.2)	124 (17.6)	23 (6.5)
Certolizumab pegol	236 (4.0)	88 (4.3)	15 (2.5)	97 (13.7)	1 (0.3)
Etanercept	2363 (39.7)	531 (26.0)	211 (35.3)	294 (41.6)	77 (21.6)
Golimumab	449 (7.5)	156 (7.7)	38 (6.4)	119 (16.9)	41 (11.5)
Infliximab	1360 (22.8)	403 (19.8)	135 (22.6)	72 (10.2)	214 (60.1)
Other anti-rheumatic treatment, *n* (%) at start of first TNFi					
Methotrexate, *n* (%)	2740 (46.0)	1219 (59.8)	338 (56.6)	402 (56.9)	125 (35.1)
Oral steroid, *n* (%)	967 (16.2)	191 (9.4)	175 (29.3)	166 (23.5)	13 (3.7)
Dose of oral steroid (mg/day)	5.0 [5.0, 10.0]	10.0 [5.0, 15.0]	5.0 [5.0, 7.5]	5.0 [5.0, 10.0]	6.00 [2.0, 6.0]
Calendar year at start of first TNFi, *n* (%)					
2001–2005	703 (11.8)	375 (18.4)	123 (20.6)	125 (17.7)	38 (10.7)
2006–2010	1540 (25.8)	1034 (50.7)	221 (37.0)	236 (33.4)	84 (23.6)
2011 – end of follow- up	3714 (62.4)	630 (30.9)	253 (42.4)	345 (48.9)	234 (65.7)
Comorbidities, *n* (%) as registered up to 10 years prior to start of first TNFi					
Cardiovascular disease	317 (5.3)	128 (6.3)	36 (6.0)	16 (2.4)	N/A
COPD	79 (1.3)	33 (1.6)	4 (0.7)	65 (9.8)	N/A
Diabetes mellitus	386 (6.5)	82 (4.0)	44 (7.4)	38 (5.7)	N/A
Hypertension	788 (13.2)	169 (8.3)	86 (14.4)	N/A	N/A
Inflammatory bowel disease	109 (1.8)	33 (1.6)	20 (3.4)	6 (0.9)	N/A
Uveitis	143 (2.4)	18 (0.9)	21 (3.5)	N/A	N/A
Urethritis	35 (0.6)	2 (0.1)	0 0	N/A	N/A
No. of hospitalizations	1.0 [0.0, 2.0]	2.0 [0.0 4.0]	2.0 [1.0, 4.0]	N/A	N/A
Hip and/or knee replacement any time prior start of first TNFi	234 (3.9)	175 (8.6)	77 (12.9)	34 (4.8)	N/A

Values are median and interquartile range (IQR) if not stated otherwise. Patients who shifted from bDMARD-naïve to TNFi-treated appear in both TNFi-treated and bDMARD-naïve groups, because all switchers have two baseline records. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; HAQ: health assessment questionnaire; N/A: not available; VAS: visual analogue scale.

Sweden (62%) followed by Denmark (21%), Norway (7%), Finland (6%) and Iceland (4%).

Relative risk of solid cancer overall in TNFi treated *vs* bDMARD-naïve PsA

Among the 9655 patients with PsA (55 850 person-years) starting a first ever TNFi, we observed 296 solid cancers corresponding to an overall crude IR of 530 per 100 000 person-years, Table 3 and Table S2, available at *Rheumatology* online. This resulted in an age-, sex- and calendar period-adjusted pooled RR of 1.0 (0.9–1.2) *vs* bDMARD-naïve PsA (disease comparator 1), Fig. 1. For country-specific RRs, see Table 3/Fig. 1.

TABLE 2 Characteristics of bDMARD-naïve patients with PsA from (i) the clinical rheumatology registers and (ii) the patient registers

	TNFi naïve patients with PsA from the clinical rheumatology registers (comparator cohort 1) *n* total = 14 809				TNFi naïve patients with PsA from the patient registers (comparator cohort 2)[a] n total = 31 350	
	Sweden 2001–2017	Denmark and Iceland[b] 2001–2014	Finland 2001–2017	Norway 2001–2017	Sweden 2001–2017	Denmark 2001–2014
All, *n*	8077	3995	1634	1103	25968	5382
Male, *n* (%)	4027 (49.9)	1729 (43.3)	800 (49.0)	541 (49.0)	12 047 (46.4)	2349 (43.6)
Age (years), mean (S.D.)	52.7 (13.7)	51.4 (13.2)	50.6 (13.7)	48.5 (12.6)	52.2 (14.2)	50.7 (13.8)
BMI (kg/m^2)	N/A	26.8 [24.2, 30.7]	27.7 [24.6, 31.4]	N/A	N/A	N/A
BMI missing (*n*, %)	8077 (100)	3759 (94.1)	118 (7.2)	1103 (100)	N/A	N/A
Smoking status, *n* (%)						
Current	347 (4.3)	176 (4.4)	252 (15.4)	358 (32.5)	N/A	N/A
Previous	998 (12.4)	180 (4.5)	N/A	357 (32.3)	N/A	N/A
Never	994 (12.3)	276 (6.9)	966 (59.1)	377 (34.2)	N/A	N/A
Missing	5738 (71.0)	3363 (84.2)	416 (25.5)	11 (1)	N/A	N/A
Disease related characteristics at start of follow-up						
Tender joint count (0–28)	2.0 [0.0, 5.0]	2.0 [0.0, 6.0]	0.0 [0.0, 1.0]	4.0 [2.0, 8.0]	N/A	N/A
Swollen joint count (0–28)	1.0 [0.0, 3.0]	0.0 [0.0, 2.0]	0.0 [0.0, 1.0]	2.0 [1.0, 5.0]	N/A	N/A
HAQ score (0–3)	0.6 [0.3, 1.0]	0.6 [0.1, 1.1]	0.8 [0.2, 1.1] 482 (29.5)	1.0 [0.7, 1.6]	N/A	N/A
Missing *n* (%)	2444 (30.0)	2597 (65.0)		32(2.9)		
DAS28-CRP (0–10)	3.3 [2.4, 4.2]	3.3 [2.4, 4.3]	2.5 [1.8, 3.4]:	4.0 [3.3, 4.7]	N/A	N/A
Missing *n* (%)	2743 (34.0)	2916 (73.0)	657 (40.2)	79 (7.2)		
CRP (mg/liter)	5.0 [2.1, 10.0]	5.0 [2.0, 10.0]	4.0 [2.0, 8.0]	8.0 [4.0, 17.0]	N/A	N/A
Other anti-rheumatic treatment, *n* (%) at start of follow-up						
Methotrexate at start of follow-up, *n* (%)	4454 (55.1)	2649 (66.3)	709 (43.4)	869 (78.8)	N/A	N/A
Oral steroid at start of follow-up, *n* (%)	1122 (13.9)	158 (4.0)	222 (13.6)	284 (25.8)	N/A	N/A
Dose of oral steroid (mg/day)	7.5 [5.0, 10.0]	10.0 [5.00, 15.00]	5.0 [5.0, 7.5]	7.5 [5.0, 10.0]	N/A	N/A
Calendar year of start of follow up						
2001–2005	164 (2.0)	87 (2.2)	13 (0.8)	538 (48.8)	7762 (29.9)	1698 (31.5)
2006–2010	1676 (20.8)	1848 (46.3)	176 (10.8)	459 (41.6)	7414 (28.6)	2318 (43.1)
2011 – end of follow-up	6237 (77.2)	2060 (51.6)	1445 (88.4)	106 (9.6)	10 792 (41.6)	1366 (25.4)
Comorbidities, *n* (%) as registered up to 10 years prior to start of follow-up						
Cardiovascular disease	579 (7.2)	239 (6.0)	118 (7.2)	29 (2.6)	2153 (8.3)	417 (7.7)
COPD	173 (2.1)	85 (2.1)	23 (1.4)	64 (5.9)	568 (2.2)	147 (2.7)
Diabetes mellitus	534 (6.6)	175 (4.4)	133 (8.1)	77 (7.0)	1673 (6.4)	254 (4.7)
Hypertension	1329 (16.4)	351 (8.8)	264 (16.2)	N/A	3628 (14.0)	523 (9.7)
Inflammatory bowel disease	104 (1.3)	29 (0.7)	22 (1.3)	13 (1.2)	415 (1.6)	62 (1.2)
Uveitis	143 (1.8)	23 (0.6)	31 (1.9)	N/A	410 (1.6)	50 (0.9)
Urethritis	47 (0.6)	6 (0.2)	0 0	N/A	100 (0.4)	5 (0.1)
No. of hospitalizations	1.0 [0.0, 2.0]	1.0 [0.0, 3.0]	1.0 [0.0, 3.0]	N/A	1.0 [0.0, 2.0]	1.0 [0.0, 4.0]
Hip and/or knee replacement any time prior to start of follow-up	316 (3.9)	268 (6.7)	124 (7.6)	32 (2.9)	952 (3.7)	188 (3.5)

[a]For Finland, Norway and Iceland, this bDMARD- naïve comparator cohort was not available. [b]As no bDMARD-naïve comparator group was available for Iceland, the bDMARD-naïve patients identified through DANBIO/Denmark served as disease comparator group 1. Values are median and interquartile range except where stated otherwise. Patients who shifted from bDMARD-naïve to TNFi-treated appear in both TNFi treated and bDMARD naïve groups, because all switchers have two baseline records. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; HAQ: health assessment questionnaire; IQR: interquartile range; N/A: not available; VAS: visual analogue scale.

When we compared TNFi-treated *vs* bDMARD-naïve PsA (disease comparator 2) in Sweden and Denmark we observed an age, sex and calendar period-adjusted pooled RR of solid cancer overall of 0.8 (0.7–1.0), Fig. 1. The pooled crude IRs for the bDMARD-naïve disease comparator 1 was 656 per 100 000 person-years, and 811 for disease comparator 2 (Table S2, available at *Rheumatology* online).

In the stratified country-specific analyses, there were no significant differences in risk of solid cancer overall with respect to sex, time since or age at start of follow-up, or when the first year of follow-up was excluded, Table 3.

Table 3 RR[a] of solid cancer overall in TNFi-treated *vs* bDMARD-naïve PsA and *vs* general population

	RR (95 % CI)[a] of cancer overall in TNFi treated *vs* bDMARD-naïve PsA from the clinical rheumatology registers (comparator cohort 1)					RR (95 % CI)[a, b] of cancer overall in TNFi treated *vs* bDMARD-naïve PsA from the patient register (comparator cohort 2)		RR (95 % CI)[c] of cancer overall in TNFi-treated PsA *vs* the general population				
	Sweden	Denmark	Finland	Norway	Iceland[d]	Sweden	Denmark	Sweden	Denmark	Finland	Norway[c]	Iceland
No. of solid cancers	171 *vs* 214	54 *vs* 50	26 *vs* 24	32 *vs* 51	7 *vs* 50	171 *vs* 1396	54 *vs* 215	171 *vs* 6908	54 *vs* N/A[c]	26 *vs* N/A[c]	32 *vs* N/A[c]	13 *vs* N/A[c]
Person-years	34395 *vs* 27281	9799 *vs* 9747	4376 *Vs* 5052	5285 *vs* 9623	1995 *vs* 9747	34 395 *vs* 172 425	9799 *vs* 26 166	34 395 *vs* N/A	9799 *vs* N/A	4376 *vs* N/A	5285 *vs* N/A	1995 *vs* N/A
Relative risks (95 % CI)												
Crude	0.9 (0.7, 1.1)	1.4 (0.9, 2.0)	1.7 (0.9, 3.0)	1.4 (0.9, 2.3)	1.3 (0.6, 2.9)	0.8 (0.7, 1.0)	0.9 (0.6, 1.2)	0.9 (0.8, 1.1)	N/A[c]	N/A[c]	N/A[c]	N/A[c]
Adjusted for sex, age and calendar time	0.9 (0.7, 1.1)	1.3 (0.8, 2.0)	1.8 (0.9, 3.6)	1.4 (0.9, 2.3)	1.4 (0.6, 3.3)	0.8 (0.7, 1.0)	0.9 (0.6, 1.2)	0.9 (0.8, 1.1)	0.9 (0.7, 1.2)	1.3 (0.8 1.9)	1.1 (0.7, 1.6)	1.3 (0.7, 2.1)
Adjusted also for comorbidities, hip/knee replacements and no. of hospitalizations	0.8 (0.7, 1.0)	1.3 (0.8, 2.0)	1.8 (0.9, 3.6)	1.3 (0.8, 2.2)[e]	N/A[f]	0.8 (0.7, 1.0)	0.9 (0.7, 1.2)	0.9 (0.8, 1.0)	N/A	N/A	N/A	N/A
Adjusted also for DAS28 and HAQ at start of follow-up	1.0 (0.8, 1.4)	1.0 (0.5, 1.8)	1.9 (0.6, 5.8)	1.6 (0.9, 2.7)[e]	N/A[f]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sex												
Female	0.9 (0.7, 1.2)	2.0 (1.1, 3.4)	1.8 (0.7, 4.9)	1.2 (0.6, 2.6)	<5	1.0 (0.8, 1.2)	1.1 (0.8, 1.7)	1.1 (0.9, 1.3)	1.2 (0.9, 1.7)	1.4 (0.8, 2.4)	1.0 (0.5, 1.7)	1.0 (0.4, 2.2)
Male	0.8 (0.6, 1.1)	0.8 (0.4, 1.6)	2.0 (0.7, 5.6)	1.6 (0.8, 2.9)	<5	0.7 (0.6, 0.9)	0.6 (0.3, 1.0)	0.8 (0.6, 1.0)	0.6 (0.3, 1.0)	1.2 (0.6, 2.1)	1.2 (0.7, 2.0)	1.6 (0.6, 3.2)
First year of follow up excluded from analysis	0.9 (0.7, 1.1)	1.4 (0.9, 2.3)	1.5 (0.7, 3.2)	1.4 (0.9, 2.4)	<5	0.9 (0.8, 1.1)	1.0 (0.7, 1.4)	1.0 (0.8, 1.1)	N/A	N/A	N/A	N/A
Time since start of follow-up (years)												
<1year	0.6 (0.3, 1.0)	0.5 (0.1, 2.4)	1.4 (0.1, 16.0)	<5	<5	0.5 (0.3, 0.8)	0.2 (<0.1, 0.8)	0.6 (0.4, 1.0)	0.2 (<0.1, 0.8)	0.5 (<0.1, 2.8)	0.3 (0.0, 1.8)	<5
1–4 years	0.9 (0.7, 1.2)	1.9 (1.1, 3.2)	0.9 (0.4, 2.4)	0.8 (0.4, 1.9)	<5	0.8 (0.7, 1.1)	1.1 (0.8, 1.6)	1.0 (0.8, 1.2)	1.2 (0.9, 1.7)	1.3 (0.6, 2.3)	1.1 (0.5, 1.8)	1.1 (0.4, 2.5)
≥5 years	1.0 (0.6, 1.4)	0.6 (0.2, 1.7)	<5 events	1.8 (1.0, 3.4)	<5	0.9 (0.7, 1.2)	0.8 (0.5, 1.5)	1.0 (0.8, 1.2)	0.8 (0.4, 1.3)	1.5 (0.8, 2.4)	1.3 (0.7, 2.2)	1.6 (0.7, 3.3)

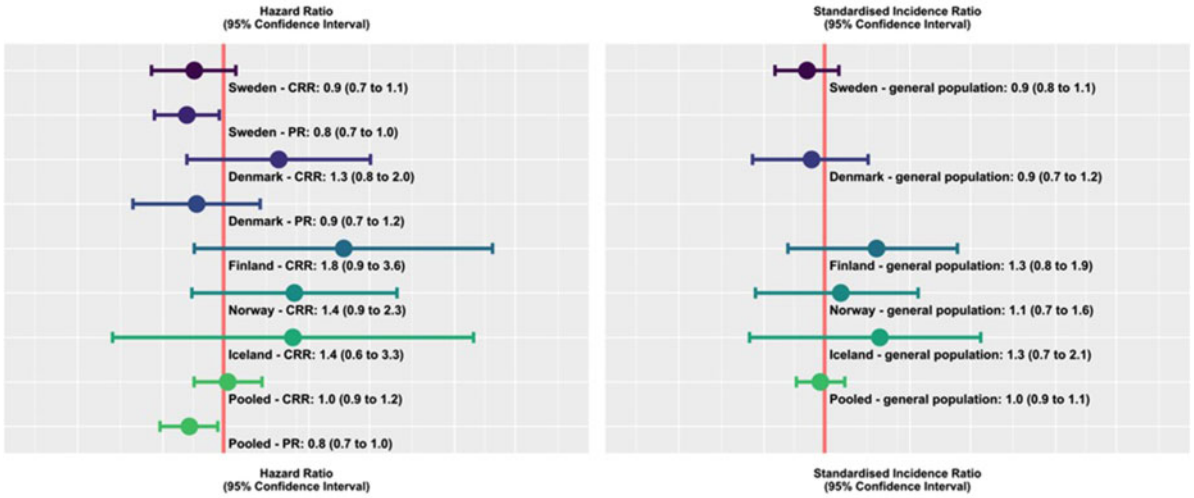
(continued)

Table 3 Continued

	RR (95 % CI)[a] of cancer overall in TNFi treated *vs* bDMARD-naïve PsA from the clinical rheumatology registers (comparator cohort 1)					RR (95 % CI)[a, b] of cancer overall in TNFi treated *vs* bDMARD-naïve PsA from the patient register (comparator cohort 2)		RR (95 % CI)[c] of cancer overall in TNFi-treated PsA *vs* the general population				
	Sweden	Denmark	Finland	Norway	Iceland[d]	Sweden	Denmark	Sweden	Denmark	Finland	Norway[c]	Iceland
Age at start of follow-up (years)												
<50 years	0.6 (0.4, 1.0)	<5	<5	2.7 (0.9, 8.4)	<5	0.7 (0.5, 1.0)	1.0 (0.5, 1.8)	0.8 (0.5, 1.1)	1.2 (0.8, 1.9)	0.9 (0.2, 3.6)	1.1 (0.5, 2.4)	<5
50–64 years	1.0 (0.8, 1.4)	0.9 (0.5, 1.6)	2.3 (0.8, 6.0)	1.1 (0.6, 2.0)	<5	0.9 (0.8, 1.1)	0.8 (0.5, 1.2)	1.0 (0.8, 1.2)	0.8 (0.5, 1.3)	1.5 (0.9, 2.3)	1.1 (0.6, 1.9)	<5
≥65 years	0.9 (0.6, 1.3)	2.0 (1.0, 4.1)	<5	<5	<5	0.9 (0.6, 1.2)	1.1 (0.6, 1.9)	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)	1.1 (0.5, 2.4)	1.0 (0.5, 1.9)	1.2 (0.7, 2.3)

[a]Multivariate Cox regression with hazard ratios with 95% CI adjusted for sex and calendar period (2001–2005, 2006–2010, 2011–end of follow-up) with age as time scale. [b]For Finland, Norway and Iceland, this bDMARD-naïve comparator cohort was not available. [c]RR of cancer in TNFi treated *vs* general population was estimated using age, sex and calendar period standardized incidence ratios (SIRs) for Denmark, Finland, Norway and Iceland. Therefore, numbers of cancer events for the general population are not given in these countries and the crude RR are not available. For Sweden, multivariate Cox regression adjusted for sex and calendar period (2001–2005, 2006–2010, 2011–2017) with age as time scale was used. [d]As no bDMARD-naïve comparator group was available for Iceland, the bDMARD-naïve patients with PsA identified through DANBIO/Denmark served as comparator group. The observation period for Denmark was 2001–2014 and there were seven events in Iceland within this period, while there were 13 events in the total observation period for Iceland (2001–2017). [e]The number of hospitalizations, as well as the comorbidity indicators for hypertension, uveitis and urethritis were not available for Norway. [f]Information on comorbidity conditions were not available in Iceland. N/A: not available; RR: relative risk.

Fig. 1 Country-specific and pooled relative risks of solid cancer overall with 95% CI, adjusted for sex, age and calendar period, in TNFi-treated *vs* bDMARD-naïve patients with PsA from (i) the clinical rheumatology registers (CRR, comparator cohort 1), (ii) the patient registers in Sweden and Denmark (PR, comparator cohort 2) and (iii) the general population



In the sensitivity analysis on Swedish data where we restricted the analyses of TNFi-treated *vs* bDMARD-naïve patients to start of follow-up after 2006 and after 2011, respectively, as well as using alternative bDMARD-naïve PsA disease comparator cohorts based on start and/or switch of csDMARD treatment, the risk estimates remained stable, spanning from 0.8–0.9 (Table S3, available at *Rheumatology* online).

Relative risks of specific cancer types in TNFi treated *vs* bDMARD-naïve PsA

In the pooled age-, sex- and calendar time-adjusted RRs for the eight cancer types in TNFi treated *vs* bDMARD-naïve PsA (disease comparator 1) we observed RRs above 1 for colorectal (1.2), liver (1.4), breast (1.3) and brain cancer (1.5) and point estimates below 1 for prostate (0.8) and pancreas cancer (0.7), none of which reached statistical significance (Table 4). When we compared TNFi-treated *vs* bDMARD-naïve PsA using disease comparator 2, we observed a statistically significant decreased pooled RR for prostate cancer 0.7 (0.5–0.9), and an RR for breast cancer of 1.3 (1.0–1.7) (Table 4).

Relative risks of solid cancer in TNFi treated PsA *vs* the general population

For solid cancer overall, the pooled age-, sex- and calendar year-adjusted RR for all countries was 1.0 (0.9–1.1) (Fig. 1). For country-specific risk estimates, see Table 3/Fig. 1. We observed no increased risks for specific cancer types, by contrast there was a pooled SIR of prostate cancer of 0.8 (0.6–1.0) (Table 4).

Occurrence and incidence rates of solid cancer overall by TNFi agent

There were no signals of different crude IRs of solid cancer by type of TNFi agent. The pooled crude IR ranged from 574 to 695/100 000 person-years for *ever* exposure (Model A) and a largely similar range; 563–692/100 000 person-years, for the *most recent* exposure (Model B) (Table 5). As expected, the majority of patients with PsA were exposed to the three older TNFis; adalimumab, etanercept and infliximab. For country-specific crude IRs for each TNFi, see Table S4, available at *Rheumatology* online.

Discussion

In this population-based collaborative study including data from five Nordic countries, we found no increased risks of solid cancer overall, nor for eight solid cancer types in TNFi treated *vs* bDMARD-naïve patients with PsA. The incidence of solid cancer overall was largely similar across TNFi agents.

To our knowledge, this is the largest study to date to demonstrate an overall lack of increased risk for solid cancer associated with TNFi in patients with PsA. The results are in line with the few existing studies on TNFi treated *vs* bDMARD-naïve patients with PsA [24–26]. Similarly, we found no increased cancer risk in TNFi-treated PsA *vs* the general population, a finding also in keeping with results from previous studies, albeit those were of smaller size and had shorter follow-up time [10, 24, 27, 28].

TABLE 4 Pooled RRs[a] of eight site-specific cancer types, in TNFi treated *vs* bDMARD-naïve PsA and *vs* general population

Cancer subtype	No. of events and RR (95% CI) of cancer types in TNFi treated *vs* bDMARD-naive PsA patients from the clinical rheumatology registers (comparator cohort 1)		No. of events and RR (95 % CI) of cancer types in TNFi treated *vs* bDMARD-naive PsA patients from the patient registers of Sweden and Denmark (comparator cohort 2)[b]		No. of events and RR (95 % CI)[c] of cancer types in TNFi treated PsA patients *vs* the general population, all countries together	
	Number of events TNFi treated / bDMARD-naïve	RR (95% CI)	Number of events TNFi treated / bDMARD-naïve	RR (95% CI)	Number of events Observed / expected	SIR (95% CI)
Colorectal	38/43	1.2 (0.7, 1.9)	25/202	0.9 (0.6, 1.3)	38/32	1.2 (0.8, 1.6)
Pancreas	9/17	0.7 (0.3, 1.6)	9/58	1.0 (0.5, 2.0)	9/8	1.1 (0.5, 2.1)
Liver	5/6	1.4 (0.4, 4.7)	<5 events	—	5/5	1.1 (0.4, 2.6)
Lung	25/30	1.0 (0.6, 1.8)	19/179	0.7 (0.4, 1.1)	25/28	0.9 (0.6, 1.3)
Corpus uteri	<5 events	—	7/50	0.8 (0.4, 1.8)	7/10	0.7 (0.3, 1.5)
Female breast	70/59	1.3 (0.9, 1.8)	58/261	**1.3 (1.0, 1.7)**	70/62	1.1 (0.9, 1.4)
Prostate	47/81	0.8 (0.6, 1.2)	36/351	**0.7 (0.5, 0.9)**	47/60	**0.8 (0.6, 1.0)**
Brain	11/8	1.5 (0.6, 3.8)	10/54	0.9 (0.5, 1.8)	11/10	1.1 (0.5, 1.9)

[a]Relative risks (RR) and 95% CI with Poisson regression adjusted for 5-year age categories, sex, calendar period (2001–2005, 2006–2010, 2011-end of follow-up) and country. [b]Comparator cohort 2 only available for Sweden and Denmark, i.e. only these two countries are included in the analysis. [c]RR of cancer in TNFi treated *vs* general population estimated using age, sex and calendar period standardized incidence ratios (SIRs). For Denmark, Finland, Norway and Iceland, population rates in each country were used to calculate SIR. For Sweden, the assembled general population cohort was the source to calculate the incidence rates in each category.

We noted, however, a non-significantly increased age-, sex- and calendar-adjusted risk of solid cancer overall in the country-specific analyses for all countries except Sweden. Although a true increased risk cannot be excluded for these countries, this more likely reflects the challenge to identify suitable bDMARD-naïve PsA comparator cohorts. Because the Nordic CRRs generally were designed for follow-up of biological treatment, the bDMARD-naïve PsA cohort was included more recently in the registers, thereby with a shorter follow-up time, in particular as many of these patients later progressed to start a TNFi. Consequently, the bDMARD-naïve PsA cohort may not in all aspects other than the TNFi treatment be comparable to the TNFi-treated PsA cohort, and this became more evident for the countries where the bDMARD-naïve PsA cohort consisted of relatively few patients. This is indirectly supported by a non-increased incidence of solid cancer overall in TNFi-treated PsA compared with the general population in Finland, Norway and Iceland. Moreover, the RR around 1 for solid cancer remained robust when we compared TNFi-treated *vs* bDMARD-naïve patients with PsA from the PRs in Sweden and Denmark (i.e. where such comparator cohorts were available) and in the sensitivity analyses where we applied alternative PsA disease comparator definitions and different times of follow-up (Sweden).

Risks of specific solid cancer types in PsA have only been evaluated in a few studies [24, 27]. One previous cohort study, based on data from the Swedish (SRQ-ARTIS) and the Danish (DANBIO) registers 2001–2011 (i.e. partly including the same study populations as ours), did not observe any increased risk of prostate-, colorectal- or lung cancer, but found an increased risk of breast cancer in TNFi-treated *vs* bDMARD-naïve PSA (1.8, 1.1–2.9), based on 20 events [24]. In the present study, with a longer follow-up and a considerably better precision, we observed a *non-significantly* increased RR of breast cancer of 1.3 (based on 70 events) in TNFi treated *vs* bDMARD-naïve PsA. Our finding might reflect an increased surveillance for cancer (such as regular mammography/screening) following treatment with TNFi rather than a 'real' increased cancer risk and should be interpreted with caution.

Additionally, we observed signals of a reduced risk of prostate cancer (based on 46 events) both for TNFi-treated vs bDMARD-naïve PsA from the CRRs (non-significant) and vs bDMARD-naïve PsA identified from the PR in Sweden and Denmark (significant). This was similar to our previous Swedish/Danish study [24] that also observed a significantly decreased risk for prostate cancer (based on seven cases). This might be attributable to the pre-treatment work-up of patients starting a TNFi, such as X-rays and blood tests, which may lead to earlier detection of incipient cancers. One could also hypothesize that an efficient reduction of chronic inflammation such as prostatitis, as a result of TNFi,

Table 5 Crude incidence rates/100 000 person-years of solid cancers overall all countries together by TNFi agent

	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Model A, ever exposure to each bDMARD[a]					
Number of treated patients, *n*	3298	709	3783	1225	2342
Number of solid cancers, *n* (%)	113 (3.4)	14 (2.0)	144 (3.8)	32 (2.6)	92 (3.9)
Person-years (pyrs)	19 671	2110	22474	4606	15 655
Crude incidence rate/100 000 person-years	574	664	641	695	588
Crude incidence rates/100 000 person-years, range lowest to highest in each country	388–1070	03–770	548–720	268–868	234–748
Model B, most recent bDMARD[b]					
Number of treated patients, *n*	3298	709	3783	1225	2342
Number of solid cancers, *n* (%)	75 (2.3)	8 (1.1)	100 (2.6)	20 (1.6)	48 (2.0)
Person-years (pyrs)	12 606	1420	14 454	2964	8100
Crude incidence rate/100 000 person-years	595	563	692	675	593
Crude incidence rates/100 000 person-years, range lowest to highest in each country	116–1541	0[c] to 624	368–937	0[d] to 949	0[e] to 1265

[a]Model A, ever exposure: follow-up from start of any bDMARD agent until end of follow-up regardless of starting a second biological and/or discontinuation. [b]Model B, most recent drug: follow-up from start of any bDMARD agent until start of a subsequent bDMARD agent ignoring any discontinuation date of the previous bDMARD. [c]No events of solid cancers in Denmark, Finland or Iceland following ever or most recent exposure to certolizumab. [d]No events of solid cancers in Finland following exposure to most recent exposure of golimumab. [e]No event of solid cancer in Finland following infliximab.

might reduce the risk of prostate cancer in PsA, although this remains a speculation [47, 48]. By contrast, the study by Carmona *et al.* [27] did not observe any signals of decreased risk of prostate cancer following TNFi treatment in patients with PsA, although the estimation was hampered by low precision, SIR =1.18 (0.03–6.59).

Previous data on cancer risk in PsA following specific TNFi agents are lacking. In this study, we did not observe any signals of different crude incidences with any particular TNFi agent. It is, however, important to point out that we did not adjust for patients' characteristics, co-morbidity or the fact that different TNFi agents became available at different time periods under study. Despite these limitations, we think that our results add to the body of knowledge in this field.

The study has some limitations. Despite a large study size and a relatively long follow-up (mean 5.8 years), some of the cancer types under study are rare, which resulted in limited precision. This was especially evident for the country-specific analyses, further highlighting the need for collaborative efforts to evaluate safety data on cancer in association with bDMARD exposure. Although we adjusted for important confounders including disease activity at start of follow-up, we were not able to adjust for smoking or BMI due to the high proportion of missing data. Additionally, as the Swedish patients made up a large part of the study population, the Swedish country-specific results tended to have a large impact on the pooled results.

A major strength of our study was the ability to combine population-based data from all five Nordic countries with a total population of 27 million people. This enabled us to assess risks of solid cancer types with a better precision than previously [10, 24, 28], to include also rarer cancer types, and to assess incidences of solid cancer by TNFi agent. Additionally, we were able to perform stratified analyses adjusted for relevant covariates. In the stratified analysis on risk of cancer with time since start of TNFi, we did not observe any significantly increased risk across categories, which indirectly points to no effect with duration of exposure; a reassuring finding from a patient safety perspective. By use of the mandatory national cancer registers, we reached a very high completeness [41–45]. We also had the possibility to identify bDMARD-naïve disease comparators from different data sources, and to apply different PsA disease comparator definitions, which allowed us to explore whether a cancer risk was specific to the comparator group rather than to the TNFi exposure. We were also able to compare the cancer rates in PsA with those of the general population.

In conclusion, our large Nordic study suggests that use of TNFi therapy in patients with PsA is not associated with increased risks of solid cancer overall, nor for

eight cancer types. There were no indications of different crude incidence of solid cancers overall by TNFi agent. The findings are consistent with results on this association from other chronic inflammatory diseases, and are of clinical importance for risk communication with patients.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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