Risk of Malignancy in Spondyloarthritis

A Systematic Review

Paras Karmacharya, MBBS[a], Ravi Shahukhal, MD[b], Alexis Ogdie, MD, MSCE[c,*]

KEYWORDS

• Spondyloarthritis • Psoriatic arthritis • Ankylosing spondylitis • Malignancy • Cancer • Tumor necrosis factor inhibitors

KEY POINTS

- There is conflicting evidence on the association between spondyloarthritis (SpA) and malignancies overall.
- There seems to be a higher incidence of nonmelanoma skin cancer in psoriatic arthritis (PsA) and both monoclonal gammopathy of unknown significance and multiple myeloma in ankylosing spondylitis (AS).
- A few studies have reported a higher incidence of lymphoma in both PsA and AS but the results were inconsistent.
- It is unclear if traditional immunosuppressive agents, tumor necrosis factor inhibitors, or nonsteroidal anti-inflammatory drugs modulate the risk of cancer in SpA. However, if there is an increased risk, it seems to be quite small.
- Although no specific screening recommendations for malignancy in SpA are available at present, it would be prudent to perform age-appropriate screening in all patients at minimum with a consideration for annual skin checks in patients with moderate-to-severe psoriasis.

INTRODUCTION

Spondyloarthritis (SpA) includes a group of chronic inflammatory diseases, such as ankylosing spondylitis (AS, or axial spondyloarthritis, AxSpA), psoriatic arthritis

[a] Division of Rheumatology, Department of Medicine, Mayo Clinic, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN 55905, USA; [b] Division of Internal Medicine, Lakes Regional General Hospital, 80 Highland Street, Laconia, NH 03246, USA; [c] Division of Rheumatology, Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 3400 Civic Center Boulevard, South Pavilion, 1st Floor, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: alogdie@pennmedicine.upenn.edu
Twitter: @paraskarmachary (P.K.)

Rheum Dis Clin N Am 46 (2020) 463–511
https://doi.org/10.1016/j.rdc.2020.04.001
rheumatic.theclinics.com

(PsA), inflammatory bowel disease–associated arthritis, and reactive arthritis. These diseases share a common tissue distribution and affect the axial and/or peripheral joints as well as entheses. In addition to the musculoskeletal involvement, they may have extra-articular manifestations, such as psoriasis, uveitis, and inflammatory bowel disease. Beyond extra-articular manifestation, these diseases also may be associated with other medical comorbidities, potentially including malignancies.

Systematic inflammatory diseases, including rheumatoid arthritis (RA), are associated with an increased risk of malignancies.[1] Chronic inflammation with high levels of elevated chemokines, cytokines (serum interleukin-1, 6, and tumor necrosis factor [TNF]-α) and growth factors can lead to DNA damage, chromosomal instability, and epigenetic alterations favoring malignant transformation in affected cells.[2,3] RA in particular is associated with an overall increased risk of malignancies, specifically lymphomas (standardized incidence ratios [SIR] up to 13 compared with the general population).[1] Similarly, the immunosuppressive agents used to treat inflammatory diseases have also been implicated in increasing the risk for cancer, although the degree of risk and difference among therapies remains unclear.

Malignancy, either related to an inflammatory disease or its treatments, is most often studied in the setting of RA; however, the pathogenesis of SpA is different from RA,[4] and the risk of malignancy and sites involved also may be different. It is important to better understand associations of SpA with site-specific cancers to facilitate proper screening. The goal of this review was to examine the association of the 2 most common types of SpA, PsA and AxSpA, with malignancy and the potential impact of therapy for SpA on development of malignancy.

METHODS

A comprehensive search of several databases from inception to January 11, 2020, was conducted. The databases included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus. ACR and EULAR abstracts published in the past 2 years were included as well. Search strategy included terms under 2 broad themes: (1) SpA (ie, spondylarthritis, spondyloarthritis, psoriatic arthritis, AS, spondylitis), and (2) malignancy (ie, cancer, neoplasms, malignancy). Studies reporting the relative association of malignancy with SpA or the prevalence/incidence of malignancy were included. Case reports, case series, nonhuman studies, and articles in language other than English were excluded. Two authors (PK and RS) screened abstracts for eligibility, retrieved full-texts, and excluded irrelevant articles. Disagreements were resolved by discussion about eligibility. Bibliographies belonging to included studies, reviews, and relevant articles were screened for additional studies. Relevant data were extracted by PK, and checked by RS.

RISK FOR MALIGNANCY IN PSORIATIC ARTHRITIS

Data on the risk of malignancy in PsA are conflicting, with most studies showing no significant association (**Table 1**). A recent systematic review and meta-analysis by Luo and colleagues[5] found a significantly higher risk of overall malignancy compared with the general population (relative risk [RR] 1.29; 95% confidence interval [CI] 1.04–1.60). However, none of the individual studies included in the meta-analysis, except Lange and colleagues,[6] showed a significantly higher overall risk of cancer. Although all included studies used cohort designs, there was significant heterogeneity (I^2 = 71%) among them. This heterogeneity may have been in part related to the differing PsA populations (eg, different therapy exposures) and varied follow-up periods (3–15 years). Interestingly, in the subgroup analysis, only patients with

Table 1
Summary of studies examining the risk of malignancy among patients with spondyloarthritis (SpA)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
SpA										
Bautista-Molano et al,[61] 2018	Cross-sectional, ASAS-COMOSPA study (from 3 Latin American countries- Argentina, Mexico, and Colombia)	NA (Cross-sectional study)	390	Pts ≥18 y fulfilling ASAS criteria (either axial or peripheral)	Overall prevalence of malignancy in SpA	GP	NSAIDs MTX SSZ TNFi	NA	Colon cancer, skin (melanoma and basocellular carcinoma), lymphoma (HL and NHL), breast, cervix, and prostate.	Prevalence of malignancies: Overall- 2.8% (95% CI 1.4–5.1) GP- 2.6% (NR) SRR for malignancies- 1.0
Fanto et al,[62] 2016	Retrospective, cohort study, single center (S. Andrea-Sapienza University, Rome, Italy)	2005–2011	197	SpA- AS or PsA PsA- pts fulfilling Moll and Wright criteria AS pts fulfilling mNY criteria Previous history of malignancy excluded	Risk of malignancy in RA and SpA patients under immunosuppressive therapy	GP of Italy matched for age, sex, and area of residence	TNF i + DMARDs or DMARDs alone	Median - 5.03 (IQ range 3.7–6.9)	All cancers- solid cancers, hematologic malignancy and NHL	SIR of malignancy in SpA vs GP: Overall malignancy- 0.88 (0.29–2.05) Solid tumors SIR- 0.69 (0.19–1.77) Hematologic SIR 2.04 (0.05–11.37) NHL SIR- 4.35 (0.11–24.23) Age and sex adjusted HR for medications only calculated for RA

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hellgren et al,[15] 2017	Population-based, nationwide cohort study-ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-17406 TNFi naïve-28,164	AS ICD-10 code (M45) PsA ICD-10 code (L40.5)	Cancer risk in SpA treated with TNFi compared with biologic naïve and GP	Swedish age-matched and sex-matched GP comparator cohort (n = 131,687)	TNFi treated TNFi naïve	Up to 10 y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma	TNFi naïve SpA vs GP (RR): 1.1 (1.0–1.2) **1.2 (1.1–1.4)** 1.0 (0.7–1.2) **0.7 (0.5–0.8)** 1.0 (0.7–1.3) 1.0 (0.8–1.2) 1.0 (0.7–1.3)

Jiang et al,[47] 2018	Cross-sectional, single-center study from Third Affiliated Hospital of Sun Yat-sen University	2013–2015	346	Pts ≥18 y fulfilling ASAS criteria for SpA were recruited from the Third Affiliated Hospital of Sun Yat-sen University.	Prevalence of comorbidities and evaluation of screening in Chinese pts with SpA	None	NSAID use DMARDs use (ever): -MTX -SSZ -Biologic therapy	NA	Prostate cancer Breast cancer	160/280 (57.1%) male pts had screening for prostate cancer with PSA, while breast cancer was optimally screened in 21/66 (31.8%) female patients. 1/160 (0.6%) was confirmed with prostate cancer. None of the female pts ever did a cervical smear. 10 pts underwent colonoscopy or digital rectal examination. Only 4 pts once went to see a dermatologist in a recent year.
Molto et al,[46] 2016	ASAS-COMOSPA study Cross-sectional, multicentric and international study (from 22 countries from 4 continents- Africa, America, Asia, Europe)	NA	3984	Patients ≥ 18 y fulfilling ASAS criteria (either axial or peripheral)	Prevalence of malignancies in SpA	None	NSAID DMARDs (methotrexate, sulfasalazine, biologic therapies)	NA	Colon cancer Skin(melanoma and basocellular carcinoma) Breast and cervix Prostate for men Lymphoma	Prevalence of malignancies: Overall- 3.0% (2.46–3.52) Cervical cancer- 1.2% (0.3–1.7) Basocellular cancer- 0.8% (0.6–1.2) Melanoma- 0.7% (0.4–1.0) Most prevalent risk factors for cancer- family history of breast (15%) and colon cancer (8%)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
PsA										
Eder et al,[24] 2012	Cross-sectional, single center (University of Toronto PsA clinic)	2008–2011	361	Pts fulfilling CASPAR criteria	Prevalence of monoclonal gammopathy in PsA	Case-MGUS, n = 35, control-no MGUS = 326	NR	NA	MGUS MM	35/361 (9.7%) had monoclonal gammopathy in at least 2 separate samples. 7/29 (24%) who were tested for Bence Jones protein tested positive. 1 patient diagnosed as MM. Longer disease duration (OR-**1.04; 95% CI 1.01–1.07**) and high ESR (OR-**1.03; 95% CI 1.01–1.04**) were associated with MGUS.
Edson-Heredia et al,[11] 2015	Retrospective study from CPRD	2006–2010	1952	Psoriasis (without PsA) and PsA as diagnosed by general practitioner or specialist	Incidence rates of malignancies in psoriasis and PsA	Cohort of pts with psoriasis (n = 27,672; mild, n = 22,174, severe, n = 5498)	NSAIDs (45.1%), Systemic therapies (mainly MTX and SSZ), and opiate and nonopiate analgesics	Mean = 3.0 (SD - 1.3)	Skin cancer (melanoma and NMSC)	HR (All psoriasis vs PsA): 0.33 (0.05–2.43) 1.14 (0.41–3.16) HR (PsA vs severe psoriasis)[a]: Melanoma - 0.12 (0.02–0.90) NMSC - 0.4 (0.14–1.16) HR adjusted for age, gender, smoking, and index year.

Gross et al,[7] 2014	Multicentered, longitudinal, prospective registry (CORRONA)	Aug 2003-Oct 2010	2970	Rheumatologist's diagnosis (at least 2 study visits during the time period)	Compare the incidence rates of malignancy among PsA and RA pts in CORRONA registry	RA pts in CORRONA (n = 19,260)	MTX Non-MTX DMARD TNFi Other biologics	PsA-7133 PY, RA-53864 PY	All malignancies NMSC All malignancies • NMSC • Non-NMSC (solid + hematologic) Solid • Breast • Prostate • Colorectal • Melanoma Hematologic • Lymphoma • MM • Leukemia	IR of cancer in PsA (per 100 PY): 0.56 (0.40–0.76) 0.21 (0.12–0.35) IRR of cancer in PsA vs RA: 1.18 (0.82–1.69) 1.05 (0.61–1.80) 0.97 (0.61–1.42) 0.90 (0.57–1.45) 1.54 (0.67–3.23) 0.56 (0.16–1.86) 1.33 (0.47–5.70) 1.33 (0.44–5.28) 1.17 (0.36–2.89) 1.00 (0.17–3.11) 7.78 (0.48–122.23) 1.00 (0.12–7.64)
Hagberg et al,[14] 2016	Retrospective cohort study from CPRD, UK	1988–2012.	8943	PsA as diagnosed by general practitioner or specialist	Incidence rate of cancers in patients with PsA vs without PsA	Pts without PsA (n = 82,601)	Systemic therapies DMARDs/ biologics (eg, MTX, SSZ, and ADA), immunosuppressants (eg, AZT and leflunomide), and corticosteroids	Solid cancer-3139 PY, Hematological cancer-261 PY, NMSC-1561 PY	Solid, hematologic, and NMSC	IRR of malignancy in PsA vs no PsA: Solid cancer- 1.01 (0.90–1.13) Hematologic cancer-1.52 (1.10–2.10) NMSC- 0.97 (0.82–1.14)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hellgren et al,[22] 2014	Population-based, prospective cohort study from Swedish National Patient Register	2001-2010	19,283	ICD codes for AS, PsA	Risk of malignant lymphoma in AS, PsA	Randomly selected from Swedish Population Register (matched for age, sex, and county of residence)	TNFi MTX/SSZ Oral GC	10,912 PY	Malignant lymphoma	HR of lymphoma in PsA vs GP: Overall- 1.2 (0.9–1.7)
Hellgren et al,[15] 2017	Population-based, nationwide cohort study- ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-3833 TNFi naïve-15,908	ICD-10 code for PsA (L40.5)	Cancer risk in SpA treated with TNFi	Swedish age-matched and sex-matched GP comparator cohort (n = 74,010)	TNFi treated TNFi naïve	Up to 10 y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma	TNFi naïve PsA vs GP (RR): 1.0 (0.9–1.1) 1.1 (0.9–1.3) 1.0 (0.7–1.3) 0.8 (0.6–1.1) 1.0 (0.6–1.4) 0.9 (0.8–1.1) 0.9 (0.6–1.3)

Kaine et al,[57] 2019	Retrospective, observational, cohort study using MarketScan Databases and Medicare Supplemental databases	Jan 2008–Sep 2015	14,898	≥1 inpatient or ≥2 outpatient diagnosis of PsA (ICD-9-CM 696.0) > 30 d apart but within ≤ 365 d of each other	Incidence rates of comorbidities in pts with PsA compared with GP	Pts without AS (matched on age, geographic region, calendar year, and sex, n = 35,037)	NR	All pts ≥ 1 y follow-up	All cancers	IRR of malignancy in PsA vs GP: 1.09 (1.01–1.17)
Rohekar et al,[50] 2008	Prospective cohort study from University of Toronto Psoriatic Arthritis Clinic	1978–2004	665	Rheumatologist's diagnosis	Prevalence of malignancy in PsA	GP (Ontario)	NSAIDs DMARDs Immunosuppressants	NR	All cancers	SIR for malignancy PsA vs GP: All cancers - 0.98 (0.77–1.24) Hematologic - 0.69 (0.26–1.83) Lung- 0.88 (0.46–1.69) Breast-1.55 (0.92–2.62) Prostate −0.65 (0.29–1.44) ESR, cm/h was the only significant predictor of malignancy in Cox regression, HR-**1.13 (1.02–1.25)**, TNFi and DMARDs were not.
Tan,[25] 2018 (abstract)	Population-based matched retrospective cohort	1997–2012	81,568 incident cases of PsO/PsA	Incident psoriasis/PsA defined as ≥ one of the	Risk of cancer in patients with psoriasis/PsA	Matched on age, sex, and calendar year	NR	623,843.5 PY 623,625.8 PY 623,818.6 PY 621,233.8	Eye and orbit Female genitals other than cervix, uteri, corpus uteri, and ovary Other urinary	IRR of cancer in psoriasis/PsA vs matched controls: 4.25 (1.21–14.91) 2.57 (1.55–4.25) 1.90 (1.04–3.47) 1.82 (1.54–2.14)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
	study from administrative health data (British Columbia, Canada)			following: 1 diagnostic code for psoriasis/PsA by a rheumatologist/dermatologist; ≥ 2 diagnostic codes for PsO/PsA, ≥ 2 mo apart in a 2-year period by a nonrheumatologist/dermatologist; or ≥1 hospitalization with diagnostic code for psoriasis/PsA.		from the database.		PY 622,877.2 PY 620,065.8 PY 622,791 PY 622,845.1 PY 623,196.9 PY	NMSC Lung Prostate Melanoma Colon Rectum	1.17 (1.05–1.31) 1.12 (1.01–1.25) 1.07 (NR) 0.84 (0.72–0.99) 0.79 (0.64–0.98)
Wilton et al,[12] 2016	Retrospective. population-	1970–2008	217	PsA meeting CASPAR criteria	Cumulative incidence of malignancy	Age and sex-matched	NR	38	Any malignancy (including NMSC) Any malignancy (excluding NMSC)	HR for incidence of malignancy in PsA vs those without PsA:

	based (Olmsted County) cohort study				in PsA	patients from Olmsted County (n = 434)			Solid tumors Hematologic NMSC Breast (female only) Prostate	1.41 (0.96–2.07) **1.64 (1.03–2.61)** 1.48 (0.89–2.48) 2.48 (0.75–8.13) 1.23 (0.72–2.09) **3.59 (1.22–10.61)** 1.83 (0.75–4.46)
AxSpA										
Alehashemi,[36] 2018 (abstract)	Retrospective, cohort study (Medicare databases)	1999–2013	13,305	2 identical AS ICD-9 codes at least 30 d apart	Cancer risk in AS compared with those without AS in the US Medicare beneficiaries	Medicare without AS, matched on age and sex (n = 6,749,053)	NR	Followed until 2015 (130841 PY)	Kidney Melanoma Thyroid Leukemia NHL MM Prostate Esophagus Stomach Colorectal Lung	SIR in AS vs no AS in Medicare beneficiaries (statistical significant only): 1.57 (1.34–1.80) 1.49 (1.27–1.71) 1.43 (1.02–1.85) 1.44 (1.24–1.65) 1.36 (1.19–1.53) 1.32 (1.01–1.64) 1.34 (1.25–1.42) **0.58 (0.36–0.81)** **0.55 (0.32–0.79)** **0.81 (0.71–0.91)** **0.72 (0.64–0.81)** SIR of cancer of upper airways, small intestine, liver/gallbladder, pancreas, female breast, uterus, bladder, connective tissue/bone, brain/eye/nervous system, HL were not statistically significant.
Anderson et al,[37] 2009	Population-based, case-control study using SEER	Lymphoid malignancies diagnosed between	44,350 lymphoid malignancy cases	ICD codes (hospital, physician, and outpatient Medicare claims)	Risk of specific lymphoid malignancies in autoimmune conditions	Medicare beneficiaries (matched on calendar year of dx,	NR	NA	NHL Diffuse large B cell lymphoma T-cell NHL Marginal zone lymphoma Follicular lymphoma	OR for prevalence of AS in pts with lymphoid malignancies vs controls: 1.1 (0.7–1.5) 0.9 (0.5–1.7) 0.9 (0.2–3.4) 2.2 (0.9–5.4)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
	database (SMAHRT study)	1993–2002,			Outcome: Malignancy Exposure: AS	age category and sex, n = 122,531)			Chronic lymphocytic leukemia	0.80 (0.3–2.3) 1.1 (0.6–2.0)
Askling et al,[63] 2006	Nationwide, population-based case-control study from the Swedish Inpatient Register	1964–2000	50,615 cases of lymphoma	ICD codes	Association between AS and malignant lymphomas Outcome: Malignancy Exposure: AS	GP (92,928 matched controls)	NR	NA	Malignant lymphomas -NHL -HL -Chronic lymphocytic leukemia	OR of AS in malignant lymphoma vs controls: 1.0 (0.6–1.7) 0.8 (0.4–1.5) 1.7 (0.2–12) 1.9 (0.6–5.9)
Becker et al,[38] 2005	Population-based, case-control study from Germany	1999–2002	710	Self-report of physician-diagnosed AS	Association between history of AS and lymphoma Outcome: Malignancy Exposure: AS	GP (matched on age, sex and study region, n = 710)	NR	NA	All lymphomas	OR of AS in pts with lymphoma vs controls: 0.79 (0.59–1.05)
Brown et al,[32] 2008	Retrospective, cohort study	from July 1, 1969,	4641 (MM) and	ICD codes	Risk of MM, MGUS among	Men without AS	None	1 y after the date	MM MGUS	RR of malignancy among men with AS vs no AS: Overall- 2.29 (1.55–3.40)

	from US VA hospitals	to September 30, 1996,	2046 (MGUS)		US male veterans with prior AS			of the first hospital discharge to the end of observation period		Whites- 1.82 (1.12–2.98) Blacks- 4.23 (2.20–8.16) Overall- 2.02 (1.14–3.56)
Burmester et al,[13] 2013	Pooled data from clinical trials (Europe, North America, South America, Asia, Australia, New Zealand, and South Africa)	Through Nov 2010	1684	SpA definition per clinical trial.	Risk of malignancy from global clinical trials of ADA in immune-mediated inflammatory diseases	GP	ADA (clinical trials)	Nearly 12 y of ADA exposure	All malignancies Lymphoma NMSC	SIR of malignancy in AS vs GP: 0.51(0.16–1.19) 1.93(0.03–10.7) 0.08(0.29–1.74)
Carmona et al,[20] 2011	Prospective cohort study- BIOBADASER 2.0 (ongoing cohort of patients with rheumatic diseases exposed to TNFi)	BIOBADASER (2001–2008)	761	Rheumatologist diagnosed rheumatic diseases starting treatment or were on a biologic response modifier	Cancer risk in RA, PsA, and AS patients exposed to TNFi	GP of Spain (source: GLOBOCON, WHO program 2002)	TNFi (IFX, ETN, ADA)	2288 PY	Colon and rectum Lung Prostate Bladder NHL Leukemia All sites but skin	SIR of cancer in AS pts exposed to TNFi: 2.38 (0.49–6.96) 1.66 (0.34–4.85) 1.10 (0.03–6.13) 0.96 (0.02–5.37) 2.72 (0.07–15.13) 3.97 (0.10–22.13) 0.92 (0.44–1.70)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Castro et al,[64] 2014	Cohort study from nationwide data registry (Sweden)	1964–2008	402462 (total autoimmune disease, AS NR separately)	ICD codes	Risk of hepatobiliary cancer after hospitalization with autoimmune diseases	Swedish population not hospitalized for autoimmune disease	NR	Until dx of cancer, death, emigration, or end of study (2008)	Hepatobiliary tract Primary liver Gallbladder Extrahepatic bile duct Ampulla of Vater	SIR of Hepatobiliary cancer in hospitalized patients with AS vs GP: SIR 1.50(0.87–2.41) SIR 1.70(0.81–3.14)
Chang et al,[28] 2017	Retrospective, cohort study from Taiwan National Health Insurance Research Database	2000–2008	5452	ICD-9-CM code 720.0 .	Association between AS and cancer	Non-AS pts in the database during the study period (age, sex-matched, n = 21,808)	NR	5.07 ± 2.07 y	All cancers Digestive tract Colon Lung Breast Female genital system Prostate cancer Hematological Upper respiratory tract	SIR of cancer in AS vs non-AS: 1.15(1.03–1.27) 1.01(0.79–1.27) **1.39(1.03–1.82)** 1.07(0.79–1.43) 0.98(0.64–1.42) 0.78(0.49–1.18) **1.64(1.04–2.47)** **2.10(1.32–3.19)** 1.30(0.92–1.79)

Dreyer et al,[30] 2013	Cohort study (DANBIO arthritis cohort)	2000–2008.	861	Rheum-atologist diagnosis	Incidence of overall and site-specific malign-ancies in TNFi-treated pts with AS	GP	TNFi	2.9 (mean).	All cancer sites	SIR: 0.82 (0.41–1.64) 8/861 pts at f/u
Fallah et al,[40] 2014 (HL)	Nation-wide cohort study (Swedish Heal-thcare data registry)	1964–2010	17,641	ICD codes	Incidence of HL after auto-immune disease by age at dx and histologic subtype	GP (Sweden)	NR	~10 (190014 PY)	HL	SIR for HL in AS vs non-AS pts: Overall- 1.3 (0.4–3.0) Men- 1.3 (0.4–3.4) Women- 1.1 (0.0–6.1) SIR for HL stratified by age at dx and histologic subtype were not statistically significant
Fallah, 2014 (NHL)[39]	Nation-wide cohort study (Swedish Heal-thcare data registry)	1964–2010	17,641	ICD codes	Incidence of NHL after autoimmune disease	GP (Sweden)	NR	10.4	NHL	SIR for NHL in AS vs non-AS pts: Overall- 1.0 (0.7–1.4) Men- 0.9 (0.6–1.4) Women- 1.2 (0.6–2.2)
Feltelius et al,[29] 2003	Popu-lation-based, national cohort study (Swedish inpatient registry)	1965–1995	6621	ICD codes	Cancer incidence among AS pts in Sweden	GP	NR	67,885 PY	All cancers Rectal cancer Unspecified kidney cancer Cancer of digestive organ Respiratory cancer Cancer of female genital Prostate cancer Cancer of urinary organs Hematopoietic cancer	SIR of cancer in AS vs non-AS pts: 1.05; 95% CI 0.94–1.17). 0.41(0.15–0.89) 5.90 (1.61–15.1) 0.96(0.74–1.21) 1.05(0.73–1.47) 0.94(0.47–1.68) 1.02(0.77–1.33) 1.05(0.64–1.62) 1.34(0.93–1.89)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hellgren et al,[22] 2014	Population-based, prospective cohort study from Swedish National Patient Register	2001-2010	8707	ICD codes for AS, PsA	Risk of malignant lymphoma in AS, PsA	Randomly selected from Swedish Population Register (matched for age-sex and county of residence)	TNFi MTX/SSZ Oral GC	7790 PY	Malignant lymphoma	HR of lymphoma in PsA vs GP: Overall- 0.9 (0.5–1.6)
Hellgren et al,[15] 2017	Population-based, nationwide cohort study- ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-3078 TNFi naïve-7023	AS ICD-10 code (M45)	Cancer risk in SpA treated with TNFi	Swedish age-matched and sex-matched GP comparator cohort (n = 32,706)	TNFi treated TNFi naïve	Up to 10 y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma	TNFi naïve AS vs GP (RR): 1.1 (1.0–1.3) 1.3 (1.0–1.6) 1.0 (0.6–1.6) **0.4 (0.3–0.8)** 0.9 (0.5–1.6) 1.4 (1.0–2.0) 0.8 (0.5–1.5)

Hemminki et al,[65] 2012 (Gynecological cancer)	Nationwide cohort study from Swedish Hospital Discharge Registry linked to Cancer Registry	1964–2008	1798	ICD codes	Effect of autoimmune diseases on risk and survival in female cancers	GP	NR	112824 PY	Breast cancer Cervical cancer Endometrial cancer Ovarian cancer Other female genital cancer	SIR for cancer in AS vs GP: 1.04 (0.79–1.35) 1.34(0.53–2.78) 1.34 (0.53–2.78) 0.94 (0.40–1.85) 2.18 (0.41–6.44)
Hemminki et al,[42] 2012 (Digestive tract)	Nationwide cohort study from Swedish Hospital Discharge Registry linked to Cancer Registry	1964–2008	5173	ICD codes	Risk of digestive tract cancer by histology in autoimmune disease	GP	NR	92,881 PY	Upper digestive tract Esophageal adeno cancer Esophageal squamous cell Stomach adeno cancer Colon adeno cancer Rectal adeno cancer Anal squamous cell cancer Carcinoid tumor-small intestine Carcinoid tumor-colorectal	SIR for cancer in AS vs GP: 1.05 (0.57–1.77) 2.99 (0.94–7.03) 0.73(0.07–2.70) 0.92 (0.49–1.57) **0.55 (0.32–0.88)** **0.35 (0.14–0.73)** 2.01 (0.19–7.41) 0.82 (0.00–4.72) 2.35 (0.22–8.63)
Hemminki et al,[34] 2012 (MM)	Nationwide cohort study from Swedish Hospital Discharge Registry linked to Cancer Registry	1964–2008.	6646	AS patients based on ICD codes.	Effect of autoimmune diseases on incidence and survival in subsequent MM	GP	NR	112824 PY 39,322 PY 73,502 PY	Multiple myeloma MM in AS between age 0–60 MM in AS at age 60+ MM in AS between 1964–1990 MM in AS between 1991–2008	SIR for cancer in AS vs GP: 2.02 (1.15–3.28) 3.31 (1.41–6.55) 1.45 0.62–2.87 1.73 (0.33–5.12) 2.09 (1.11–3.59)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hemminki et al,[66] 2015 (unknown primary)	Nationwide cohort study from Swedish Hospital Discharge Registry, linkage with Swedish census data and National Swedish cancer registry	1964–2012	17,471	AS patients based on ICD codes.	Risk of cancer of unknown primary after hospitalization for autoimmune diseases	GP	Aspirin, NSAIDs or immunosuppressive medications (not specified)	189,971 PY of follow-up	Cancer of unknown primary after hospitalized for autoimmune diseases Risk based on follow-up: <1 y 1–4 y 5+year Risk based on age at dx: <60 y 60+ years Risk based on histology: Adenocarcinoma squamous cell cancer melanoma Undifferentiated Risk based on location: Respiratory system Liver Abdomen Unspecified	SIR for cancer in AS vs GP: Overall- 0.68 (0.42–1.04) Female- 1.05 (0.52–1.89) Male- **0.49 (0.23–0.90)** 2.45 (0.64–6.33) 0.67 (0.17–1.74) **0.55 (0.29–0.95)** 0.72 (0.41–1.17) 0.57 (0.18–1.35) 0.63 (0.30–1.16) 1.5 (0.28–4.44) 1.09 (0.9–3.99) 0.37 (0.03–1.36) 0.59 (0.15–1.53) 0.19 (0–1.06) 0.93 (0.24–2.39) 0.72 (0.29–1.5)

Lee,[35] 2019 (abstract)	Nationwide population-based, cohort study from National Health Information Database in Korea	2010–2015	15,979	ICD-10-CM (M45.0)	Cancer risk in patients with AS	age- and sex-matched population without AS (1:3, n = 47,937)	NR	Until 2017	Lymphoma Leukemia MM	HR for AS vs non-AS patients: 3.05 (1.45–6.45) 2.32 (0.91–5.91) 2.83 (1.16–6.90). Risk of solid cancers was not statistically different between the 2 groups.
Lindqvist et al,[33] 2011	Population-based, case-control study from Sweden	1965–2004	19,112 (MM), 5403 (MGUS)	AS diagnosis based on ICD codes Hematological malignancy diagnosed by clinicians/pathologists and recorded in nationwide Swedish Cancer Register since 1958 (diagnostic accuracy 93%)	Risk of plasma cell disorder with personal and family history of immune-related conditions	96,617 matched control subjects, and 262931 first-degree relatives.	NR		MM MGUS	OR of MM and MGUS in AS patients: 1.2 (0.6–2.3) **2.7 (1.4–5.2)** OR of MGUS with >5 y' latency in AS patient: 2.8 (1.3–5.9)

(*continued on next page*)

Table 1
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period, y	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Liu et al,[67] 2013	Population-based, cohort study from national Swedish database	1964-2008	6646	AS patients based on ICD codes.	Risk of subsequent urologic cancer in autoimmune diseases	Pts not hospitalized for autoimmune disease from Swedish discharge registry (expected number)	NR	112824 PY	Prostate Kidney Bladder	SIR and HR for subsequent urologic cancer in individuals hospitalized for autoimmune disease: SIR 1.09 (0.92–1.29) HR 0.96 (0.68–1.36) Before 1990: SIR 1.55 (0.97–2.35) 1991–2008: SIR 1.01 (0.66–1.47) SIR 1.51 (0.98–2.24) HR 0.30 (0.11–0.81) SIR 0.90 (0.61–1.28) HR 0.33 (0.08–1.31)
Mellemkjaer et al,[41] 2008	A population-based case-control study from the Swedish Family-Cancer Database	1964–1998	Cases: 24,728 NHL pts in Denmark (1977–1997) and Sweden (1964–1998)	AS cases identified based on ICD codes (8 and 10) in discharge diagnosis	Risk of NHL associated with a personal or family history of autoimmune diseases	Randomly selected (1:2) from Family-Cancer Database (n = 55,632)	None	NA	NHL	OR of NHL with personal history of autoimmune disease >1 y before lymphoma diagnosis: 0.9 (0.6–1.5) OR of NHL with family history of autoimmune disease and related conditions: 0.8 (0.5–1.1)

Walsh et al,[27] 2018	Retrospective, observational cohort study from MarketScan and Medicare databases	2912–2014	6679	≥1 inpatient or ≥2 non–rule-out outpatient medical claims for AS (ICD-9-CM 720.0) > 30 d apart but within ≤ 365 d of each other. Non–rule-out claims were defined as those not related to a diagnostic or rule-out procedure (eg, laboratory, pathology, or radiology)	Evaluation of comorbidity burden in AS pts in US	Pts without AS (matched on age, geographic region, index calendar year, and sex, n = 19,951)	NR	At least 12 mo after index date	Malignant neoplasms (malignant solid tumors) Hematologic malignancies, Neuroendocrine tumors	HR of overall malignancy in AS vs matched controls: 1.39 (1.19–1.62) Patients <45 y: 1.76 (1.06–2.91) Patients ≥45 to <65 y: 1.46 (1.18–1.79) Patients ≥65 y: 1.26 (0.98–1.63) HR of malignancy in male vs female pts with AS: 0.76 (0.62–0.94)

Abbreviations: ADA, adalimumab; ARTIS, Anti-Rheumatic Therapy in Sweden; AS, ankylosing spondylitis; ASAS-COMOSPA, Assessment of spondyloarthritis international society of comorbidities in SpA study; AxSpA, axial spondyloarthritis; AZT, azathioprine; BIOSPAR, Leuven spondyloarthritis biologics cohort; CASPAR, ClASsification criteria for Psoriatic ARthritis; CI, confidence interval; CM, Clinical Modification; CORRONA, Consortium of Rheumatology Researchers of North America registry; CPRD, Clinical Practice Research Datalink; DANBIO, Danish Biologics Registry; DMARDs, disease-modifying antirheumatic drugs; dx, diagnosis; ESR, erythrocyte sedimentation rate; ETN, etanercept; f/u, follow-up; GC, glucocorticoids; GP, general population; HL, Hodgkin lymphoma; HR, hazard ratio; ICD, International Classification of Diseases; IFX, infliximab; IQ, interquartile; IR, incidence rate; IRR, incidence rate ratio; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; mNY, modified New York; MTX, methotrexate; NA, not applicable; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds radio; PSA, prostate-specific antigen; PsA, psoriatic arthritis; PsO, psoriasis; pts, patients; PY, person years; RA, rheumatoid arthritis; RR, relative risk; SD, standard deviation; SIR, standardized incidence ratio; SMAHRT, Surveillance Epidemiology and End Results (SEER)-Medicare Assessment of Hematopoietic Malignancy Risk Traits Study; SpA, spondyloarthritis; SRR, Standardized risk ratios; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitor; VA, Veterans Affairs; WHO, World Health Organization.

[a] Severe psoriasis defined as presence of referral to secondary care or use of systemic medications.

Data from Refs.[7,11–15,20,22,24,25,27–30,32–42,46,47,50,57,61–67]

conventional disease-modifying antirheumatic drugs (DMARDs) were found to have increased risk for cancer (RR 1.75; 95% CI 1.40–2.18), but not patients on biological DMARDs (RR 0.96; 95% CI 1.84–3.28). The studies, however, do not consistently specify the amount of drug exposure.

Skin Cancer in Psoriatic Arthritis

Skin cancer, particularly nonmelanoma skin cancer (NMSC) is among the most commonly reported cancers in patients with PsA. Subgroup analysis of cancer types in the meta-analysis by Luo and colleagues[5] showed an increased risk of NMSC (RR 2.46; 95% CI 1.84–3/28).[5] Similar results were also seen in the Consortium of Rheumatology Researchers of North America (CORRONA) PsA cohort in which the incidence of NMSC was elevated (0.21 per 100 patient years).[7] However, it remains unclear what portion of this risk is related to the skin psoriasis rather than the PsA itself. A recent meta-analysis found higher risk of NMSC (RR 1.72; 95% CI 1.46–2.02) in psoriasis compared with patients without psoriasis.[8] Several factors may impact the risk of NMSC in psoriasis. Phototherapy, including high-dose psoralen plus ultraviolet A (PUVA) and narrowband UVB, used in patients with psoriasis has a reported association with an increased risk of NMSC and melanoma. Studies in psoriasis report up to a sevenfold increase in the risk of skin cancer in patients treated with PUVA, methotrexate, and both combined,[9] with a dose-related effect of PUVA and methotrexate on the risk of squamous cell carcinoma (but not basal cell carcinoma).[10]

Although there are studies finding an increased risk of NMSC in PsA, this was not consistent across studies; several studies found no increased risk.[7,11–14] One long-term safety study of adalimumab found an increased risk of NMSC in psoriasis (SIR 1.76; 95% CI 1.26–2.39), but did not find a significant association in PsA (SIR 1.25; 95% CI 0.46–2.72).[13]

The risk of other skin cancers, such as melanoma, does not seem to be increased in PsA.[7,15,16] Edson-Heredia and colleagues[11] found significantly lower incidence of melanoma in PsA as compared with severe psoriasis (hazard ratio [HR] 0.12; 95% CI 0.02–0.90), but no statistically significant difference was seen between PsA and psoriasis as a whole for melanoma and NMSC. In a meta-analysis of malignancy risk in psoriasis, the risk of squamous cell carcinoma (SCC) was also significantly higher than those without psoriasis (RR 2.15; 95% CI 1.32–3.50), and the risk was much higher in the severe psoriasis subgroup (RR 11.74; 95% CI 1.52–90.66).[17] Similarly, the risk of basal cell carcinoma (BCC) was increased only in the severe psoriasis subgroup (RR 3.17; 95% CI 1.32–7.60) and not psoriasis as a whole (RR 1.29; 95% CI 0.73–2.26), suggesting this risk is tied to severity of skin disease. However, we did not find studies specifically addressing the risk of SCC or BCC in PsA (only reported as NMSC group); it is unclear if the risk is different in these 2 subgroups.

Hematologic Malignancies

Lymphoma is among the most worrisome cancers for rheumatologists, particularly given the perceived relationship with therapy and the known association with RA.[18,19] Unlike RA, most studies in PsA have not found an increased risk of lymphoma.[7,13,15,20–23] Only 2 studies found an increased risk of overall hematologic malignancies in patients with PsA. Data from Clinical Practice Research Datalink (CPRD), a general practice database in the United Kingdom, found an increased risk of hematologic malignancies in PsA compared with those without PsA (incidence rate ratio 1.52; 95% CI 1.10–2.10),[14] and a large, prospective cohort study from 4 Nordic countries (Sweden, Denmark, Iceland, and Finland) showed higher risk of lymphoma in patients with PsA on tumor necrosis factor inhibitors (TNFi) compared with

the general population (SIR 1.84; 95% CI 1.20–2.82).[16] A higher prevalence of monoclonal gammopathy of unknown significance (MGUS) (9.7%, 35/361) was seen in a cross-sectional study from University of Toronto.[24] Only 1 of these patients was diagnosed as multiple myeloma. Another multicentric, longitudinal, prospective (CORRONA) study found no definite evidence of an increased risk of multiple myeloma in PsA (IRR 7.78; 95% CI 0.48–122.23).[7]

Solid Tumor Malignancies

Data on malignancies at other sites in PsA are inconsistent. A retrospective, population-based study in Olmsted County showed an increased risk of female breast cancer (HR 3.59; 95% CI 1.22–10.61) as well as overall malignancies, excluding NMSC, in patients with PsA (HR 1.64; 95% CI 1.03–2.61).[12] The risk of several other solid organ cancers (eye/orbit, female genital, urinary, NMSC, lung, prostate) was noted to be higher compared with subjects from the general population matched on age, sex, and calendar year in a retrospective cohort study (abstract) from British Columbia, Canada, that used health administrative data.[25] Lower risk of colon (IRR 0.84; 95% CI 0.72–0.99) and rectal carcinoma (IRR 0.79; 95% CI 0.64–0.98) was reported. Interestingly, unlike psoriasis, no increased risk of lymphoma and colorectal cancer was seen.[17] On the contrary, data from the CORRONA registry found similar risk of malignancy in PsA compared with RA (IRR 1.18; 95% CI 0.82–1.69).[7] Risk of malignancy by subtypes was not different, including that for NMSC and lymphoma. However, this study did not compare risk of malignancy to the general population.

RISK OF MALIGNANCY IN ANKYLOSING SPONDYLITIS

In AS, there seem to be more studies suggesting an increased risk for malignancy. A meta-analysis by Deng and colleagues[26] found an increased risk for overall malignancy (RR 1.14; 95% CI 1.03–1.25). Subgroup analysis in the study showed a higher risk in Asian populations, but not American or European populations. Also, the study design seems to influence the results, with cohort studies showing a higher risk than case-control studies and clinical trials. Another more recent study (not included in the meta-analysis) by Walsh and colleagues[27] also supports this conclusion, finding an overall risk for malignancy compared with population controls in MarketScan and Medicare (HR 1.39; 95% CI 1.19 to 1.62). However, several other studies did not show an overall increased risk of malignancy in AS.[13,15,20,28–30]

Hematologic Malignancies

In contrast to PsA, there may be a higher risk of hematological malignancies in AS although with some disagreement among individual studies within subtypes of hematologic malignancies (ie, lymphoma, multiple myeloma, and MGUS). Increased risk of malignancy was reported in axial SpA historically in patients undergoing radiation therapy where a threefold increase in risk of lymphoma was described with 28% higher mortality compared with the general population.[31] More recent studies have similarly found an increased risk of hematological malignancies, albeit with attenuated associations. Chang and colleagues[28] noted a higher risk of overall hematological malignancies (SIR 2.10; 95% CI 1.32 to 3.19) in a study from the national Taiwan database. In addition, a meta-analysis found a higher risk of multiple myeloma (RR 1.92; 95% CI 1.37–2.69) and lymphoma (RR 1.32; 95% CI 1.11–1.57). An increased risk of MGUS and multiple myeloma in AS has been reported in several studies: Brown and colleagues[32] noted an increased risk of MGUS (RR 2.02; 95% CI 1.14–3.56) and multiple myeloma (RR 2.29; 95% CI 1.55–3.40) in patients with AS from US

Department of Veterans Affairs hospitals. In a case-control study from Sweden, Lindqvist and colleagues[33] noted an increased risk of MGUS (odds ratio [OR] 2.7; 95% CI 1.4–5.2), but not multiple myeloma (OR 1.2; 95% CI 0.6–2.3). Increased risk of multiple myeloma was also noted in several other studies.[34–36] Similarly, a higher risk of leukemia (SIR 1.44; 95% CI 1.24–1.65) and non-Hodgkin lymphoma (SIR 1.36; 95% CI 1.19–1.53) was reported among Medicare beneficiaries[36]; and Lee and colleagues[35] reported increased risk of lymphoma (HR 3.05; 95% CI 1.45–6.45), but not leukemia (HR 2.32; 95% CI 0.91–5.91) from the national database of Korea. However, several other studies included in our review did not report an increased risk of hematologic malignancies, such as lymphoma, in AS.[13,15,20,22,37–41]

Solid Tumor Malignancies

Although there is mixed reporting of the relationship between hematologic malignancies and AS, there remains an even more unclear association between solid organ malignancies and AS. Chang and colleagues[28] noted a higher risk of colon cancer (SIR 1.39; 95% CI 1.03–1.82) and prostate cancer (SIR 1.64; 95% CI 1.04–2.47) in patients with AS. In contrast, data from the Anti-Rheumatic Therapy in Sweden (ARTIS) and Danish Biologics (DANBIO) registries showed a lower risk of colorectal cancer (RR 0.40; 95% CI 0.3–0.8) in the TNFi-naïve patients with AS compared with the general population, and very few colorectal cancers were seen in those on TNFi (<5 events).[15] Lower risk of colorectal cancer was also reported in a study from the Medicare database (SIR 0.81; 95% CI 0.71–0.91)[36] and in a national Swedish study (colon adenocarcinoma: SIR 0.55; 95% CI 0.32–0.88; rectal adenocarcinoma: SIR 0.35; 95% CI 0.14–0.73).[42] Higher risk of renal carcinoma (SIR 5.90; 95% CI 1.61–15.1) was noted in a study from the Swedish inpatient registry.[29] A study on Medicare beneficiaries by Alehashemi and colleagues[36] reported very different results from the rest of the studies, finding higher SIR in AS compared with patients without AS for kidney, thyroid, prostate, esophagus, stomach, colorectal, and lung cancers, and melanoma.

Over the past 10 years, the nomenclature for AS has been changing. As we discuss these studies with regard to associations with malignancy, it is important to keep in mind that most studies to date have focused on AS (more recently referred to as radiographic AxSpA), and some use general codes for AS that mix the radiographic and nonradiographic AxSpA populations.[43,44] In our review of the literature, we did not find studies on the risk of malignancy in nonradiographic axial spondyloarthritis (nr-AxSpA). As we move forward, an important research objective should be to understand the potentially differential malignancy risk in each of these subgroups.

CANCER AND SPONDYLOARTHRITIS (COMBINED AXIAL SPONDYLOARTHRITIS AND PSORIATIC ARTHRITIS)

Although most studies have separately examined AS and PsA, several have examined malignancy risk across the SpA category. In the cross-sectional Assessment of SpondyloArthritis international Society of COMOrbidities in SpA (ASAS-COMOSPA) study, a cohort of patients fulfilling either axial or peripheral ASAS criteria,[45] the prevalence (at any point up to the study visit date) of overall malignancy was approximately 3% (95% CI 2.46–3.52). The most prevalent cancers identified were cervical cancer (1.2%), BCC (0.8%), and melanoma (0.7%).[46] A similar study in China did not find an increased prevalence of malignancies in SpA relative to the general poulation.[47] Disparate results could be related to the fact that patients in this study were relatively young, and very few patients with SpA had cervical smears or saw a dermatologist for skin check in China.[47] Also malignancy rates reported in Northern Europe and the

United States are generally higher than reported rates in Asian countries.[48] Similarly, Hellgren and colleagues[15] reported a slightly increased risk of prostate cancer in the biologic-naïve group in the ARTIS and DANBIO biologics registries compared with the general population (RR 1.2; 95% CI 1.1–1.4). These results suggest that the association with malignancy may not be a class effect of SpA, but rather results from a complex interaction of specific comorbidities (eg, severe psoriasis in PsA) and medication use. Therefore, it would be helpful to study the risk of malignancies separately in PsA and AxSpA, rather than lumping into a single SpA category.

ASSOCIATION OF PHARMACOTHERAPIES FOR SPONDYLOARTHRITIS WITH CANCER

Nonsteroidal anti-inflammatory drugs (NSAIDs) and TNFi are the most commonly used therapeutic agents in the treatment of AxSpA, with interleukin-17 inhibitors recently added (and thus with very few data on malignancy outside of clinical trials). In SpA, there are relatively few data on the risk of malignancy by therapy class, particularly when compared with the available literature in RA, which is also limited. Among the available studies, most have addressed the risk for malignancy among those using TNFi (**Table 2**).

Among patients with PsA on TNFi, no increased risk of overall malignancy was noted.[13,16,30,49] However, some studies noted increased risk of specific types of malignancies. A recent study from British Society for Rheumatology Biologics Register found an increased risk of NMSC among those using TNFi compared with general population (SIR 2.12; 95% CI 1.19–3.50) but this elevated risk was only among women (SIR 2.41; 95% CI 1.10–4.58) and not men (SIR 0.85; 95% CI 0.51–1.35).[49] An increased risk for NMSC was similarly found among patients with PsA using methotrexate compared with the general population in a study by Lange and colleagues[6] (SIR-5.91; 95% CI 3.56–9.22). Neither of these studies report prior phototherapy exposure. Besides skin cancer, a higher risk of breast cancer in patients with PsA treated with TNFi compared with TNFi-naïve patients (RR 1.8; 95% CI 1.1–2.9) but not compared with the general population (RR 0.9; 95% CI 0.8–1.1) was seen in the ARTIS and DANBIO registries.[15] Lange and colleagues[6] also reported a lower risk of prostate cancer in patients with PsA treated with TNFi compared with TNFi naïve (RR 0.4; 95% CI 0.2–0.8) and the general population (RR 0.4; 95% CI 0.2–0.8). A retrospective study from CPRD also noted an increased risk of solid organ malignancies, site not specified (IRR 1.84; 95% CI 1.46–2.32), and NMSC (IRR 2.54; 95% CI 1.84–3.51) in patients with PsA on methotrexate, sulfasalazine, or adalimumab compared with those with PsA not using these medications.[14] Finally, pooled data from long-term extension studies did not find a higher than expected risk of malignancies in patients with PsA on adalimumab.[13]

As noted previously, there is variability in the reported risk of hematological malignancies in PsA as a disease; and this is similarly true when examining therapies and the association with hematologic malignancies in PsA. No increased risk of hematologic malignancies was observed in patients with PsA on TNFi in most studies.[13,15,21–23,50] A retrospective cohort study using data from CPRD found increased risk of hematologic malignancies in PsA (IRR 3.59; 95% CI 1.96–6.60) on DMARDs/biologics (methotrexate, sulfasalazine, and adalimumab).[14] Similarly, a large prospective cohort study including patients from 4 Nordic countries (Sweden, Denmark, Iceland, and Finland) reported a higher risk of Hodgkin and non-Hodgkin lymphoma in patients with PsA ever treated with TNFi.[16]

Among patients with AS, none of the studies reported an increased risk of any cancer with immunosuppressive medications or TNFi.[15,21–23,51] We did not find any

Table 2
Summary of studies examining the risk of cancer with medications used to treat spondyloarthritis (SpA)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
SpA										
Atzeni et al,[54] 2018	Cohort study from GISEA registry, Italy	2003–2015	3321	Pts ≥18 y with physician diagnosis of RA, PsA, AS, enteropathic arthritis, undifferen-tiated SpA	Incidence of cancer in SpA treated with TNFi	GP (rates per Italian Association of Medical Oncology)	TNFi- ETN or ADA	12	56 malignancies including lung breast, colorectal, reproductive system malignancies.	Overall incidence of malignancies/1000 PY: SpA- 6.3 (4.7–8.2) PsA- 6.8 (4.5–9.7) AS-6.8 (4.2–10.4) Enteropathic arthritis- 6.7 (0.2–37.5) Undifferentiated SpA- 4.4 (1.4–10.3) GP- 5.1 (NR) HR of cancer in SpA with TNFi vs. SpA with no TNFi: TNFi- HR = **1.04 (1.01–1.06)** ADA- HR = 1.56 (0.8–3.2) ETN- HR = 1.05 (0.5–2.0) Previous neoplasia was a significant predictor of new malignancy, HR = 10.6 (4.2–27.0).

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hellgren et al,[15] 2017	Population-based, nationwide cohort study-ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-17406 TNFi naïve-28,164	AS ICD-10 code (M45) PsA ICD-10 code (L40.5)	Cancer risk in SpA treated with TNFi compared with biologic naïve and GP	Swedish age-matched and sex-matched GP comparator cohort (n = 131,687)	TNFi treated TNFi naïve	Up to 10 y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma	TNFi treated vs TNFi naïve SpA (RR): 0.8 (0.7–1.0) **0.5 (0.3–0.8)** 0.6 (0.3–1.3) 1.0 (0.5–2.0) 0.8 (0.4–1.8) 1.3 (0.9–2.0) 1.4 (0.7–2.6) TNFi treated SpA vs GP (RR): 0.9 (0.7–1.0) **0.6 (0.4–0.9)** 0.6 (0.3–1.2) 0.7 (0.4–1.2) 0.8 (0.4–1.9) 1.3 (0.9–1.9) 1.3 (0.7–2.3)
Westhovens et al,[53] 2014	Single-center, prospective, longitudinal cohort study (BIOSPAR)	Sep 2000-Mar 2010	231 (PsA-103)	Rheumatologist's diagnosis	Incidence of malignancy in SpA cohort treated with TNFi (BIOSPAR) compared with GP of Belgium	Belgian population of 2008 (45–50 y old), rates per Belgian Cancer Registry	TNFi (ETN, IFX, ADA, GOL)	1020.74 PY of treatment and 1199.83 PY F/U after the start of treatment.	All malignancies	SIR of malignancy in SpA on TNFi vs GP: Female- 1.54 (NR) Male- 1.31 (NR) 6/231 SpA patients (2.6%) developed malignancy

PsA

Ballegaard,[16] 2019 (abstract)	Prospective, cohort study from ARTIS (Sweden), DANBIO (Denmark), ICEBIO (Iceland) or ROB-FIN (Finland) and linked to the national Cancer Registry in each country	NR	ARTIS-5218, DANBIO-2039, ICEBIO-270 and ROB-FIN-526	Rheumatologist's diagnosis	Risk of cancer in TNFi-treated PsA patients compared with standardized rates from the general population in Denmark, Finland, Iceland, and Sweden	GP	TNFi (ever treated)	44,041 PY across all 4 countries	All cancers Colorectal Hodgkin's and NHL Lung Malignant melanoma Pancreas Brain Female breast Corpus uteri Prostate	SIR of malignancy in SpA with TNFi (ever treated) vs GP: 1.00 (0.89–1.13) 1.21 (0.85–1.71) **1.84 (1.20–2.82)** 0.79 (0.51–1.22) 1.07 (0.69–1.66) 1.21 (0.60–2.41) 0.95 (0.45–1.99) 1.20 (0.93–1.55) 0.67 (0.30–1.49) 0.70 (0.50–0.98)
Burmester et al,[13] 2013	Pooled data from clinical trials (Europe, North America, South America, Asia, Australia, New Zealand, and South Africa)	Through Nov 2010	837	SpA definition per clinical trial.	Risk of malignancy from global clinical trials of ADA in immune-mediated inflammatory diseases	GP	ADA (clinical trials)	Nearly 12 y of ADA exposure	All malignancies Lymphoma NMSC	SIR for cancer in PsA vs GP: 0.68 (0.22–1.59) 5.88 (0.66–21.2) 1.25 (0.46–2.72) Note: Melanoma <0.1/100 PYs SIR for cancer in psoriasis vs GP- 1.76 (1.26–2.39)
Carmona et al,[20] 2011	Prospective cohort study-BIOBADASER 2.0 (ongoing cohort of patients with rheumatic diseases exposed to TNFi)	BIOBADASER (2001–2008)	727	Rheumatologist diagnosed rheumatic diseases starting treatment or were on a biologic response modifier	Cancer risk in RA, PsA, and AS patients exposed to TNFi	GP of Spain (source: GLOBOCON, WHO program 2002)	TNFi (IFX, ETN, ADA)	2323 PY	Colon and rectum Prostate Bladder NHL All sites but skin	SIR for cancer in PsA pts exposed to TNFi: 1.28(0.15–4.62) 1.18(0.03–6.59) 2.06(0.25–7.42) 4.84(0.59–17.48) 0.73(0.33–1.39)

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Costa et al,[68] 2016	Prospective, single-center (University Federico II of Naples) cohort study	2001–2014	618	Pts fulfilling CASPAR criteria at the time of diagnosis (after 2006) or retrospectively (before 2006 and then obtaining first dx using Moll and Wright criteria)	Incidence of malignancies in PsA pts conventional DMARDs and TNFi	none	TNFi (ETN, ADA, IFX, GOL) Conventional DMARDs	9 (median)	Squamous cell Breast Meningioma Colorectal cancer Kidney cancer Ovarian cancer NHL Uterine cancer Seminoma Papillary thyroid cancer	Incidence of overall malignancy: TNFi- 4.7% (2.8–7.8); IR- 0.52 cases/100 PY DMARD-9.3% (6.6–13.0); IR-1.03 cases/100 PY
Dreyer et al,[30] 2013	Cohort study (DANBIO arthritis cohort)	2000–2008.	656	Rheumatologist's diagnosis	Incidence of overall and site-specific malignancies in TNFi-treated pts with PsA	GP	TNFi	2.9 (mean).	All cancer sites	SIR of malignancy in PsA on TNFi vs GP: 1.16 (0.66–2.04) 12/656 pts during f/u HR of malignancy with PsA on TNFi vs no TNFi- NR.

Fagerli et al,[49] 2019	Cohort study from BSRBR	2002–2006	709 (males, n = 331, females, n = 378)	Rheumatologist's diagnosis	Malignancy and mortality rates in PsA pts requiring TNFi	GP	TNFi	8.4 (SD-1.5), followed until 2012	NMSC Malignant melanoma Genital cancer Lymphatic and hema-tological cancer Orophar-yngeal cancer	SIR for PsA on TNFi vs GP: All malignancies - 0.94 (0.65–1.34) NMSC- **2.12 (1.19–3.50)** SIR for PsA on TNFi vs GP (males): All malignancies- 1.06 (0.61–1.72) NMSC- 0.85 (0.51–1.35) SIR for PsA on TNFi vs GP (females): All malignancies- 0.85(0.51–1.35) NMSC- **2.41(1.10–4.58)**
Hagberg et al,[14] 2016	Retrospective cohort study from CPRD, UK	1988–2012.	8943	PsA as diagnosed by general practitioner or specialist	Incidence rate of cancers in patients with PsA vs without PsA	Pts without PsA (n = 82,601)	Systemic therapies DMARDs/ biologics (eg, MTX, SSZ, and ADA), immunos-uppressants (eg, AZT and leflunomide),	Solid cancer- 3139 PY, Hematological cancer- 261 PY, NMSC- 1561 PY	Solid, hema-tologic, and NMSC	IRR of solid cancer in PsA on different drugs vs PsA with no drug: Any drug- 1.80 (1.44–2.27) DMARDs/ biologics- 1.84 (1.46–2.32)

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
							and corticosteroids			Immuno-suppressant- 1.99 (1.02–3.87) 3.69 (1.37–9.91) IRR of hematologic cancer in PsA on different drugs vs PsA with no drug: Any drug- 3.50 (1.92–6.36) DMARDs/ biologics- 3.59 (1.96–6.60) Immuno-suppressant- 6.79 (2.04–22.62) IRR of NMSC in PsA on different drugs vs PsA with no drug: Any drug- 2.42 (1.76–3.34) DMARDs/ biologics- 2.54 (1.84–3.51) Immuno-suppressant- 2.63 (1.07–6.45)

										Corticosteroid-4.19 (1.03–17.01) Drug exposure defined as first PsA drug prescription occurred at least 1 y before cancer dx date
Haynes et al,[21] 2013	Retrospective cohort study (SABER study)-Medicare, Medicaid, New Jersey's Pharmaceutical Assistance, Kaiser Permanente (US)[a]	1992–2007 [a] (variable study periods in 4 different databases)	Total PsA-2498 (PsA on TNFi, n = 1036)	ICD-9 diagnostic codes for PsA	Cancer risk with TNFi in chronic immune-mediated diseases	PsA with no TNFi (on MTX or sulfasalazine, n = 1462)	TNFi	618 PY	Any lymphoma, any hematologic cancer, any solid cancer other than nonmela-noma skin cancer, and nonmela-noma skin cancer, defined as squamous cell or basal cell cancer	HR of incident c ancer for PsA on TNFi vs no TNFi: Any leukemia or lymphoma-<5 events Any solid cancer-0.74 (0.20–2.76) NMSC-0.74 (0.06–8.72)

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Hellgren et al,[22] 2014	Population-based, prospective cohort study from Swedish National Patient Register	2001-2010	19,283	ICD codes for AS, PsA	Risk of malignant lymphoma in AS, PsA	Randomly selected from Swedish Population Register (matched for age-sex and county of residence)	TNFi MTX/SSZ Oral GC	10,912 PY	Malignant lymphoma	HR for lymphoma in PsA on drug vs no drug: MTX and/or SSZ-1.7 (1.0–3.1). The numbers and incidence of lymphoma were not different in TNFi-exposed vs TNFi-naïve PsA patients, although the number of lymphoma was very small.

Hellgren et al,[15] 2017	Population-based, nationwide cohort study- ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-3833 TNFi naïve-15,908	ICD-10 code for PsA (L40.5)	Cancer risk in SpA treated with TNFi	Swedish age-matched and sex-matched GP comparator cohort (n = 74,010)	TNFi treated TNFi naïve	Up to 10 Y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma	TNFi treated vs TNFi naïve PsA (RR): 0.9 (0.7–1.1) **0.4 (0.2–0.8)** <5 events 1.1 (0.5–2.4) 1.0 (0.4–2.7) 1.8 (1.1–2.9) 1.7 (0.7–4.2) TNFi treated PsA vs GP (RR): 0.9 (0.7–1.1) **0.4 (0.2–0.8)** <5 events 0.9 (0.4–1.8) 1.1 (0.4–2.60) 1.6 (1.0–2.5) 1.5 (0.7–3.3) TNFi naïve PsA vs GP (RR): 1.0 (0.9–1.1) 1.1 (0.9–1.3) 1.0 (0.7–1.3) 0.8 (0.6–1.1) 1.0 (0.6–1.4) 0.9 (0.8–1.1) 0.9 (0.6–1.3)
Lange, 2016[6]	Retrospective cohort study (2 private rheumatology practices in Hobart, Tasmania)	1978–2005	RA/PsA, n = 405; PsA, n = 60	Rheumatologist's diagnosis	NMSC risk with DMARDs in inflammatory arthritis (RA and PsA)	GP (expected rates)	MTX CSA + MTX Penicillamine D + MTX	First presentation to Dec 2005	NMSC	SIR of NMSC for PsA pts treated with MTX vs GP: 5.91 (3.56, 9.22)

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Rohekar et al,[50] 2008	Prospective cohort study from University of Toronto Psoriatic Arthritis Clinic	1978–2004	665	Rheumatologist's diagnosis	Prevalence of malignancy in PsA	GP (Ontario)	NSAID DMARD Immuno-suppressants	NR	All cancers	SIR for malignancy PsA vs GP: All cancers - 0.98 (0.77–1.24) Hematologic - 0.69 (0.26–1.83) Lung- 0.88 (0.46–1.69) Breast-1.55 (0.92–2.62) Prostate −0.65 (0.29–1.44) ESR, cm/h was the only significant predictor of malignancy in Cox regression, HR-**1.13 (1.02–1.25)**. TNFi and DMARDs were not.

Saad, 2011[69,70]	Prospective, multicenter, longitudinal, cohort study from BSRBR	2002–2006	596	Rheumatologist's diagnosis	Efficacy and safety of anti-TNF therapies in PsA	Seronegative RA control cohort in BSRBR receiving nonbiologic DMARDs, adjusting for age, sex, and baseline comorbidity	ETN (n = 333), IFX (n = 171) ADA (n = 92)	1776.2 PY (median 3.07 per pt),	All cancers	IRR of cancer in PsA on TNFi vs seronegative RA on nonbiologic DMARDs: 0.9 (0.5–1.6)[b] In total, there were 81 malignancies reported at various sites (14 on anti-TNF and 67 on DMARD control). Of note, there were 5 cases of lymphoma in the control group and no cases in the anti-TNF group. 29 reports of skin cancer in total: 17 basal cell cancer (13 in controls, 4 in anti-TNF), 8 NMSC (6 in controls, 2 in anti-TNF) and 4 melanomas (2 in each group).

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
Saliba et al,[23] 2016	Disproportionality analysis (case/noncase study) from the French National Pharmaco Vigilance Database	2000–2010	128	Labeled indication of TNFi in database	Risk of cancer with TNFi + nonbiologic immuno suppressants (NBIS) vs NBIS only in autoimmune diseases (RA, AS, PsA, and IBD)	NBIS only	TNFi + NBIS NBIS only	Minimum 3 mo exposure to non-biologics	Overall Hematological cancer -Lymphoma Solid cancer	RR of malignancy with TNF + NBIS vs NBIS in psoriasis/PsA pts: 3.45 [1.09–10.92] 2.46 (0.52–11.62) 2.43 (0.36–16.68) 4.46 (0.84–23.82)
AxSpA										
Haynes et al,[21] 2013	Retrospective cohort study (SABER study)	1992–2007 [a](variable study periods in 4 different databases)	Total AS-1486 (AS on TNFi, n = 783)	ICD-9 diagnostic codes for AS	Cancer risk with TNFi in chronic immune-mediated diseases	AS with no TNFi (on MTX or sulfasalazine, n = 703)	TNFi	433.1 PY	Any lymphoma, any hematologic cancer, any solid cancer other than nonmelanoma skin cancer, and nonmelanoma skin cancer, defined as squamous cell or basal cell cancer	HR of incident cancer for AS on TNFi vs no TNFi: Any leukemia or lymphoma-<5 events Any solid cancer-0.03 (0.002–0.45) NMSC <5 events

Hellgren et al,[22] 2014	Population-based, prospective cohort study from Swedish National Patient Register	2001-2010	8707	ICD codes for AS, PsA	Risk of malignant lymphoma in AS, PsA	Randomly selected from Swedish population register (matched for age-sex and county of residence)	TNFi MTX/SSZ Oral GC	7790 PY	Malignant lymphoma	HR for lymphoma in AS on DMARD vs no DMARD: MTX and/or SSZ- 1.2 (0.3–4.3) The numbers and incidence of lymphoma were not different in TNFi-exposed vs TNFi-naïve AS patients, although the number of lymphoma was very small.
Hellgren et al,[15] 2017	Population-based, nationwide cohort study- ARTIS and DANBIO biologics registers, linked with the nationwide Swedish and Danish Cancer Registers	2001–2011	TNFi-3078 TNFi naïve-7023	AS ICD-10 code (M45)	Cancer risk in SpA treated with TNFi	Swedish age-matched and sex-matched GP comparator cohort (n = 32,706)	TNFi treated TNFi naïve	Up to 10 y	Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma Cancer overall Prostate Lung Colorectal Malignant lymphoma Breast Melanoma Cancer overall Prostate Lung Colorectal Malignant	TNFi treated vs TNFi naïve AS (RR): 0.8 (0.6–1.1) 0.5 (0.2–1.1) <5 events <5 events <5 events 0.6 (0.2–1.6) 1.6 (0.5–4.6) TNFi treated AS vs GP: 1.0 (0.7–1.2) 0.6 (0.3–1.3) <5 events <5 events <5 events 0.9 (0.4–2.3)

(*continued on next page*)

Table 2
(*continued*)

Author, Year	Study Design	Study Period	No. of SpA Pts	SpA Definition	Relevant Study Questions	Comparison Group	Therapies	Follow-up Period (y)	Types of Malignancies Reported	Estimate of Risk, Measure of Effect (95% CI)
									lymphoma Breast Melanoma	1.4 (0.6–3.6) TNFi naïve AS vs GP: 1.1 (1.0–1.3) 1.3 (1.0–1.6) 1.0 (0.6–1.6) **0.4 (0.3–0.8)** 0.9 (0.5–1.6) 1.4 (1.0–2.0) 0.8 (0.5–1.5)
Saliba et al,[23] 2016	Disproportionality analysis (case/noncase study) from the French National Pharmaco Vigilance Database	2000–2010	92	Labeled indication of TNFi in database	Risk of cancer with TNFi + nonbiologic immuno-suppressants vs nonbiologic immuno-suppressants only in autoimmune diseases (RA, AS, PsA, and IBD)	Nonbiologic immuno-suppressants only	TNFi + nonbiologic immuno-suppressants Nonbiologic immuno-suppressants only	Minimum 3 mo exposure to nonbiologics	Overall Hematological cancer -Lymphoma Solid cancer	RR of malignancy with TNF + NIBIS vs NBIS AS pts: 2.84 (0.32–24.87) - - 1.86 (0.16–22.05) RR adjusted for age, gender, year of reporting, history of cancer, exposure to TNFi and nonbiologic immuno-suppressants

										Too few events to report RR for hematological cancer separately.
van der Heijde et al,[51] 2014	A pooled analysis from 5 RCTs and 4 open label studies from Pfizer/Amgen	Dec 2001-Jan 2008	1323	Clinical trial definition of AS	Rates of malignancies in AS pts receiving ETN vs controls	GP (SEER database)	ETN SSZ	1131 PY of exposure to ETN	All malignancies NMSC -Basal cell cancer -Squamous cell cancer	SIR for malignancy in ETN treated pts vs GP: 1.47 (0.54–3.21) 0.12 (0.00–0. 65) 0.56 (0.01–3.11)

Abbreviations: ADA, adalimumab; ARTIS, Anti-Rheumatic Therapy in Sweden; AS, ankylosing spondylitis; AxSpA, axial spondyloarthritis; AZT, azathioprine; BIOSPAR, Leuven spondyloarthritis biologics cohort; BSRBR, British Society for Rheumatology Biologics Register; CASPAR, Clinical Classification of Psoriatic Arthritis; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CSA, cyclosporine; DANBIO, Danish Biologics Registry; DMARDs, disease-modifying antirheumatic drugs; dx, diagnosis; ESR, erythrocyte sedimentation rate; ETN, etanercept; F/U, follow-up; GC, glucocorticoids; GISEA, Italian Group for the Study of Early Arthritis; GOL, golimumab; GP, general population; HR, hazard ratio; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; ICEBIO, Icelandic nationwide database of biologic therapy; IFX, infliximab; IR, incidence rate; IRR, incidence rate ratio; MTX, methotrexate; NBIS, nonbiologic immunosuppressants; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis;; pts, patients; PY, person years; RA, rheumatoid arthritis; RCT, randomized controlled trial; ROB-FIN, Finnish Register of Biological Treatment; RR, relative risk; SABER, The Safety Assessment of Biological Therapeutics study using data from 4 sources: National Medicaid and Medicare databases, Tennessee Medicaid, pharmacy benefits plans for Medicare beneficiaries in New Jersey and Pennsylvania, and Kaiser Permanente Northern California; SD, standard deviation; SEER, surveillance, epidemiology, and end results; SIR, standardized incidence ratio; SpA, spondyloarthritis; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitor; WHO, World Health Organization.

[a] (1) national Medicaid and Medicare databases (Medicaid Analytical eXtract, 2000–2005, excluding Tennessee; Medicare, 2000–2006; and Medicare Part D, 2006); (2) Tennessee Medicaid (TennCare, 1998–2005); (3) New Jersey's Pharmaceutical Assistance to the Aged and Disabled and Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (1992–2006); and (4) Kaiser Permanente Northern California (1998–2007).

[b] Corrected data published as correction.

Data from Refs.[6,13–16,20–23,30,49–51,53,54,68–70]

studies examining the risk of cancer with NSAIDs in the SpA population (AS or PsA).The potential benefit of NSAIDs, in particular selective Cox-2 inhibitors, has been described in patients with recurrent colorectal cancer.[52] In a study by Hellgren and colleagues,[15] patients with AS who were TNFi naïve had a lower risk of colorectal cancer compared with the general population. It is possible that a high proportion of the TNFi-naïve population was using NSAID therapy, which may partially explain the results.

Few studies reported the risk of malignancy in relation to TNFi use in SpA population as a whole. Hellgren and colleagues[15] noted that the risk of malignancy was lower in patients with SpA on TNFi from ARTIS and DANBIO registries compared with the general population (RR 0.6; 95% CI 0.4–0.9) and compared with TNFi-naïve SpA (RR 0.6%, 95% 0.4–0.9). On the contrary, a study from the Leuven spondyloarthritis biologics cohort (BIOSPAR) reported an increased SIR of malignancy in SpA on TNFi compared with general population (SIR of 1.54 in women, and 1.31 in men, CI not reported).[53] A similar, although relatively lower, risk of malignancy in SpA treated with TNFi compared with the general population (HR 1.04; 95% CI 1.01–1.06) was also noted by the Italian Group for the Study of Early Arthritis (GISEA).[54]

In all studies examining the malignancy risk associated with pharmacotherapies, it is unclear if the effect seen is truly a medication effect or associated with features of disease that results in the patient receiving the medication (ie, confounding by indication).

RISK OF MALIGNANCY FOLLOWING THERAPEUTICS IN SPONDYLOARTHRITIS WITH PRIOR MALIGNANCY

Most of the studies included in the review are limited to study of the first occurrence of cancer and excluded patients with a history of malignancy (particularly for randomized controlled trials and their subsequent extension studies). Thus, little is known about treatment of patients with a prior malignancy. In a study from the Italian Group for the Study of Early Arthritis (GISEA) registry, history of neoplasia was a significant predictor of new malignancy in SpA patients on etanercept or adalimumab (HR 10.6; 95% CI 4.2–27.0); approximately 80% of which were solid organ malignancies and the rest NMSC.[54] In another study from the BIOBADASER study cohort, no significant risk of malignancy was reported in patients with previous cancers (IRR 5.22; 95% CI 0.79–34.34); however, only 1% of the patients in the cohort had a previous history of malignancy and more than 50% of patients had RA (results were not separately reported for SpA).[20] Finally, the risk for NMSC was greater among patients with a history of cancer (solid organ, hematologic, or NMSC); however, rates were similar in the PsA and non-PsA cohorts. More data are needed to better inform how to manage patients with SpA who have a prior history of malignancy.

OTHER RISK FACTORS FOR CANCER IN SPONDYLOARTHRITIS

There are relatively few studies specifically examining risk factors for malignancy in SpA, and those that exist have found risk factors that are also typical of those seen in the general population. Atzeni and colleagues[54] noted previous malignancy to be a significant predictor of new malignancy (HR 10.6; 95% CI 4.2–27, $P<.001$). Other risk factors noted in multivariate analysis were age at the time of diagnosis (HR 1.04; 95% CI 1.01–1.1) and Health Assessment Questionnaire-Disability Index score (HR 2.42; 95% CI 1.3–4.7).[54] Similarly, as would be expected, the rate of solid organ, hematologic cancers increased with age in a cohort study from CPRD, UK.[14] Female sex was associated with increased risk of overall malignancy in a population-based study from Olmsted County, MN (HR 2.17; 95% CI 1.05–4.48, $P = .037$).[12] Erythrocyte

sedimentation rate (ESR) was the only significant predictor of malignancy in Cox regression (HR 1.13; 95% CI 1.02–1.25) in a prospective cohort study from University of Toronto Psoriatic Arthritis Clinic.[50] Longer disease duration (OR 1.04; 95% CI 1.01–1.07) and high ESR (OR 1.03; 95% CI 1.01–1.04) were associated with MGUS in PsA in a cross-sectional analysis.[24] Furthermore, the increased prevalence of known malignancy risk factors in SpA, such as obesity,[55,56] smoking,[46] and excess alcohol intake[57] may be a possible explanation for an association of SpA with malignancy in certain cohorts for particular cancers.

SPONDYLOARTHRITIS AND CANCER SCREENING

Regardless of whether there is a true increase in the risk for malignancy among patients with SpA, following general population guidelines for screening is important. Two studies found that cancer screening was suboptimal in at-risk patients with SpA (based on age and sex): 32% to 44% for breast cancer (>75% in most European countries, ~50% in China for the general population[58]), 40% for cervical cancer (~80% in Europe), 57% for prostate cancer, 33% for colon cancer (46.8% in Europe) and only 10.7% for skin cancer.[46,47] Patients with PsA should be referred for yearly skin checks with dermatology, especially those with severe psoriasis and on long-term phototherapy. The benefit of systematic screening for skin cancer in AxSpA has been reported in a prospective, 12-month randomized controlled trial.[59] The intervention consisted of nurse-led screening of 5 SpA comorbidities (ie, cardiovascular disease, osteoporosis, cancer, infection, and peptic ulcer), according to recommendations from the French Society of Rheumatology. Skin cancer screening rates increased in the intervention group (36.3% vs 17.2%; $P = .04$), and a decrease in comorbidity score (−3.20 vs −1.85) in the active nurse-led screening intervention group at 1 year was noted, although not statistically significant. This suggests possible short-term benefit of comorbidity screening even in this relatively young AxSpA population.

CONSIDERATIONS IN INTERPRETATION OF AVAILABLE DATA

Although most studies used a cohort design (ideal for studying the association of SpA with outcomes such as malignancy), a number of studies used case-control and cross-sectional designs. These may result in biased conclusions because of the inability to establish a temporal association. Data from TNFi trials were used for assessment as well, which typically have a shorter follow-up period and are thus not as helpful in studying the long-term risk of cancer. In observational studies, patients may have been exposed to multiple medications during or before the follow-up period, making it difficult to attribute the risk to a particular therapy or therapy class. Next, among studies of cancer in SpA, the definitions of SpA varied. Most often the diagnosis and outcomes were based on diagnostic codes, which may impact the validity of the results depending on the setting and validity of the individual codes used. Observation bias may also be problematic when comparing patients with SpA with the general population, and likewise when comparing patients on a particular therapy (ie, TNFi) given that they may be followed more closely than those without the disease. This bias may be exacerbated when reporting incidence of malignancy in one population versus an external general population (ie, not using internal matched controls). Most studies of SpA and malignancy reported an SIR in comparison with expected rates in the general population. Geographic, racial, and ethnic differences might exist; and screening practices across different countries might be highly variable. In addition, survival bias also has to be considered in the study of incident malignancies, as rapidly progressive malignancies might be underrepresented, as these patients

might have died prematurely or patients may have died from other causes before diagnosis with malignancy. Finally, study of cancer subtypes is challenging, as some subtypes are quite rare and even large patient populations often lack power to detect differences in these rare outcomes.

Studies on the risk of malignancy with medications are especially difficult, as the results might be influenced by confounding by indication; that is, phototherapy, DMARDs, and TNFi are prescribed for those with severe or refractory disease, which in itself could be a risk factor. Similarly, in RA, older and less healthy patients seem to get conventional DMARDs as opposed to biological agents, leading to a channeling bias.[60]

CLINICS CARE POINTS

- In the literature, there are conflicting points about the association of malignancy with SpA/PsA. However, in caring for patients with PsA using biologic therapies or methotrexate, the increased risk for nonmelanoma skin cancers should be recognized.
- Age-appropriate cancer screening should be considered for all patients with SpA/PsA.

SUMMARY

In reviewing the literature, there is a mix of studies that support and refute an association between SpA and malignancies overall. However, there seems to be a higher incidence of NMSC in PsA, and increased incidence of both MGUS and multiple myeloma was noted in AS. Few studies showed a higher incidence of lymphoma in both PsA and AS, but the results were inconsistent. A higher risk of digestive tract cancers was noted in AS in some studies. No studies have addressed the risk of malignancy in nr-AxSpA. It is unclear if traditional immunosuppressive agents, TNFi or NSAIDs modulate the risk of cancer in SpA. However, overall, if there is an increased risk, it seems to be quite small.

Although no specific screening recommendations for malignancy in SpA are available at present, age-appropriate screening should be performed in all patients at minimum. In addition, annual dermatology checks for malignancy should be considered in PsA, especially in patients with moderate-to-severe psoriasis. Future studies of larger cohort studies with a better understanding of prior therapy history may help better understand the risk for malignancy in SpA.

DISCLOSURE

A. Ogdie has served as a consultant for AbbVie, Amgen, BMS, Celgene, Corrona, Janssen, Lilly, Novartis, and Pfizer and has received grants from Novartis and Pfizer to Penn and from Amgen to Forward.

REFERENCES

1. Mercer LK, Davies R, Galloway JB, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology (Oxford) 2013;52(1):91–8.
2. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357(9255):539–45.
3. Chai EZP, Siveen KS, Shanmugam MK, et al. Analysis of the intricate relationship between chronic inflammation and cancer. Biochem J 2015;468(1):1–15.

4. Coates LC, FitzGerald O, Helliwell PS, et al. Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same? Semin Arthritis Rheum 2016; 46(3):291–304.
5. Luo X, Deng C, Fei Y, et al. Malignancy development risk in psoriatic arthritis patients undergoing treatment: A systematic review and meta-analysis. Semin Arthritis Rheum 2019;48(4):626–31.
6. Lange E, Blizzard L, Venn A, et al. Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. Rheumatology (Oxford) 2016;55(9):1594–600.
7. Gross RL, Schwartzman-Morris JS, Krathen M, et al. A comparison of the malignancy incidence among patients with psoriatic arthritis and patients with rheumatoid arthritis in a large US cohort. Arthritis Rheumatol 2014;66(6):1472–81.
8. Wang X, Liu Q, Wu L, et al. Risk of non-melanoma skin cancer in patients with psoriasis: An updated evidence from systematic review with meta-analysis. J Cancer 2020;11(5):1047–55.
9. Mali-Gerrits MG, Gaasbeek D, Boezeman J, et al. Psoriasis therapy and the risk of skin cancers. Clin Exp Dermatol 1991;16(2):85–9.
10. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. Cancer 1994;73(11):2759–64.
11. Edson-Heredia E, Zhu B, Lefevre C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. J Eur Acad Dermatol Venereol 2015;29(5):955–63.
12. Wilton KM, Crowson CS, Matteson EL. Malignancy incidence in patients with psoriatic arthritis: a comparison cohort-based incidence study. Clin Rheumatol 2016; 35(10):2603–7.
13. Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis 2013;72(4):517–24.
14. Hagberg KW, Li L, Peng M, et al. Rates of cancers and opportunistic infections in patients with psoriatic arthritis compared with patients without psoriatic arthritis. J Clin Rheumatol 2016;22(5):241–7.
15. Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis 2017;76(1):105–11.
16. Ballegaard C, Hellgren K, Cordtz R, et al. OP0005 incidence of overall and sites-pecific cancers in tnf inhibitor treated patients with psoriatic arthritis: a population-based cohort study from 4 Nordic countries. Available at: https://ard.bmj.com/content/78/Suppl_2/67.3
17. Trafford AM, Parisi R, Kontopantelis E, et al. Association of psoriasis with the risk of developing or dying of cancer: a systematic review and meta-analysis. JAMA Dermatol 2019. https://doi.org/10.1001/jamadermatol.2019.3056.
18. Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008; 10(2):R45.
19. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015;17:212.
20. Carmona L, Abasolo L, Descalzo MA, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. Semin Arthritis Rheum 2011;41(1):71–80.

21. Haynes K, Beukelman T, Curtis JR, et al. Tumor necrosis factor α inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum 2013; 65(1):48–58.
22. Hellgren K, Smedby KE, Backlin C, et al. Ankylosing spondylitis, psoriatic arthritis, and risk of malignant lymphoma: a cohort study based on nationwide prospectively recorded data from Sweden. Arthritis Rheumatol 2014;66(5): 1282–90.
23. Saliba L, Moulis G, Abou Taam M, et al. Tumor necrosis factor inhibitors added to nonbiological immunosuppressants vs. nonbiological immunosuppressants alone: a different signal of cancer risk according to the condition. A disproportionality analysis in a nationwide pharmacovigilance database. Fundam Clin Pharmacol 2016;30(2):162–71.
24. Eder L, Thavaneswaran A, Pereira D, et al. Prevalence of monoclonal gammopathy among patients with psoriatic arthritis. J Rheumatol 2012;39(3):564–7.
25. Risk of Cancer in Patients with Psoriasis/Psoriatic Arthritis: A Population-Based Study in the Province of British Columbia. ACR Meeting Abstracts. Available at: https://acrabstracts.org/abstract/risk-of-cancer-in-patients-with-psoriasis-psoriatic-arthritis-a-population-based-study-in-the-province-of-british-columbia/. Accessed January 15, 2020.
26. Deng C, Li W, Fei Y, et al. Risk of malignancy in ankylosing spondylitis: a systematic review and meta-analysis. Sci Rep 2016;6:32063.
27. Walsh JA, Song X, Kim G, et al. Evaluation of the comorbidity burden in patients with ankylosing spondylitis using a large US administrative claims data set. Clin Rheumatol 2018;37(7):1869–78.
28. Chang C-C, Chang C-W, Nguyen P-AA, et al. Ankylosing spondylitis and the risk of cancer. Oncol Lett 2017;14(2):1315–22.
29. Feltelius N, Ekbom A, Blomqvist P. Cancer incidence among patients with ankylosing spondylitis in Sweden 1965-95: a population based cohort study. Ann Rheum Dis 2003;62(12):1185–8.
30. Dreyer L, Mellemkjær L, Andersen AR, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis 2013; 72(1):79–82.
31. Darby SC, Doll R, Gill SK, et al. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987;55(2): 179–90.
32. Brown LM, Gridley G, Check D, et al. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood 2008;111(7):3388–94.
33. Lindqvist EK, Goldin LR, Landgren O, et al. Personal and family history of immune-related conditions increase the risk of plasma cell disorders: a population-based study. Blood 2011;118(24):6284–91.
34. Hemminki K, Liu X, Försti A, et al. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. J Hematol Oncol 2012;5:59.
35. Cancer Risk in Patients with Ankylosing Spondylitis: A Nationwide Population-based Dynamic Cohort Study from Korea. ACR Meeting Abstracts. Available at: https://acrabstracts.org/abstract/cancer-risk-in-patients-with-ankylosing-spondylitis-a-nationwide-population-based-dynamic-cohort-study-from-korea/. Accessed January 15, 2020.

36. Cancer Risk in Ankylosing Spondylitis in United States Medicare Beneficiaries: Detection of a Chronic Non Steroidal Anti-Inflammatory Drug Use Signature. ACR Meeting Abstracts. Available at: https://acrabstracts.org/abstract/cancer-risk-in-ankylosing-spondylitis-in-united-states-medicare-beneficiaries-detection-of-a-chronic-non-steroidal-anti-inflammatory-drug-use-signature/. Accessed January 15, 2020.
37. Anderson LA, Gadalla S, Morton LM, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int J Cancer 2009;125(2):398–405.
38. Becker N, Deeg E, Rüdiger T, et al. Medical history and risk for lymphoma: results of a population-based case-control study in Germany. Eur J Cancer 2005;41(1):133–42.
39. Fallah M, Liu X, Ji J, et al. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Ann Oncol 2014;25(10):2025–30.
40. Fallah M, Liu X, Ji J, et al. Hodgkin lymphoma after autoimmune diseases by age at diagnosis and histological subtype. Ann Oncol 2014;25(7):1397–404.
41. Mellemkjaer L, Pfeiffer RM, Engels EA, et al. Autoimmune disease in individuals and close family members and susceptibility to non-Hodgkin's lymphoma. Arthritis Rheum 2008;58(3):657–66.
42. Hemminki K, Liu X, Ji J, et al. Autoimmune disease and subsequent digestive tract cancer by histology. Ann Oncol 2012;23(4):927–33.
43. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390(10089):73–84.
44. Boel A, Molto A, van der Heijde D, et al. Do patients with axial spondyloarthritis with radiographic sacroiliitis fulfil both the modified New York criteria and the ASAS axial spondyloarthritis criteria? Results from eight cohorts. Ann Rheum Dis 2019;78(11):1545–9.
45. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70(1):25–31.
46. Moltó A, Etcheto A, van der Heijde D, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis 2016;75(6):1016–23.
47. Jiang Y, Zhang P, Tu L, et al. Prevalence of comorbidities and evaluation of screening in Chinese patients with spondyloarthritis. Clin Rheumatol 2018;37(2):423–8.
48. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87–108.
49. Fagerli KM, Kearsley-Fleet L, Mercer LK, et al. Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha inhibition: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2019;58(1):80–5.
50. Rohekar S, Tom BDM, Hassa A, et al. Prevalence of malignancy in psoriatic arthritis. Arthritis Rheum 2008;58(1):82–7.
51. van der Heijde D, Zack D, Wajdula J, et al. Rates of serious infections, opportunistic infections, inflammatory bowel disease, and malignancies in subjects receiving etanercept vs. controls from clinical trials in ankylosing spondylitis: a pooled analysis. Scand J Rheumatol 2014;43(1):49–53.
52. Veettil SK, Lim KG, Ching SM, et al. Effects of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas: a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. BMC Cancer 2017;17(1):763.

53. Westhovens I, Lories RJ, Westhovens R, et al. Anti-TNF therapy and malignancy in spondyloarthritis in the Leuven spondyloarthritis biologics cohort (BIOSPAR). Clin Exp Rheumatol 2014;32(1):71–6.
54. Atzeni F, Carletto A, Foti R, et al. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint Bone Spine 2018;85(4):455–9.
55. Maas F, Arends S, van der Veer E, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. J Rheumatol 2016;43(2):383–7.
56. Queiro R, Lorenzo A, Tejón P, et al. Obesity in psoriatic arthritis. Medicine (Baltimore) 2019;98(28). https://doi.org/10.1097/MD.0000000000016400.
57. Kaine J, Song X, Kim G, et al. Higher incidence rates of comorbidities in patients with psoriatic arthritis compared with the general population using U.S. administrative claims data. J Manag Care Spec Pharm 2019;25(1):122–32.
58. Feng R-M, Zong Y-N, Cao S-M, et al. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun 2019;39(1):22.
59. Moltó A, Etcheto A, Poiraudeau S, et al. OP0303 Systematic screening of comorbidities improves vaccination rates, skin cancer screening and vitamin d supplementation in patients with axial spondyloarthritis: results of the comedspa prospective, controlled, one year randomised trial. Ann Rheum Dis 2018;77(Suppl 2):198.
60. Frisell T, Baecklund E, Bengtsson K, et al. Patient characteristics influence the choice of biological drug in RA, and will make non-TNFi biologics appear more harmful than TNFi biologics. Ann Rheum Dis 2018;77(5):650–7.
61. Bautista-Molano W, Landewé R, Burgos-Vargas R, et al. Prevalence of comorbidities and risk factors for comorbidities in patients with spondyloarthritis in Latin America: a comparative study with the general population and data from the ASAS-COMOSPA Study. J Rheumatol 2018;45(2):206–12.
62. Fantò M, Peragallo MS, Pietrosanti M, et al. Risk of malignancy in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis under immunosuppressive therapy: a single-center experience. Intern Emerg Med 2016;11(1):31–40.
63. Askling J, Klareskog L, Blomqvist P, et al. Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study. Ann Rheum Dis 2006;65(9):1184–7.
64. Castro FA, Liu X, Försti A, et al. Increased risk of hepatobiliary cancers after hospitalization for autoimmune disease. Clin Gastroenterol Hepatol 2014;12(6):1038–45.e7.
65. Hemminki K, Liu X, Ji J, et al. Effect of autoimmune diseases on risk and survival in female cancers. Gynecol Oncol 2012;127(1):180–5.
66. Hemminki K, Sundquist K, Sundquist J, et al. Risk of cancer of unknown primary after hospitalization for autoimmune diseases. Int J Cancer 2015;137(12):2885–95.
67. Liu X, Ji J, Forsti A, et al. Autoimmune disease and subsequent urological cancer. J Urol 2013;189(6):2262–8.
68. Costa L, Caso F, Del Puente A, et al. Incidence of malignancies in a cohort of psoriatic arthritis patients taking traditional disease modifying antirheumatic drug and tumor necrosis factor inhibitor therapy: an observational study. J Rheumatol 2016;43(12):2149–54.

69. Saad AA, Ashcroft DM, Watson KD, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49(4):697–705.
70. Saad AA, Ashcroft DM, Watson KD, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2017;56(4):672–3.