Supplementary figure and tables

Supplementary Figure A. Flowchart of register sources used to assemble the study populations.

Supplementary Table A. Seminal studies of non-melanoma skin cancer in rheumatoid arthritis (RA); number of events, type of events and relative risks.

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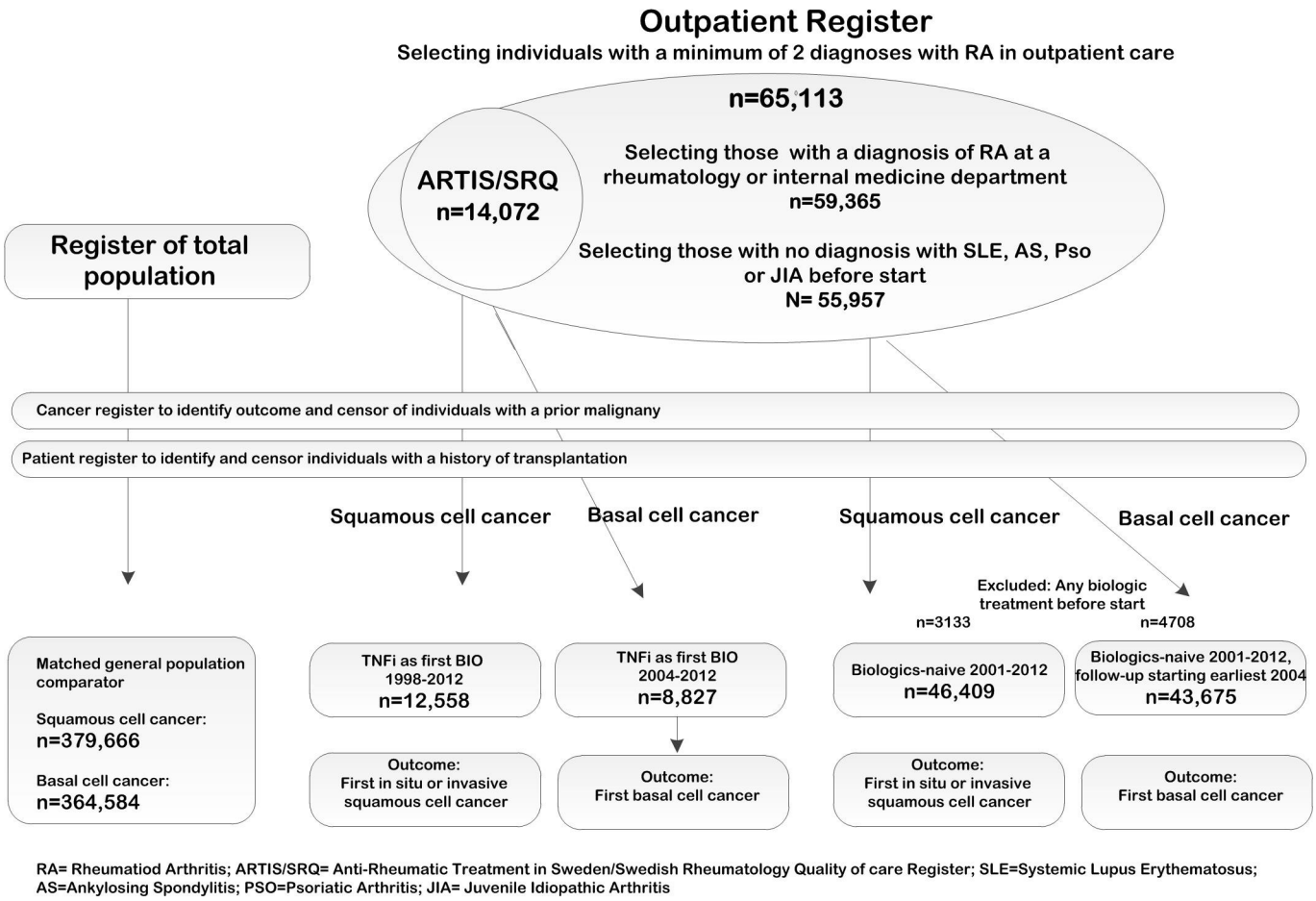
Supplementary Table E. Occurrence and hazard ratios (HR) of first invasive or in situ squamous cell cancer (SCC) in 7,817 rheumatoid arthritis (RA) - patients initiating TNFi as first biologic 2005-2012 (76 SCC, comparison 1 & 2) or 12,558 rheumatoid arthritis (RA) - patients initiating TNFi as first biologic 1998-2012 (191 SCC, comparison 3), compared with 3 different definitions of the biologics-naïve RA cohort

Supplementary Table F. Impact of immunosuppressive drug use on hazard ratios (HR) of squamous cell cancer (SCC) in 4,815 incident RA-patients starting TNFi 2005-2012, compared with 23,139 incident biologics-naïve Swedish rheumatoid arthritis (RA)-patients, h 95% confidence intervals (CI) and of basal cell cancer (BCC) in 4,782 incident RA-patients starting TNFi 2005-2012, compared with 22,981 incident biologics-naïve Swedish RA-patients.



RA= Rheumatiod Arthritis; ARTIS/SRQ= Anti-Rheumatic Treatment in Sweden/Swedish Rheumatology Quality of care Register; SLE=Systemic Lupus Erythematosus; AS=Ankylosing Spondylitis; PSO=Psoriatic Arthritis; JIA= Juvenile Idiopathic Arthritis

Supplementary Figure A.

Supplementary Table A. Seminal studies of non-melanoma skin cancer in rheumatoid arthritis (RA); number of events, type of events and relative risks.

	Relative Risk (95% confidence interval)
Biologics-naive RA versus General population	
1993 Gridley et al. [1] *Swedish population based:*	
27 NMSC (bio-naive RA)	SIR 1.2 (0.8 to 1.7)
1996 Mellemkjaer et al.[2] *Danish population based:*	
51 SCC (bio-naive RA)	RR 1.3 (1.1 to 1.4)
253 BCC (bio-naive RA)	RR 1.4 (1.1 to 1.9)
2005 Chakravarty et al.[3] *NDB database*	
738 NMSC (bio-naive RA)	HR 1.2 (1.0 to 1.4)*
2005 Askling et al.[4] ARTIS/SRQ	
374 NMSC (RA Inpatient cohort)	SIR 1.7 (1.5 to 1.8)
5 NMSC (Early RA cohort)	SIR 0.7 (0.2 to 1.6)
2012 Mercer et al.[5] BSRBR	
39 NMSC (bio-naive RA)	SIR 1.8 (1.3 to 2.5)
2013 Dreyer et al.[6] DANBIO	
34 NMSC (bio-naive RA)	SIR 1.8 (1.3 to 2.5)
TNFi-treated RA versus General Population	
2005 Askling et al.[4] ARTIS/SRQ	
TNFi (11 NSMC) vs. GenPop control	SIR 3.6 (1.8 to 6.5)
TNFi-treated versus Biologics-naive RA	
2005 Chakravarty et al.[3] NDB database	
TNFi non MTX vs. bio-naive RA	HR 1.2 (1.0 to 1.6)
TNFi with MTX vs. bio-naive RA	HR 2.0 (1.5 to 2.6)
2007 Wolfe et al.[7] NDB database	
TNFi (623 NMSC) vs. bio-naive RA	OR 1.5 (1.2 to 1.8)
2011 Amari et al.[8] Administrative data	
TNFi (283 NMSC) vs. bio-naive RA	RR 1.4 (1.2 to1.6)
2012 Mercer et al.[5] BSRBR	
TNFi (150 BCC) vs. bio-naive RA	HR 1.2 (0.8 to 1.7)
TNFi (23 SCC) vs. bio-naive RA	HR 1.8 (0.6 to 5.4)
2013 Dreyer et al.[6] DANBIO	
TNFi (42 NMSC) vs. bio-naive RA	HR 1.1 (0.7 to 1.8)
2013 Haynes et al.[9] 29,555 patients with RA	
TNFi (54 NMSC) vs. bio-naïve RA	HR 0.8 (0.5 to 1.4)
RCT-data TNFi versus Control	
2009 Leombruno et al.[10] 8800 patients with RA	OR 1.3 (0.7 to 2.4)
2011 Askling et al. [11] >22000 patients across indications	HR 2.0 (1.1 to 4.0)

SIR= Standardized Incidence Rate; RR= Relative Risk; HR= Hazard Ratio; OR= Odds Ratio; NMSC= non-melanoma skin cancer; SCC= squamous cell cancer; BCC=basal cell cancer; TNFi= tumor necrosis factor inhibitor, bio-naïve= biologics-naïve
NDB= The National Data Bank for Rheumatic Diseases, ARTIS/SRQ=Swedish Biologics Register/Swedish Rheumatology Quality Register, DANBIO= Dansk Rheumatologisk Database, BSRBR=British Society for Rheumatology Biologics Register
** Bio-naive RA versus osteoarthritis*

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Supplementary Table B. Definitions, ICD codes and source of potential confounders used for statistical adjustments.

Potential confounder	Definition	Source
Country of birth	Nordic; Other (including missing <0.1%)	National Population Register
Education level	≤9 yrs; 10-12 yrs; >12yrs; Missing[¥]	The Swedish Register of Education
County (sun-exposure)	4 categories based on CIE weighted total sun irradiation 1999-2011 in Sweden (lat. 55˚-69˚)	Swedish Meterological and Hydrological Institute (SMHI) National Population Register
Immunosuppressive drug use	First dispensing of either cyclosporine, cyclophosphamide or azathioprine as registered in the Prescribed Drug Register during follow up	National Prescribed Drug Register
Co-morbidity	**ICD 10**	
COPD	J41-J44	National Patient Register
Ischemic heart disease	I20-I25	National Patient Register
Diabetes mellitus, type 1&2	E10-E14	National Patient Register
Benign skin disorder †	D485, L21,L23-25, L26-27, L30, L40-41, L57.8 L71, L82, L93, D485	National Patient Register
Invasive malignancy Including melanoma	140-208	National Cancer Register
Organ transplantation	Z94	National Patient Register
	Surgical procedure codes	
Knee replacement surgery Hip replacement surgery	NGB, 8423-8424, 8426 NFB, 8400-8415, 8419	National Patient Register

The National Population Register includes data on residency and dates of immigration and emigration for all subjects ever resident in Sweden since 1961 and onwards, and coverage is virtually complete.
The Swedish Register of Education is updated annually to contain the highest level of education for each individual from 1985 and onwards.
[¥] Missing: 13.2% (biologics-naïve) 6.7% (TNFi-treated) 8.2 % (General Population).
The Prescribed Drug Register contains information on all prescribed drugs dispensed at Swedish pharmacies from July 2005 onwards, with an estimated coverage of close to 100%.
The National Patient Register covers virtually all hospital discharges since 1987, and outpatient visits in specialized care e.g., a visit to the rheumatologist, since 2001. Diagnoses are coded according ICD (since 1997: version 10). The coverage of the outpatients component is around 80% overall, but varies with specialty and care-provider.
The National Cancer Register is described in detail in methods section
CIE=Commission Internationale de l'Éclairage
COPD=Chronic obstructive pulmonary disease
† Seborrheic dermatitis (L21), Contact (L23-25) and other (L26-27) dermatitis, Eczema (L30), Psoriatic disease (L40-41), Sun dermatitis (L57.8), Rosacea (L71), Seborrheic keratosis (L82), Discoid Lupus (L93), Dysplastic naevi (D485). Actinic keratosis is not included (often co-diagnosed with SCC).

Supplementary Table C. Diagnosis codes according to International Classification of Disease Swedish versions 10 and 7 (ICD10/ ICD7) used to define Rheumatoid Arthritis (RA) and related diseases, and outcomes

Diagnosis	Abbreviation	ICD 10
Rheumatoid Arthritis	RA	M05, M060, M062, M063, M068, M069, M123
Juvenile Idiopathic Arthritis	JIA	M08, M09
Ankylosing Spondylitis	AS	M45
Psoriatic Arthritis	PSA	L405, M070, M071, M073
Systemic Lupus Erythematosus	SLE	M320, M321, M328, M329

Outcomes		SNOMED	ICD 10/ICD 7
Squamous cell cancer	SCC		C44/191
Squamous cell cancer in situ		80702 and 80701	
Mb Bowen		80812	
Actinic keratosis with advanced atypia		72850	
Invasive		80703	
Basal cell cancer	BCC	80913,80931,80932, 80933 80953,80903	C44/191

Supplementary Table D. Occurrence and hazard ratios (HR) with 95% confidence intervals (CI) of a second primary squamous cell cancer (SCC) and a second primary basal cell cancer (BCC) during follow-up. 74 TNFi-treated patients with rheumatoid arthritis (RA) and a history of at least one in situ or invasive SCC before start of follow-up were compared with 466 biologics-naïve patients with RA and a history of at least one in situ or invasive SCC before start of follow-up. 91 TNFi-treated patients with RA and a history of at least one BCC before start of follow-up were compared with 250 biologics-naïve patients with RA and a history of at least one BCC before start of follow-up

	TNF-treated RA N events (pyr; crude inc.)	Biologics-naïve RA N events (pyr; crude inc.)	HR
Squamous cell cancer	10 (390; 2,562)	97 (1,845; 5,259)	0.99 (0.44 to 2.10)
Basal cell cancer	17 (269; 6,310)	41 (602; 6,810)	1.19 (0.67 to 2.15)

HR: Adjusted for age and stratified for sex, country of birth, county, birth year, and education level.
Pyr: Person-years of follow-up
Crude incidence: Number of events per 100.000 person-years of follow-up

Supplementary Table E. Occurrence and hazard ratios (HR) of first invasive or in situ squamous cell cancer (SCC) in 7,817 rheumatoid arthritis (RA) - patients initiating TNFi as first biologic 2005-2012 (76 SCC, comparisons 1) and 2)) or 12,558 rheumatoid arthritis (RA) - patients initiating TNFi as first biologic 1998-2012 (191 SCC, comparison 3)), compared with 3 different definitions of biologics-naïve RA comparators.

Biologics-naïve RA Comparator	Number of patients / number of events in biologics-naïve comparator	HR (95% CI) ** TNFi vs. biologics-naive comparator
1. DMARD « switchers »	4277/50	1.27 (0.82 to 1.97)
2. « Stable » MTX users	28127/453	1.25 (0.96 to 1.63)
3. DMARD newstarters	10,676/103	1.59 (1.19 to 2.12)

DMARD= Disease-Modifying Anti-rheumatic Drug. MTX=Methotrexate.

HRs Adjusted for age, sex, birth year, country of birth, county of residency, educational level and comorbidities up until start of follow-up (hospital admissions/outpatient visits for chronic obstructive pulmonary disease, ischemic heart disease, diabetes mellitus, knee/hip joint replacement surgery, psoriatic disease and any other diagnosis of benign skin disease except actinic keratosis.Patients with a diagnosis of solid organ transplantation and/or invasive malignancy prior to, or during follow-up, were considered not at risk.

1. RA-patients with two or more visits listing RA in the Outpatient Register 2001-2012, initiating a new non-biologic DMARD after 1 July 2006, as noted in the Prescribed Drug Register (1 July 2005 -1 July 2006 serving as baseline period). This definition is supposed to reflect RA patients with unsatisfactory disease control, in need for medication adjustment. The Prescribed Drug Register started in July 2005 and therefore we restricted the TNFi-treated comparator to include only those initiating therapy 2005-2012.

2. RA-patients with two or more visits listing RA in the Outpatient Register 2001-2012, with two consecutive dispensing of methotrexate within 6 months as noted in the Prescribed Drug Register. This is supposed to reflect RA patients stable on methotrexate treatment. The Prescribed Drug Register started in July 2005 and therefore we restricted the TNFi-treated comparator to include only those initiating therapy 2005-2012.

3. RA-patients registered in the Swedish Rheumatology Quality register with new-onset RA 1997-2012 (incident RA) who were followed from the initiation of their first non-biologic DMARD after RA diagnosis.

Supplementary Table F. Impact of immunosuppressive drug use on hazard ratios (HR) of squamous cell cancer (SCC) in 4,815 incident RA-patients starting TNFi 2005-2012, compared with 23,139 incident biologics-naïve Swedish rheumatoid arthritis (RA)-patients, and of basal cell cancer (BCC) in 4,782 incident RA-patients starting TNFi 2005-2012, compared with 22,981 incident biologics-naïve Swedish RA-patients.

	TNF-treated RA N events (pyr; crude inc.)	Biologics-naïve RA N events (pyr; crude inc.)	**HR 1** Adjusted for co-morbidities and demographics	**HR 2** Further adjusted for immunosuppressive drug use
Squamous cell cancer	35 (16,082; 218)	259 (75,236; 344)	1.35 (0.93 to 1.96)	1.28 (0.89-1.86)
Basal cell cancer	93 (15,837; 587)	548 (74,158; 739)	1.20 (0.95 to 1.53)	1.17 (0.93-1.49)

HR1 Adjusted for age, sex, birth year, country of birth, county of residency, educational level and comorbidities up until start of follow-up (hospital admissions/outpatient visits for chronic obstructive pulmonary disease, ischemic heart disease, diabetes mellitus, knee/hip joint replacement surgery, psoriatic disease and any other diagnosis of benign skin disease except actinic keratosis.Patients with a diagnosis of solid organ transplantation and/or invasive malignancy prior to, or during follow-up, were considered not at risk.

HR2 Adjusted for all the covariates above (HR1) and for any use of oral cortisone, cyclosporine, cyclophosphamide and/or azathioprine during follow-up

Pyr Person-years of follow-up

Crude inc. Number of events per 100.000 person-years of follow-up

Incident TNFi-treated and biologics-naïve RA defined as patients with RA-diagnosis in the outpatient register earliest 1 July 2005 (no diagnosis with RA in the register 2001-2004).