



EXTENDED REPORT

Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden

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ABSTRACT

Objectives To examine screening patterns and the risk of cervical neoplasia in women with rheumatoid arthritis (RA) treated or not with tumour necrosis factor inhibitors (TNFi).

Methods We performed a nationwide register-based cohort study in Sweden of women with RA who started a first TNFi (n=9629), biologics-naive women with RA (n=34 984) and general population comparators (matched 1:10, n=300 331), followed up from 1999 to 2012. Outcomes were first cytology screening with normal outcome, first ever cervical intraepithelial neoplasia (CIN) grade 1, first ever CIN 2–3 or adenocarcinoma in situ and first ever invasive cervical cancer during follow-up. HRs were assessed through Cox regressions adjusted for age, educational level, prior cervical screens, comorbidities, marital status and prior hospitalisations.

Results Biologic-naive women with RA had more screenings (HR 1.08, 95% CI 1.06 to 1.10), were at greater risk of CIN 1 (HR 1.53, 1.23 to 1.89) and CIN 2–3 (HR 1.39, 1.16 to 1.66), but not of invasive cervical cancer (HR 1.09, 0.71 to 1.65) compared with the general population. Patients who initiated TNFi therapy had similar screening patterns (HR 1.01, 0.98 to 1.05), were not at increased risk of CIN 1 (HR 1.23, 0.87 to 1.74), but were at increased risk of CIN 2–3 (HR 1.36, 1.01 to 1.82) and invasive cervical cancer (HR 2.10, 1.04 to 4.23) compared with biologics-naive women with RA. Estimates varied little with successive adjustments, but were attenuated/absent in sensitivity analyses restricted to 2006–2012 and a disease-modifying antirheumatic drugs-treated comparator.

Conclusions Women with RA in general are at elevated risk of cervical dysplasia. Compared with biologics-naive patients, women treated with TNFi are at increased risk of cervical cancer. Whether this increase is causally linked with TNFi could not be fully disentangled.

INTRODUCTION

Data on the occurrence and progression of malignancies in patients with chronic systemic inflammatory diseases and with immunomodulatory treatments are limited. Immunosuppression is an established risk factor for virus-associated cancers including cervical cancer.^{1–3} Polymorphisms in the *TNF* gene have been associated with cervical cancer risk.⁴ Tumour necrosis factor inhibitors (TNFi), a cornerstone in the treatment of patients with

rheumatoid arthritis (RA), are believed to decrease host defence against viral infections.⁵ Whether TNFi treatment increases the risk of virus-associated malignancies, such as cervical cancer, is not known.

Most guidelines suggest caution with TNFi treatment in patients with a history of cancer. Whether TNFi should be avoided in women with a history of premalignant cervical lesions is unknown. Two recent studies examined genital cancer risk among women with RA and a history of carcinoma in situ⁶ and any premalignant lesion of the cervix.⁷ In both, zero events were observed during follow-up of the TNFi groups, but the numbers of patients included (n=190 and 233)^{6 7} were too small to rule out clinically meaningful risks.

Any increased risks among patients treated with TNFi should be interpreted in light of the risk associated with RA itself. A recent study found a 50% increased risk of high-grade dysplasia (cervical intraepithelial neoplasia (CIN) 2–3) or invasive cervical cancer among biologics-naive women with RA.⁸ Others have found decreased risks of invasive cervical cancer in RA^{9 10} or no association.¹¹ Cervical screening is an important determinant for cervical dysplasia and invasive malignancies, with a several-fold higher risk of cervical cancer in women not attending screening, already within 3–5 years.¹²

The aim of this study was to assess the incidence of premalignant and malignant cervical neoplasia in women with RA and in relation to TNFi treatment, taking cervical screening patterns and other risk factors into account.

METHODS**Study design**

We performed a nationwide register-based cohort study, comparing the incidence of mild to severe cervical dysplasias CIN 1, CIN 2–3 (including cervical cancer in situ and adenocarcinoma in situ (AIS)), invasive cervical cancer and the use of cervical screening, across three large and population-based cohorts: (a) biologics-naive women with RA starting a TNFi as the first ever biologic; (b) biologics-naive women with RA in general; and (c) the general Swedish female population.

Setting

The Swedish healthcare system is public and tax funded. Patients with RA are diagnosed and treated

by rheumatologists. During the study period, TNFi was introduced in RA and use gradually increased to one-third of all patients.

Data sources

The registers used in this study have been described elsewhere.¹³ The Swedish biologics register (ARTIS) covers 90–95% of all patients with RA treated with biologics in Sweden from 1999 to today.^{14–15} The *Swedish Patient Register* is a nationwide register with near complete coverage of all inpatient (since 1987) or non-primary outpatient visits (since 2001). Validations against medical files suggest that for many diagnoses (including RA), the validity is around 90%.^{16–18} This register was used to identify biologics-naive women with RA and comorbidities. The nationwide *Prescribed Drug Register* (data since 2005) was used to identify non-biological disease-modifying antirheumatic drug (DMARD) prescriptions. The *Total Population Register* was used to identify general population comparator subjects, date of birth and emigration or immigration.¹³ The *Swedish Cancer Register* has an estimated coverage of >95% and was used to identify CIN 3 and invasive cervical cancer.¹⁹ The National Cervical Screening Program invites all women aged 23–60. The *Swedish National Cervical Screening Registry* gathers data on all Pap smears (and ensuing histology tests) in Sweden, both opportunistic and preplanned. More than 90% of all cervical cytology and histology tests are captured in the register. This register was used to identify screening visits 1995 or later, and histopathology for premalignant lesions (CIN 1–3 and AIS).

Study population and follow-up

Using ARTIS, we identified a cohort of patients with RA who initiated TNFi as their first ever biologic. Start of follow-up was defined as date of TNFi start.

Using the Patient Register, we identified all women with two or more visits in non-primary outpatient care listing a main or contributory diagnosis of RA. At least one of these had to be at a rheumatology or internal medicine department. We excluded patients who had ever received a diagnosis of juvenile idiopathic arthritis, ankylosing spondylitis, systemic lupus erythematosus or psoriatic arthritis. Through linkage to ARTIS, we could thus define a cohort of patients with RA who were biologics-naive (and followed prospectively until first biologics initiation). Patients who started a TNFi treatment during follow-up thereafter contributed to the TNFi cohort. Start of follow-up was defined as the first date when all the inclusion criteria were fulfilled 2001–2012.

Through linkage of the biologics-naive cohort to the Population Register, we matched (1:10, by year of birth, sex, county of residence and vital status at the date of first identification of RA) a general population comparator cohort. The inclusion date was set to that of their corresponding biologics-naive patient with RA.

End of follow-up was defined as first of 31 December 2012, death, last emigration, a total hysterectomy, date of any solid organ transplantation and occurrence of the outcome under study.

Outcomes

Considering the exploratory nature of our study, we assessed the following outcomes in parallel:

1. First cytology screening (planned or opportunistic) with a normal outcome during follow-up.
2. First CIN 1 (including atypical glandular cells) during follow-up in individuals without any history of cervical

dysplasia or invasive cervical cancer before (excluded) or during (censored) follow-up.

3. First CIN 2–3 or AIS (CIN 2+) during follow-up in individuals without any history of CIN 2+ at start of follow-up or invasive cervical cancer before or during follow-up, but irrespective of CIN 1.
4. First invasive cervical cancer during follow-up in individuals without a history of invasive cervical cancer at start of follow-up, but irrespective of any cervical dysplasia before or during follow-up. We also assessed the risks for invasive cervical cancer among patients with a history of cervical dysplasia ever, a history of cervical dysplasia during the five years before start of follow-up and a history of a normal screening test (and no subsequent pathological screening tests) during the five years before start of follow-up.

Covariates and statistical analyses

We quantified the cumulative number of Pap smears and time since the most recent Pap smear, during the five years prior to start of follow-up, whether as preplanned or opportunistic screening, and also identified any occurrence of cervical dysplasia or invasive cervical cancer during the same time period. Data on marital status and highest achieved education at the index date were retrieved from Statistics Sweden.

Through linkage to the Swedish Patient Register, we identified hospitalisation or outpatient visits listing ischaemic heart disease, chronic obstructive pulmonary disease, diabetes mellitus and knee/ankle/hip/shoulder-joint surgery as proxies for intensity of healthcare contacts. These comorbidities were treated as separate time-varying covariates and were allowed to change (from absent to present, but not back) up until 365 days before end of follow-up. Overall healthcare utilisation was measured as total days spent in hospital during the five years prior to start of follow-up. The effect of previous invasive cancer other than cervical cancer was assessed in a sensitivity analysis. Information on parity and family history was only available for a study subset through 2010.

We calculated the total number of events, person-years at risk and incidence rate of each outcome in each cohort. We used Cox regression (where the smallest cell contained five or more events) with age as timescale to estimate HRs. In the first Cox model, we stratified by decade of birth, in the second we further adjusted for educational level, marital status and number of Pap smears before start of follow-up, and in the full model we further added the above-mentioned comorbidities. Alternative timescales (here, follow-up time and calendar time) and the three model specifications yielded similar results. The main analysis was stratified by time since start of follow-up. To investigate any non-proportionality of HRs, we plotted hazard functions, stratified the analyses on attained age (three age bands) and estimated crude as well as age-standardised incidences of each outcome in each cohort. SAS V9.4 was used.

Sensitivity analyses

To assess more contemporary biologics-initiators and to reduce the potential for channelling, we restricted the study period to 1 January 2006 through 31 December 2012 and the biologics-naive RA cohort to patients who (in addition to fulfilling the entry criteria to this cohort) initiated or were on treatment (concomitantly or successively) with at least two non-biological DMARDs.

To assess the impact of risk window definition, follow-up for the TNFi cohort was stopped 90 days after discontinuation of the biologic in question ('on drug'), with or without attention

to the individual TNFi drug ('on class') instead of 'ever-since first exposure'.

RESULTS

The main analysis included 9629 TNFi initiators, 34 984 biologics-naive women with RA and 300 331 general population comparators. The TNFi cohort was younger (56 years), had higher educational level and had a burden of comorbidities that was intermediate to the rates in the general population and the biologics-naive cohort (table 1). In the subset below 60 years of age, the screening intensity was similar across all cohorts.

Occurrence and relative risk of cervical malignancies: biologics-naive RA versus the general population

The crude incidence of a first screening with a normal outcome during follow-up was similar between the biologics-naive RA cohort and the general population cohort, although the fully adjusted HR was statistically significantly increased (HR 1.08, 95% CI 1.06 to 1.10). There were statistically significant higher rates in the biologics-naive RA cohort of CIN 1 (HR 1.53, 95% CI 1.23 to 1.89) and CIN 2+ (HR 1.39, 95% CI 1.16 to 1.66) but not of invasive cancer (HR 1.09, 95% CI 0.71 to 1.65)

(table 2). When we restricted the analyses to individuals with a history of CIN 1 or CIN 2+ ever and during the five years before start of follow-up, we observed four and two cases of invasive cervical cancer, respectively, in the RA population. When restricting to individuals with a history of a normal screening test before start of follow-up, we observed seven cases of invasive cervical cancer, corresponding to an HR of 0.78 (95% CI 0.36 to 1.70) (table 2).

Occurrence and relative risk of cervical malignancies: TNFi initiators versus biologics-naive RA

In the TNFi cohort, the crude but not the adjusted incidence of a first screening with a normal outcome was higher than in the biologics-naive RA cohort (HR 1.01, 95% CI 0.98 to 1.05). There was no statistically significant difference in risk for CIN 1 (HR 1.23, 95% CI 0.87 to 1.74), a higher rate of CIN 2+ (HR 1.36, 95% CI 1.01 to 1.82) and a doubled risk of invasive cervical cancer in the TNFi cohort (HR 2.10, 95% CI 1.04 to 4.23) (table 2). When we restricted the analyses to individuals with a history of CIN 1 or CIN 2+ ever, and during the five years before start of follow-up, we observed three and one case (s) of invasive cervical cancer, respectively. When restricting to

Table 1 Characteristics of the study population of Swedish women with rheumatoid arthritis (RA) (biologics-naive and starting a first ever tumour necrosis factor inhibitor (TNFi) treatment 1999–2012, respectively), and matched general population comparator subjects

Characteristics at start of follow-up n	TNFi initiators 9629	Biologics-naive RA 34 984	General female population 300 331
Age at entry (median, min–max)	56 (18–92)	62 (18–97)	61 (18–96)
Year of birth (median, min–max)	1949 (1907–1994)	1943 (1906–1994)	1944 (1906–1994)
Year of entry (median, min–max)	2006 (1999–2012)	2004 (2001–2012)	2004 (2001–2012)
Time since RA onset (years)	8.2	NA	NA
DAS28 (median, IQR) at biologics start	5.30 (4.40–6.13)	NA	NA
HAQ (median, IQR) at biologics start	1.25 (0.88–1.75)	NA	NA
Concomitant DMARDs (%)	71	NA	NA
Concomitant oral steroids (%)	47	NA	NA
Educational level, years (%)			
≤9	25	36	33
9–12	44	40	40
>12	31	22	26
Comorbidities (%)			
Chronic obstructive pulmonary disease	2.4	3.3	1.9
Diabetes mellitus	5.2	5.8	4.2
Ischaemic heart disease	4.2	7.8	5.7
Previous joint surgery	27.8	20.4	5.2
Total n days spent in hospital during last five years, median (IQR)	1 (0–10)	1 (0–9)	0 (0–2)
Cervical screening characteristics, all individuals			
Mean n cervical screens during last five years preceding start of follow-up (range)	1.17 (0–12)	0.89 (0–15)	0.91 (0–19)
Median time since last cervical screening visit at date of start of follow-up (days, range)	825 (1–6198)	937 (1–7718)	895 (1–16 626)
CIN 1 within five years before start of FU (%)	0.5	0.4	0.3
CIN 2+ within five years before start of FU (%)	0.7	0.5	0.4
Mean number of cervical screens during follow-up, (range)	1.08 (0–19)	0.65 (0–18)	0.87 (0–24)
Cervical screening characteristics, individuals below 60 years of age at baseline			
Mean n cervical screens during last five years preceding start of follow-up (range)	1.44 (0–12)	1.39 (0–15)	1.39 (0–19)
Median time since last cervical screening visit at date of start of follow-up (days, range)	655 (1–6198)	686 (1–6476)	676 (1–6520)
CIN 1 within five years before start of follow-up (%)	0.7	0.7	0.5
CIN 2+ within five years before start of follow-up (%)	1.0	1.0	0.8
Mean number of cervical screens during follow-up, (range)	1.56 (0–19)	1.23 (0–18)	1.60 (0–24)

CIN, cervical intraepithelial neoplasia; DAS28, disease activity score 28; DMARD, disease-modifying antirheumatic drug; FU, follow-up; HAQ, health assessment questionnaire; NA, not available.

Table 2 Number of persons, crude incidence, average follow-up time and HRs for the different cervical outcomes under study

Outcome definition	Cohort	Number of patients at risk	Mean follow-up	Number of events	Crude incidence per 100 000 person-years	HR*	HR*
First screening with normal result	TNFi	9072	3.29	4362	14 599	1.01 (0.98 to 1.05)	
	Biologics-naive RA	33 253	3.57	10 958	9224	Ref	1.08 (1.06 to 1.10)
	General population	287 602	4.18	114 943	9556		Ref
CIN 1	TNFi	8943	6.10	52	95.3	1.23 (0.87 to 1.74)	
	Biologics-naive RA	32 947	5.26	99	57.1	Ref	1.53 (1.23 to 1.89)
	General population	285 232	6.66	852	44.8		Ref
CIN 2+	TNFi	9018	6.11	75	136.0	1.36 (1.01 to 1.82)	
	Biologics-naive RA	33 130	5.27	137	78.5	Ref	1.39 (1.16 to 1.66)
	General population	286 731	6.67	1332	69.7		Ref
Invasive cervical cancer, overall	TNFi	9629	6.15	14	23.7	2.10 (1.04 to 4.23)	
	Biologics-naive RA	34 984	5.27	25	13.6	Ref	1.09 (0.71 to 1.65)
	General population	300 331	6.68	275	13.7		Ref
Invasive cervical cancer†	TNFi	107	6.76	1	138.2	‡	
	Biologics-naive RA	260	5.47	2	140.6	Ref	‡
	General population	2119	6.72	5	35.1		Ref
Invasive cervical cancer§	TNFi	685	6.05	3	72.3	‡	
	Biologics-naive RA	2036	5.06	4	38.8	Ref	‡
	General population	15 069	6.47	20	20.5		Ref
Invasive cervical cancer¶	TNFi	6418	6.50	10	24.0	3.77 (1.35 to 10.48)	
	Biologics-naive RA	18 520	5.47	7	6.9	Ref	0.78 (0.36 to 1.70)
	General population	162 543	7.08	112	9.7		Ref

*Stratified on decade of birth and adjusted for educational level, number of cervical screens past five years, comorbidities, marital status and total days spent in hospital during last five years, also implicitly adjusted for age since age was used as the model's timescale.

†In individuals with a history of CIN 1 or CIN 2+ during the five years before start of follow-up.

‡Not computed due to low number of events.

§In individuals with a history of CIN 1 or CIN 2+ ever.

¶In individuals with a normal screening test as the most recent screening test less than five years before start of follow-up.

CIN, cervical intraepithelial neoplasia; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

individuals with a normal screening test as the last screening before start of follow-up, we observed 10 cases of invasive cervical cancer, corresponding to an HR of 3.77 (95% CI 1.35 to 10.48) (table 2).

Time since start of treatment

For CIN 1 and CIN 2+ and comparing TNFi initiators versus biologics-naive RA, there were no obvious differences in HR across follow-up (if anything a downward trend in HRs) (table 3). For invasive cervical cancer, small numbers limited comparisons.

Stage at diagnosis of invasive cervical cancer

There were no obvious differences in stage at diagnosis of invasive cervical cancer according to the International Federation of Gynecology and Obstetrics staging system,²⁰ although numbers were small and missingness was not negligible though equal across cohorts (see online supplementary table S4).

Sensitivity analyses

When the study period was restricted to 2006–2012 and the biologics-naive comparator restricted to those individuals who had received dispensing of two or more different csDMARDs, the association with TNFi (defined as incident or ongoing 2006 or later) and invasive cervical cancer was attenuated (HR 1.36, 95% CI 0.59 to 3.13) and absent when restricted to new users of TNFi 2006 or later (one case during 18 110 person-years). Further sensitivity analyses of the full cohort and study period but with risk windows defined as 'on drug' (HR 1.46, 95% CI 0.54 to 3.94) and 'on class' (HR 1.81, 95% CI 0.78 to 4.18)

attenuated the strength of the observed association between TNFi initiation and risk of invasive cervical cancer. All other sensitivity analyses provided results similar to the main analysis (table 4 and online supplementary tables S1–S3).

DISCUSSION

We noted a modest increase in risk of CIN 1 and CIN 2+ but not of invasive cervical cancer in biologics-naive women with RA versus the general population, a finding that was not readily explained by differences in cervical screening. Among women with RA initiating TNFi therapy, the screening patterns were largely similar to those of other women with RA, the risks for CIN 1 and CIN 2+ were 20–40% increased and the risk for invasive cervical cancer was doubled, although with wide confidence limits.

A previous study by Kim *et al*²¹ reported similar cervical screening attendance in RA and the general population. Most other studies have demonstrated suboptimal screening attendance among women with chronic diseases, including RA.^{22–24} The finding in our study that RA might be, but is not strongly, linked with CIN 3/invasive cervical cancer is in line with most,^{8 11 25} but not all,^{9 10} previous studies. The three available studies on TNFi and aspects of cervical malignancy have not demonstrated an increased risk with TNFi.^{6 7 26} Two of them only included women with a history of cervical neoplasia. The third study did not condition on a history of cervical neoplasia but was smaller than this study (about 8000 person-years vs 60 000 person-years in our TNFi cohort)²⁶ and did not accommodate, for example, cervical screening.

Table 3 HRs and 95% CIs, number of persons, events and person-years, comparing tumour necrosis factor inhibitor (TNFi) versus biologics-naive rheumatoid arthritis (RA) for each outcome

Outcome	0–2 years	2–5 years	5+ years	Overall
CIN 1				
HR*	1.77 (1.14 to 2.73)	1.05 (0.61 to 1.79)	0.74 (0.37 to 1.49)	1.23 (0.87 to 1.74)
N events, TNFi	27	16	9	52
N patients, TNFi	8943	7418	5007	8943
Pyr, TNFi	16 474	18 609	19 499	54 581
CIN 2+				
HR*	1.55 (1.04 to 2.32)	1.39 (0.92 to 2.10)	1.06 (0.63 to 1.78)	1.36 (1.01 to 1.82)
N events, TNFi	30	28	17	75
N patients, TNFi	9018	7493	5066	9018
Pyr, TNFi	16 629	18 808	19 707	55 144
Invasive cervical cancer				
HR*	†	†	3.22 (1.37 to 7.58)	2.10 (1.04 to 4.23)
N events, TNFi	4	2	8	14
N patients, TNFi	9629	8021	5449	9629
Pyr, TNFi	17 774	20 166	21 251	59 191

Stratified by time since start of follow-up (<2 years, 2–5 years, 5+ years).

*Stratified on decade of birth and adjusted for educational level, number of cervical screens past five years, comorbidities, marital status and total days spent in hospital during last five years, also implicitly adjusted for age since age was used as the model's timescale.

†Not computed due to low number of events.

CIN, cervical intraepithelial neoplasia.

Table 4 Sensitivity analyses restricted to 2006–2012, on first tumour necrosis factor inhibitor (TNFi) ('on drug') and continuous time on TNFi treatment ('on class'), respectively

Analysis	Outcome	Cohort comparison	n events	Person-years	HR*
2006–2012 and stricter definition of biologics-naive RA†	CIN 1	TNFi	40	41 938	1.02 (0.67 to 1.54)
		New TNFi users‡	21	16 725	1.12 (0.67 to 1.87)
		Biologics-naive RA	59	88 696	Ref
		General population	637	1 394 519	0.59 (0.45 to 0.78)
	CIN 2+	TNFi	58	42 429	1.10 (0.72 to 1.68)
		New TNFi users‡	30	16 916	1.09 (0.72 to 1.66)
		Biologics-naive RA	89	89 385	Ref
		General population	1003	1 403 802	0.59 (0.47 to 0.73)
	Invasive cervical cancer	TNFi	10	45 557	1.36 (0.59 to 3.13)
		New TNFi users‡	1	18 110	§
		Biologics-naive RA	17	94 590	Ref
		General population	207	1 474 695	0.73 (0.44 to 1.21)
On drug	CIN 1	TNFi	30	29 094	1.23 (0.81 to 1.88)
		Biologics-naive RA	99	173 369	Ref
	CIN 2+	TNFi	50	29 407	1.60 (1.15 to 2.22)
		Biologics-naive RA	137	174 514	Ref
	Invasive cervical cancer	TNFi	5	31 499	1.46 (0.54 to 3.94)
		Biologics-naive RA	25	184 391	Ref
On class	CIN 1	TNFi	37	36 699	1.21 (0.82 to 1.78)
		Biologics-naive RA	99	173 369	Ref
	CIN 2+	TNFi	59	37 100	1.50 (1.09 to 2.05)
		Biologics-naive RA	137	174 514	Ref
	Invasive cervical cancer	TNFi	8	39 845	1.81 (0.78 to 4.18)
		Biologics-naive RA	25	184 391	Ref

HRs (HRs model a–c) and 95% CIs comparing each outcome between cohorts.

*Stratified on decade of birth and adjusted for educational level, number of cervical screens past five years, comorbidities, marital status and total days spent in hospital during last five years, also implicitly adjusted for age since age was used as the model's timescale.

†The biologics-naive RA cohort was restricted to patients who initiated or were on treatment with at least two of any of the commonly used non-biological DMARDs (methotrexate, sulfasalazine, antimalarials or leflunomide).

‡TNFi cohort restricted to patients who started their first TNFi treatment 2006 or later.

§Not computed due to low number of events.

CIN, cervical intraepithelial neoplasia; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

Assessments of the role of specific antirheumatic treatments on the risk of cervical cancer pose methodological challenges including confounding and channelling bias, detection/lead time bias and statistical precision, each of which may have a bearing on the interpretation of our results: unlike many other cancer types, the age–incidence curve for cervical cancer in screened populations is almost flat from age 30.¹² Further, the ‘risk’ of having a malignancy detected through screening decreases as the screening programme ends at 60 years of age. In our study, there were age differences between the cohorts, the mean age of which was around 60 years of age, such that a crude comparison of baseline characteristics and crude incidences would be biased. Therefore, age was used as timescale in our Cox regressions, and sensitivity analyses restricted to ages 18–60 were performed.

Invasive cervical cancer arises from human papillomavirus (HPV) infection via mild to severe dysplasia to invasive malignancies,²⁷ providing the rationale for screening aimed at detecting premalignant lesions and reducing longer-term risks of invasive cancer. Since almost all observed premalignant lesions are detected through screening, screening intensity is a strong driver of the reported incidence of cervical premalignancies. Conversely, screening non-attendance is a strong risk factor for the development of invasive cervical cancer.^{12–28} Although we adjusted for screening attendance before start of follow-up, and although there were no marked differences in screening attendance between the cohorts, there might be residual confounding or qualitative differences in the number, timing, reasons for and outcome of the screening tests delivered. Conversely, analyses restricted to individuals with a normal screening visit during the five years preceding follow-up fell close to the main analyses, and adjustment for screening as a time-fixed binary or time-varying binary covariate did not markedly alter the results.

While we could adjust for several potential confounders, our analyses could not fully accommodate any differences in the accumulated burden of RA disease or the accumulated exposure to antirheumatic drugs other than TNFi/biologics. Patients in our study whose RA was severe enough to warrant TNFi treatment probably have a higher lifetime exposure to DMARDs and cytotoxic agents. This in turn may be linked with an increased susceptibility to virus-associated malignancies. For this reason, unmeasured and residual confounding as well as channelling bias cannot be excluded as explanations for the observed differences between the TNFi cohort and the biologics-naïve RA comparator, which were not seen when the study period was restricted to 2006 or later and treatment criteria were added to the RA comparator. Unfortunately, we could not adjust for HPV/sexually transmitted diseases or smoking.^{29–30} However, differences in prevalence of smoking between biologics-naïve and TNFi-treated patients with RA in Sweden are small.³¹ Even though we were able to use nationwide registers with high coverage as a source for data on screening attendance and cervical (pre-)malignancies, small numbers limited comparisons across different strata, models and sensitivity analyses.

Despite the inherent methodological challenges, our study has several strengths: it is based on national registers with almost complete coverage, ensuring generalisability. Although statistical precision was sometimes limited, our study is among the largest to date. Through linkage to national registers and the cervical screening register, we had the possibility to assess and adjust for several important potential confounders. Besides cervical screening, we could adjust for level of education, which is a risk factor for developing RA, for starting a biologic, for screening non-attendance and for cervical cancer. We could also adjust for

comorbidities and number of healthcare contacts, serving as markers of frailty and proxies for accumulated RA disease severity, which was also associated with a lower use of screening services. We could demonstrate that parity and family history of malignancies were probably not important confounders.

To conclude, our study suggests that women with RA in general are at elevated risk of cervical dysplasia and that women with RA who initiate TNFi treatment may be at increased risk of cervical cancer, though the extent to which this is reflective of bias or causality could not be fully disentangled. Whether causally linked or not, translated to the clinical setting, our finding of a 50–100% increase in the risk of invasive cervical cancer in women initiating TNFi therapy is weaker than, for example, the risk associated with screening non-attendance (around 100–200% increase in risk)²⁸ and would correspond to one additional annual case for every 7000–15 000 treated women, which needs to be weighed against any benefit of TNFi treatment or its alternatives.

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Contributors HW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HW conducted the statistical analyses. All authors participated in designing the analyses, interpreting the results and writing the manuscript.

Competing interests TF has served on an advisory board for Pfizer. JA has/had research grants with AstraZeneca, Pfizer, BMS, UCB, Abbvie, Roche and Merck.

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Supplementary table 1. Effect of additionally adjusting for parity and family history of cervical cancer in a smaller subset of the study population. Hazard ratios and 95% confidence intervals

Main outcome definition	At risk	Cohort comparison	HR[†]	HR[‡]
CIN 3*	Individuals with no history of CIN 3 or invasive cervical cancer	TNFI vs. Bio-naïve RA	1.42 (0.94-2.13)	1.43 (0.95-2.15)
Invasive cervical cancer	Individuals with no history of invasive cervical cancer at start of follow-up	TNFI vs. Bio-naïve RA	1.89 (0.88-4.07)	1.88 (0.88-4.05)

*=CIN 3 only includes cases identified in the cancer register

[†]=Stratified on decade of birth and adjusted for educational level, co-morbidities, marital status and total days spent in hospital during last 5 yrs, also implicitly adjusted for age since age was used as the model's time scale

[‡]=Stratified on decade of birth and adjusted for family history of cervical cancer, parity, educational level, co-morbidities, marital status and total days spent in hospital during last 5 yrs, also implicitly adjusted for age since age was used as the model's time scale

Supplementary table 2. Effect of additionally adjusting for any invasive cancer prior to start of follow-up, number of persons, crude incidence, average follow-up time and hazard ratios for the different cervical outcomes under study.

Outcome definition	Cohort	Number of patients at risk	Mean follow-up	Number of events	Crude incidence per 100,000 pys	HR*	HR*
First screening with normal result	TNFi	9072	3.29	4362	14 599	1.02 (0.98-1.05)	
	Bio-naïve RA	33 253	3.57	10 958	9224	REF	1.08 (1.06-1.10)
	Gen pop	287 602	4.18	114 943	9556		REF
CIN 1	TNFi	8943	6.10	52	95.3	1.22 (0.86-1.74)	
	Bio-naïve RA	32 947	5.26	99	57.1	REF	1.53 (1.23-1.89)
	Gen pop	285 232	6.66	852	44.8		REF
CIN 2+	TNFi	9018	6.11	75	136.0	1.36 (1.01-1.82)	
	Bio-naïve RA	33 130	5.27	137	78.5	REF	1.39 (1.16-1.66)
	Gen pop	286 731	6.67	1332	69.7		REF
Invasive cervical cancer, overall	TNFi	9629	6.15	14	23.7	2.12 (1.05-4.27)	
	Bio-naïve RA	34 984	5.27	25	13.6	REF	1.09 (0.72-1.66)
	Gen pop	300 331	6.68	275	13.7		REF

*=Stratified on decade of birth and adjusted for previous invasive cancer, educational level, number of cervical screens past five years, co-morbidities, marital status and total days spent in hospital during last 5 yrs, also implicitly adjusted for age since age was used as the model's time scale

Supplementary table 3. Number of persons, crude incidence, and average follow-up time for the different cervical outcomes under study, analyses restricted to those under 60 years of age at start of follow-up, also censored at their 60th birthday.

Outcome definition	Cohort	Number of patients at risk	Mean follow-up	Number of events	Crude incidence per 100,000 pys	HR*	HR*
First screening with normal result	TNFi	5627	2.13	3489	29 081	0.98 (0.94-1.02)	
	Bio-naïve RA	14 638	1.80	8076	30 696	REF	1.04 (1.02-1.07)
	Gen pop	133 489	2.14	86 598	30 278		REF
CIN 1	TNFi	5520	5.03	43	154.8	1.10 (0.75-1.62)	
	Bio-naïve RA	14 410	3.98	84	146.5	REF	1.53 (1.21-1.92)
	Gen pop	131 637	5.33	725	103.4		REF
CIN 2+	TNFi	5578	5.05	63	223.4	1.22 (0.89-1.67)	
	Bio-naïve RA	14 539	3.99	115	198.2	REF	1.39 (1.14-1.69)
	Gen pop	132 759	5.34	1137	160.4		REF
Invasive cervical cancer, overall	TNFi	5975	5.08	4	13.2	†	
	Bio-naïve RA	15 486	4.00	5	8.1	REF	0.61 (0.25-1.52)
	Gen pop	140 269	5.36	106	14.1		REF

* = Stratified on decade of birth and adjusted for educational level, number of cervical screens past five years, co-morbidities, marital status and total days spent in hospital during last 5 yrs, also implicitly adjusted for age since age was used as the model's time scale

†= Not computed due to low number of events

Supplementary table 4. Stage at diagnosis of invasive cervical cancer according to FIGO classification, for each cohort, n (%).

Cohort	Stage 0	Stage I	Stage II	Stage III	Stage IV	Missing
TNFi initiators	0	6 (43%)	2 (14%)	0	1 (7%)	5 (36%)
Bio-naïve RA	0	9 (36%)	3 (12%)	5 (20%)	1 (4%)	7 (28%)
General population	4 (1%)	100 (34%)	44 (15%)	31 (10%)	19 (6%)	98 (33%)

Women with rheumatoid arthritis and those treated with TNF inhibitors may be at increased risk of cervical cancer

Women with rheumatoid arthritis have a higher risk of cervical cancer, and those treated with TNF inhibitors have a further increased risk, though the link is not conclusive.

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints, causing pain and disability. It can also affect internal organs. Rheumatoid arthritis is more common in older people, but there is also a high prevalence in young adults, adolescents and even children, and it affects both men and women. People with rheumatoid arthritis also have an increased risk of getting cancer.

TNF inhibitors belong to a group of medicines called biologic disease modifying antirheumatic drugs, or biologics (sometimes also called bDMARDs), and include adalimumab, etanercept, infliximab, golimumab and certolizumab-pegol. These drugs work by targeting specific molecules that cause inflammation. By doing so, they reduce inflammation in the joints and decrease pain and disease worsening in rheumatoid arthritis.

Cervical dysplasia refers to abnormal changes in the cells on the surface of the cervix – the opening of the uterus (womb) that can be felt inside the vagina. Dysplasia changes are not cancer, but they are considered to be precancerous. Cancer of the cervix (cervical cancer) in women has been linked to the human papilloma virus (HPV). It has been suggested that TNF inhibitors might affect the immune system's ability to deal with viruses. Whether treatment with TNF inhibitors increases the risk of cancers associated with viruses is not known.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to find out whether there is an increased risk of cervical cancer in women with rheumatoid arthritis, and if this was affected by use of TNF inhibitors. They also hoped to be able to say whether cervical screening had an impact on detecting cervical cancer.

WHO WAS STUDIED?

The study looked at Swedish women with rheumatoid arthritis treated with TNF inhibitors (9629 women), or not (34,984 women), during 1999–2012. Women with a previous medical history of cervical cancer were excluded.

HOW WAS THE STUDY CONDUCTED?

This was a retrospective observational study, which means that the authors used existing databases of patient records to look back and find women for each group. There was no interventional treatment given. They used large national Swedish registers with information on inpatients and outpatients, cancer, comorbidities (other diseases people had), and the treatment and education they received. The women were classified into three groups: people with rheumatoid arthritis that had not been treated with TNF inhibitors, people with rheumatoid arthritis had been treated with TNF inhibitors, and a general population cohort to compare against. The authors then compared how many cases of cervical dysplasia and cervical cancer there were in each group.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The main findings of the study was that women with rheumatoid arthritis have an increased risk of developing cervical dysplasia, and that women with rheumatoid arthritis treated with TNF inhibitors were also at an increased risk of developing invasive cervical cancer. Lastly, the authors found no major differences in the use of cervical screening between women with rheumatoid arthritis and those in the general population, or between those women with rheumatoid arthritis that were treated with TNF inhibitors and those that were not.

ARE THESE FINDINGS NEW?

Yes. This is the first study to show an increased risk of cervical cancer among women with rheumatoid arthritis treated with TNF inhibitors.

WHAT ARE THE LIMITATIONS OF THE STUDY?

People selected for treatment with TNF inhibitors are likely to suffer from more severe disease, and are also likely to have tried more different types of medicine. This means it is difficult to separate the effects of worse

disease or previous medicines from the specific effects of TNF inhibitors. There were other limitations in the accuracy of the statistics.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors are currently working on a study of cervical cancer among patients with systemic lupus erythematosus to see if the findings are similar in other inflammatory diseases.

WHAT DOES THIS MEAN FOR ME?

If you have rheumatoid arthritis and are treated with TNF inhibitors, your risk of cervical cancer might be moderately increased. However, it is important to remember that even though the relative risk might be increased compared to someone without rheumatoid arthritis, or taking different medicines, the absolute risk is still very low. You can limit your risk by making sure you have been vaccinated against human papilloma virus (HPV) and going for regular smear tests (cervical screening), which can help to identify early cell changes.

If you are taking TNF inhibitors and are concerned about the risks of cancer, you should talk to your doctor. It is important that you do not stop taking your treatment without seeking medical advice.

FURTHER READING

EULAR recommendations for management. Available at: http://www.eular.org/recommendations_management.cfm

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