

Comparative Cancer Incidence by Organ Site in Rheumatoid Arthritis Treated with Janus Kinase Inhibitors versus Tumor Necrosis Factor Inhibitors: A Retrospective Real-World Cohort Analysis

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Objective: We aim to evaluate the malignancy risk between Janus kinase inhibitors (JAKi) users and tumor necrosis factor inhibitors (TNFi) users in rheumatoid arthritis (RA) patients, using a large real-world electronic health record database (TriNetX).

Methods: In this retrospective cohort study, we identified adult RA patients initiating JAKi or TNFi therapy between January 1, 2018, and December 31, 2022, within the TriNetX global federated network. The hazard ratio (HR) and confidence intervals (CI) of incident-specific cancers, overall cancer incidence, and all-cause mortality, were calculated between the propensity score matched JAKi and TNFi cohorts. The probability of the outcome of interest was estimated using the Kaplan–Meier analysis.

Results: After propensity score matching, there were 4045 each in JAKi or TNFi user cohorts. The mean (standard deviation) age was 57.7 (13.3) and 57.6 (13.9) years, 81.4% and 80.8% were female, and median (interquartile range) follow-up time 3.69 (2.61) years vs 3.69 (2.68) years, in the JAKi and the TNFi cohorts, respectively. No significant differences were observed in risks of overall cancer incidence and all-cause mortality between the two cohorts. JAKi users had a reduced risk of incident digestive organ cancers compared with TNFi users (adjusted HR: 0.599, 95% CI: 0.439–0.817), mainly observed among females. The risks of incident respiratory and intrathoracic organs cancers were increased in JAKi users compared to TNFi users among females (adjusted HR: 2.582, 95% CI: 1.109–6.011) but not in males.

Conclusion: In a large real-world database, we did not find an increased risk of overall cancer incidence in JAKi compared to TNFi users among RA patients. JAKi users had a lower risk of incident digestive organs cancers, and a higher risk of respiratory cancer in females, when compared with TNFi users.

Keywords: rheumatoid arthritis, JAK inhibitors, TNF inhibitors, malignancy risk

Introduction

Janus kinase inhibitors (JAKi) are effective and approved therapies for myeloproliferative disorders, rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, alopecia areata, and in patients hospitalized for COVID-19.¹ However, concerns about cardiovascular risks and malignancy from JAKi have been raised. The Oral Rheumatoid Arthritis Trial (ORAL) Surveillance trial that recruited RA patients with a high risk of cardiovascular events had shown a higher risk (noninferiority) of both major cardiovascular events and cancer for patients randomized to

tofacitinib compared to those on tumor necrosis factor inhibitors (TNFi).² This resulted in a boxed warning against the class of JAKi (tofacitinib, baricitinib and upadacitinib) approved for RA by the Food and Drug Administration regarding the risk of cardiovascular diseases and malignancy.³ This is particularly relevant in patients with RA that is a chronic autoimmune disease with an elevated risk of cardiovascular disease and malignancy.^{4–6}

Contrary to results from the ORAL Surveillance study, data from randomized controlled trials (RCTs), their long-term extension (LTE) studies, and registries did not show a higher risk of cancers among RA patients exposed to JAKi compared to other agents. In an open-label LTE study up to 9.5 years pooling 7,061 RA patients who received tofacitinib from the prior completed Phase I to IV studies, showed a stable and low absolute incidence rate (IR; events/100 patient-years) over time for malignancy.⁷ The IR (95% confidence interval [CI]) for malignancy (excluding non-melanoma skin cancer [NMSC]), NMSC and lymphoma, were 0.8 (0.7–0.9), 0.6 (0.5–0.7), 0.1 (0.0–0.1), respectively,⁷ which is consistent with the previous LTE data up to 8.5 years.⁸ Similarly, results from the LTE study and integrated database of 3,770 RA patients receiving baricitinib have shown a stable and low IR for malignancy (excluding NMSC) over 9.3 years.⁹ A meta-analysis of randomized controlled trials (RCTs) and cohort studies did not show an increased risk of malignancy in patients with inflammatory bowel diseases, RA, ankylosing spondylitis or psoriasis receiving JAKi compared with those receiving placebo or other treatments.¹⁰ In addition, results from real-world cohorts or registries did not show evidence of increased risk of malignancy in RA patients on JAKi compared with those on TNFi.^{11–14} A meta-analysis of observational studies, involving over 40,587 patients also did not show any increased risk of malignancy in RA patients receiving tofacitinib compared to those receiving conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or TNFi.¹⁵

Given the controversy regarding JAKi-associated malignancy risk and the limited real-world evidence on organ-specific cancer outcomes, we performed a retrospective cohort study to compare overall and site-specific cancer incidence in RA patients initiating JAK inhibitors versus TNF inhibitors using the TriNetX, a large geographically diverse real-time database of patient electronic medical records.

Methods

Study Design and Data Source

This is a retrospective cohort study using data aggregated from the TriNetX, a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across over 120 large healthcare organizations (HCOs). TriNetX contains about 120 million patients from countries in North and South America, Europe, the Middle East and Africa, and Asia-Pacific, mostly from large academic medical centers. The database has been used for many other studies, including those for rheumatic diseases.^{16–18} The TriNetX database uses a harmonized framework for assessing data quality that recognizes conformance, completeness, and plausibility three categories of quality metrics.¹⁹ Data extraction and analysis were done in January, 2023. To develop a parsimonious model in the medical system and related regulations, we limited the analysis to the US collaborative network that included 57 HCOs. For the scope of our analysis, we restricted the study period from the index date on January 1, 2018, until December 31, 2022.

Ethics Statement

The Western Institutional Review Board has granted TriNetX a waiver of consent as it only aggregated counts and statistical summaries of de-identified information. As an HCO member of TriNetX, Chung Shan Medical University Hospital (CSMUH) can access the de-identified data in the TriNetX platform. In addition, the use of TriNetX for the present study was also approved under the authority of the Institutional Review Board of CSMUH (No: CS2-21176). The reporting is adherent to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement for cohort studies.²⁰

Study Subjects

We included subjects who had at least two or more healthcare visits enrolled in the TriNetX network during the study period, to ensure that these individuals regularly sought care at these HCOs. Subjects diagnosed with RA were identified

by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code M05 or M06. Adult subjects (≥ 19 years old at the index date) with these ICD codes registered at least twice were included.

The study population was then divided into two cohorts based on their prescription regimens. The JAKi cohort was defined by prescribed regimens including tofacitinib, baricitinib, ruxolitinib, upadacitinib, fedratinib, abrocitinib, or pacritinib (Anatomical Therapeutic Chemical, ATC code: L01EJ) at least twice recorded in their electronic health records within the study period. The TNFi cohort was identified by prescribed infliximab, etanercept, adalimumab, certolizumab pegol, or golimumab (ATC: L04AB) registered for at least two instances within the study period. Switchers between drug classes (from JAKi to TNFi or from TNFi to JAKi) were excluded to better explore the effect of the regimen. The date of the regimen's first prescription was set as the index date. Subjects who deceased or diagnosed with cancers before or on the index date were excluded.

Outcome Definition

The primary outcomes of the study were incident (new) cancers identified by the corresponding ICD-10-CM codes. We included malignant neoplasms of lip, oral cavity and pharynx (ICD-10-CM code: C00-C14), digestive organs (C15-C26), respiratory and intrathoracic organs (C30-C39), bone and articular cartilage (C40-C41), melanoma and other malignant neoplasms of skin (C43-C44), malignant neoplasms of mesothelial and soft tissue (C45-C49), breast (C50), female genital organs (C51-C58), male genital organs (C60-C63), urinary tract (C64-C68), eye, brain and other parts of the central nervous system (C69-C72), thyroid and other endocrine glands (C73-C75), ill-defined, other secondary and unspecified sites (C76-C80), lymphoid, hematopoietic and related tissue (C81-C96), and neuroendocrine tumors (C7A, C7B) and overall cancer incidence (any cancers mentioned above). To address competing risks, we also included all-cause mortality as a secondary outcome. We used a 90-day timeframe as a washout period for the outcome measures to alleviate protopathic bias. Both cohorts were followed after 90 days after the index date till the incidence of any cancer, mortality or the last record date within the study period whichever occurred earlier.

Definition of Covariates

The following covariate factors (within 365 days prior to the index date) were incorporated in a propensity score matching (PSM) framework to reduce the confounding effect.

Demographics

Demographic covariates included age at index date, sex, race, and socioeconomic status (SES) (ICD-10-CM code Z55-Z65) that may have potential health hazards. In addition, we incorporated family history of primary malignancy (Z80) that may have a hereditary or genetic influence on the development of cancer.

Lifestyles

Lifestyle variables included nicotine dependence (ICD-10-CM code F17, proxy for smoking), tobacco use (Z72.0 proxy for smoking), and alcohol-related disorders (F10, as a proxy for alcohol drinking).

Comorbidities

The comorbidities used in the present study included prevalent depressive episode (ICD-10-CM code F32), essential (primary) hypertension (I10), ischemic heart diseases (I20-I25), cerebrovascular diseases (I60-I69), diabetes mellitus (DM, E08-E13), overweight and obesity (E66), hyperlipidemia, unspecified (E78.5), noninfective enteritis and colitis (K50-K52), diseases of liver (K70-K77), sleep disorders (G47), psoriasis (L40), chronic kidney disease (CKD, N18), chronic lower respiratory diseases (J40-J47), systemic lupus erythematosus (SLE, M32), and dermatopolymyositis (M33) within 365 days prior to the index date.

Medical Services Utilization

To adjust for the confounding influences by medical services utilization between cohorts, outpatient services (Current Procedural Terminology, CPT code 1013626), hospital inpatient services (CPT code 1013659), preventive medicine services (1013829), and emergency department services (1013711) utilization were also incorporated.

Concurrent Medications

Concurrent usage of relevant medication within 365 days prior to the index date was divided into current user or non-user based on the prescribed information documented in their electric health record. Medications were identified by coded in Veterans Affairs (VA) National Formulary, or Anatomical Therapeutic Chemical (ATC) code. In the present study, non-steroidal anti-inflammatory drugs (NSAIDs, ATC: M01A), glucocorticoids for systemic use (ATC: H02) and other csDMARDs/biologic DMARDs, such as abatacept (ATC code: L04AA24), leflunomide (L04AA13), rituximab (L01FA01), sulfasalazine (A07EC01), minocycline (J01AA08), cyclophosphamide (L01AA01), methotrexate (L01BA01, L04AX03), azathioprine (L04AX01), penicillamine (M01CC01), hydroxychloroquine (P01BA02), and cyclosporine (L04AA01) were incorporated.

Statistical Analyses

We generated 1:1 matching by a propensity score framework using the built-in capability of TriNetX. A greedy nearest neighbor matching was performed with a caliper of 0.1 pooled standard deviations (SD) of the two cohorts for all variables mentioned above (age at index, sex, race, SES, family history, lifestyles, comorbidities, medical service utilization, and concurrent medications). Comparisons between two cohorts before and after matching were explored with a standardized difference. It is considered well-matched if the standardized difference is lower than 0.1.

Kaplan–Meier analysis was used to estimate the probability of the outcome of interest (any cancer incidence, overall cancer incidence, and all-cause mortality) in the propensity score matched JAKi or TNFi cohorts. Log Rank test results indicate whether the survival curves were different between cohorts. The hazard ratio (HR) and 95% CI for the outcomes of interest comparing JAKi users to TNFi users were derived. The HR, 95% CI, together with the test for proportionality were calculated. The proportional hazard assumption was tested using the generalized Schoenfeld approach built in the TriNetX. All statistical analyses were performed using the TriNetX platform.

Subgroup analyses were done on three subgroups, including sex (male, female), age groups (19–64 years old, ≥65 years old), and race (White, Black/African American). We further explored for consistency across patients with newly diagnosed RA (diagnosed after January 1, 2018), different definitions of cohorts (prescription ≥3 times, switchers not excluded), and follow-up duration (90 days to 1 year, 90 days to 3 years, and 90 days to 5 years).

Results

Characteristics of Study Subjects

We identified 4,069 RA patients in the JAKi cohort and 26,501 in the TNFi cohort after applying a set of exclusion criteria (Figure 1). The baseline characteristics of patients are shown in Table 1. The mean ± standard deviation (SD) age in the JAKi cohort (57.7 ± 13.3 years) was older than those in the TNFi cohort (55.2 ± 14.4 years). Compared to the TNFi cohort, the JAKi cohort consisted of a higher proportion of females (81.4% vs 75.6%) and use of abatacept (5.7% vs 2.4%), a lower proportion of concomitant noninfective enteritis and colitis (3.2% vs 5.9%), psoriasis (3.8% vs 7.7%), systemic lupus erythematosus (3.8% vs 2.0%), dermatomyositis (1.5% vs 0.2%), use of NSAIDs (37.7% vs 44.0%) and methotrexate (31.4% vs 44.6%).

After PSM, we included 4,045 JAKi users and the same number in the TNFi cohort for all subsequent analyses. The two cohorts were well-matched regarding the distribution of age, sex, SES, family history of malignancy, smoking and drinking lifestyles, comorbidities, medical utilizations and medication usage (all standardized differences < 0.1) (Table 1). As shown in Table 1, all variables were numerically comparable and none remained imbalanced in the TNFi and JAKi cohorts. The mean ± SD age was 57.7 ± 13.3 years vs 57.6 ± 13.9 years, 81.4% vs 80.8% females, and 72.9% vs 73.5% white in the JAKi and TNFi cohorts, respectively.

Risk of Cancer Incidence Among the JAKi Cohort versus the TNFi Cohort

After a median (interquartile range) follow-up time was 3.69 (2.61) years for JAK inhibitor users and 3.69 (2.68) years for TNF inhibitor users respectively, there were no significant differences in the risk of overall cancer incidence between the propensity score matched JAKi and TNFi cohorts (HR 0.853, 95% CI 0.718–1.014) (Table 2 and Figure 2). The Kaplan–Meier curves showed no differences in overall cancer incidence comparing JAKi to TNFi users (Log Rank test, $p=0.070$; Figure 3A).

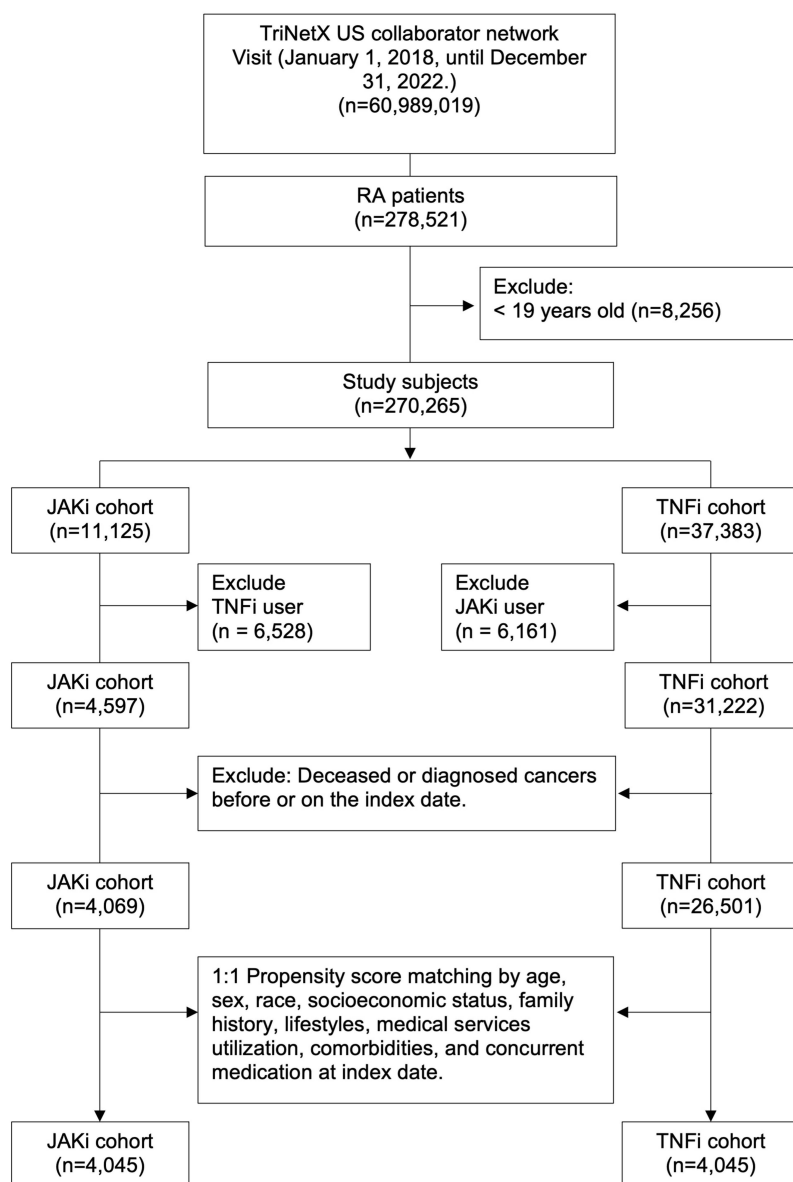


Figure 1 Flow chart of patient selections.

Abbreviations: RA, rheumatoid arthritis; JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor inhibitors.

Compared to the TNFi cohort, the JAKi cohort had a significantly lower risk of digestive organs cancers incidence (HR: 0.599, 95% CI: 0.439–0.817, [Table 2](#), [Figure 2](#)) and illustrated in the Kaplan–Meier curves (Log Rank test, $p=0.001$; [Figure 3B](#)).

Risk of All-Cause Mortality Among the JAKi Cohort versus the TNFi Cohort

There were no significant differences in the risk of all-cause mortality between the JAKi and TNFi cohort (HR: 1.191, 95% CI: 0.932–1.522, [Table 2](#), [Figure 2](#)).

Subgroup Analyses

When stratified by sex ([Supplementary material Table S1](#)), no increased risk of overall cancer incidence was observed in either sex. The reduced risk of incident digestive organs cancers (HR: 0.532, 95% CI: 0.373–0.759), and ill-defined/unspecified sites cancers (HR: 0.608, 95% CI: 0.389–0.949) was seen among females, but not seen in the male model as

Table I Baseline Characteristics of Study Subjects (Before and After Propensity Score Matching)

Variables	Before Matching			After Matching*		
	JAKi user (n=4069)	TNFi user (n=26501)	Std Diff.	JAKi user (n=4045)	TNFi user (n=4045)	Std Diff.
Age at index						
Mean $\pm$ SD	57.7 $\pm$ 13.3	55.2 $\pm$ 14.4	0.180	57.7 $\pm$ 13.3	57.6 $\pm$ 13.9	0.005
Sex, n (%)						
Female	3313 (81.4)	20,037 (75.6)	0.142	3293 (81.4)	3267 (80.8)	0.016
Male	755 (18.6)	6394 (24.1)	0.136	751 (18.6)	777 (19.2)	0.016
Unknown gender/Missing	1 (0.0)	70 (0.3)	<0.001	1 (0.0)	1 (0.0)	<0.001
Race, n (%)						
White	2963 (72.8)	19,118 (72.1)	0.015	2948 (72.9)	2973 (73.5)	0.014
Black or African American	537 (13.2)	3319 (12.5)	0.020	533 (13.2)	512 (12.7)	0.015
Asian	88 (02.2)	582 (02.2)	0.002	86 (02.1)	88 (02.2)	0.003
American Indian or Alaska Native	25 (00.6)	239 (00.9)	0.033	24 (00.6)	23 (00.6)	0.003
Native Hawaiian or Other Pacific Islander	10 (00.2)	42 (00.2)	0.019	10 (00.2)	10 (00.2)	<0.001
Unknown race	452 (11.1)	3201 (12.1)	0.030	450 (11.1)	447 (11.1)	0.002
Social economic status, yes (%)						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	74 (01.8)	618 (02.3)	0.036	74 (01.8)	77 (01.9)	0.005
Family history, yes (%)						
Family history of primary malignant neoplasm	118 (02.9)	1127 (04.3)	0.073	118 (02.9)	112 (02.8)	0.009
Lifestyles, yes (%)						
Tobacco use (proxy smoking)	131 (03.2)	1094 (04.1)	0.048	131 (03.2)	129 (03.2)	0.003
Nicotine dependence (proxy smoking)	287 (07.1)	2331 (08.8)	0.065	286 (07.1)	265 (06.6)	0.021
Alcohol related disorders (proxy alcohol drinking)	37 (00.9)	386 (01.5)	0.051	37 (00.9)	40 (01.0)	0.008
Comorbidities, yes (%)						
Depressive episode	467 (11.5)	3085 (11.6)	0.005	464 (11.5)	431 (10.7)	0.026
Essential (primary) hypertension	1323 (32.5)	7779 (29.4)	0.068	1315 (32.5)	1298 (32.1)	0.009
Ischemic heart diseases	324 (08.0)	1704 (06.4)	0.059	320 (07.9)	341 (08.4)	0.019
Cerebrovascular diseases	154 (03.8)	947 (03.6)	0.011	154 (03.8)	155 (03.8)	0.001
Diabetes mellitus	558 (13.7)	3253 (12.3)	0.043	555 (13.7)	571 (14.1)	0.011
Overweight and obesity	504 (12.4)	3462 (13.1)	0.020	501 (12.4)	485 (12.0)	0.012
Hyperlipidemia, unspecified	671 (16.5)	3681 (13.9)	0.072	669 (16.5)	676 (16.7)	0.005
Noninfective enteritis and colitis	131 (03.2)	1573 (05.9)	0.130	130 (03.2)	132 (03.3)	0.003
Diseases of liver	189 (04.6)	1449 (05.5)	0.038	186 (04.6)	171 (04.2)	0.018
Sleep disorders	554 (13.6)	3461 (13.1)	0.016	552 (13.6)	532 (13.2)	0.015
Psoriasis	156 (03.8)	2033 (07.7)	0.165	156 (03.9)	140 (03.5)	0.021
Chronic kidney disease	248 (06.1)	1322 (05.0)	0.048	248 (06.1)	266 (06.6)	0.018
Chronic lower respiratory diseases	653 (16.0)	3699 (14.0)	0.059	649 (16.0)	621 (15.4)	0.019
Systemic lupus erythematosus	156 (03.8)	532 (02.0)	0.109	151 (03.7)	134 (03.3)	0.023
Dermatopolymyositis	62 (01.5)	52 (00.2)	0.144	45 (01.1)	36 (00.9)	0.022

Note: All data given in n (%) unless specified. If the patient is less or equal to 10, results show the count as 10. Bold font represents a standardized difference greater than 0.100. *Propensity score matching was performed on all listed characteristics (age at index, sex, race, socioeconomic status, family history, lifestyles, comorbidities, medical utilization, and medication usage).

Abbreviations: JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor inhibitors; Std Diff., standardized difference; SD, Standard Deviation; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drugs.

Table 2 Risk of Incident Cancers and All-Cause Mortality Comparing JAKi and TNFi Users (90 days to 5 Years)

Outcomes	Patients with Outcome/ Cumulative Incidence (%)		Risk Difference	Adjusted ^a Hazard Ratio (95% CI)
	JAKi Cohort	TNFi Cohort		
Cancer incidence				
Lip, oral cavity and pharynx cancers	10/0.204%	10/0.189%	0.015%	0.888 (0.271–2.911)
Digestive organs cancers	61/2.966%	116/5.469%	–2.503%	0.599 (0.439–0.817)
Respiratory and intrathoracic organs cancers	22/2.125%	25/1.497%	0.628%	1.049 (0.590–1.866)
Bone and articular cartilage cancers	0/0.000%	10/0.094%	–0.094%	NA
Melanoma and other skin cancers	62/5.970%	76/3.497%	2.473%	0.930 (0.665–1.302)
Mesothelial and soft tissue cancers	10/0.056%	10/0.283%	–0.227%	0.460 (0.089–2.385)
Breast cancers	28/1.366%	37/1.446%	–0.080%	0.830 (0.507–1.357)
Female genital organs cancers [§]	15/1.296%	14/0.783%	0.513%	1.242 (0.598–2.581)
Male genital organs cancers [¶]	10/0.257%	10/0.472%	–0.215%	0.983 (0.355–2.720)
Urinary tract cancers	10/0.482%	12/0.851%	–0.369%	0.983 (0.424–2.282)
Eye, brain and other parts of CNS cancers	0/0.000%	10/0.057%	–0.057%	NA
Thyroid and other endocrine glands cancers	10/0.683%	10/0.355%	0.328%	1.268 (0.514–3.131)
Ill-defined, other unspecified sites cancers	46/2.010%	66/2.948%	–0.938%	0.782 (0.537–1.141)
Malignant neuroendocrine tumors	10/0.152%	10/0.293%	–0.141%	0.975 (0.217–4.378)
Lymphoid, hematopoietic and related tissue cancers	27/2.666%	41/1.828%	0.838%	0.753 (0.463–1.226)
Overall cancer (any cancers mentioned above)	230/16.27%	298/12.87%	3.399%	0.853 (0.718–1.014)
All-cause mortality				
Deceased	128/8.558%	130/8.734%	–0.176%	1.191 (0.932–1.522)

Note: a. After propensity score matching was performed on all listed characteristics (age at index, gender, race, socioeconomic status, family history, lifestyles, comorbidities, medical services utilization, and concurrent medication); § only applies to female; ¶ only applies to male. If the patient is less or equal to 10, results show the count as 10. Bold values indicate results that reached statistical significance.

Abbreviations: JAKi, Janus kinase inhibitors; TNFi, Tumor necrosis factor inhibitors; CI, Confidence interval; CNS, central nervous system; NA, not applicable (Not estimable due to zero events).

limited by sample size. The incident respiratory and intrathoracic organ cancers were higher in the JAKi cohort compared with the TNFi cohort among female patients (HR: 2.582, 95% CI: 1.109–6.011), but not among male patients.

Results from subgroup analyses stratified by age (19–64 vs ≥65 years old) were generally consistent with that of the entire cohort. No increased risk of overall mortality and a lower risk of digestive organs cancers incidence was seen in both age groups (19–64 years and ≥65 years) ([Supplementary material Table S2](#)). A lower risk of overall cancer incidence was observed for JAKi users compared to TNFi users in the age group of 19–64 years (HR: 0.713, 95% CI: 0.567–0.897) ([Supplementary material Table S2](#)).

Subgroup analyses stratified by race (White vs Black/African) revealed no increased risk of overall cancer incidence, a significantly lower risk of digestive organs cancers and ill-defined/unspecified site cancers incidence (HR:0.566, and 0.624, respectively) in the white population comparing JAKi to TNFi users. Grossly limited by the sample size, there were no statistically significant differences in the risk of cancer incidence between the JAKi and the TNFi cohorts among Blacks/African American ([Supplementary material Table S3](#)).

Results for risk of incident cancers and all-cause mortality among patients with newly diagnosed RA, different definitions of cohorts, and different follow-up duration were consistent with the results of analysis of the entire cohort ([Supplementary material Table S4–6](#)).

Discussion

From a large population-based registry, and propensity score matched cohorts, we did not find a higher overall cancer incidence risk among patients using JAKi compared with those using TNFi. We found a reduced risk of incident digestive organ cancers in RA patients using JAKi compared with those using TNFi. The results were consistent across young vs old age groups, race, early vs late RA, different definitions of cohorts, and different follow-up duration. The reduced risk of incident digestive organs cancers was mainly seen in female patients, while there was an increased risk of

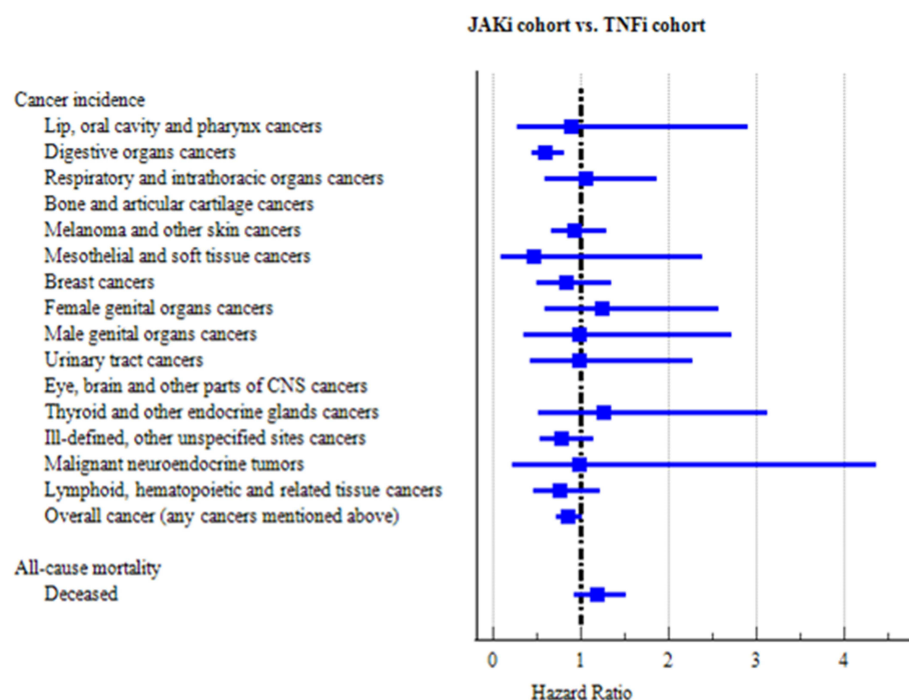


Figure 2 Forest plots of incidence of any cancer, overall cancer, and all-cause mortality.

Abbreviations: JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor inhibitors; CNS, central nervous system.

incident respiratory and intrathoracic organs cancers observed in female patients, and the absence of significant findings in male patients is likely due to the limited sample size.

In the ORAL surveillance trial, a phase 3b-4 RCT, patients randomized to tofacitinib had a higher (non-inferior) risk of malignancy compared to TNFi users. The HR of incidence of malignancy (excluding NMSC) was 1.48 (95% CI: 1.04–2.09) in the tofacitinib group compared with that in the TNFi group.² Lung cancer was the most common cancer in the tofacitinib group in the ORAL surveillance trial.^{2,21} Consistent with the ORAL surveillance trial, we found a higher risk of respiratory and intrathoracic organs cancers in females receiving JAKi. Yet, our current study did not show an increased risk of overall cancer incidence in patients on JAKi compared to those on TNFi, which is congruent with LTE studies of RCTs,^{7–9} meta-analyses,^{10,15} and other real-world data.^{11–14} Uniquely observed in our study, the incidence of digestive organ cancers was significantly lower in the JAKi cohort compared with that in the TNFi cohort. The incidence rate of digestive organ cancers in our cohort appeared to be higher than that in other cohorts. There were a total of 12 cases and 5 cases of colorectal and pancreatic cancers observed in the ORAL surveillance trial data over the study period,²¹ compared to 177 cases of digestive organ cancers observed in the current study. A higher number of cases allowed us to reveal the relative risk of digestive organ cancers between groups. The reason for observing a higher incidence of digestive organ cancer in our propensity score matched cohorts is not certain. Yet the IR of cancer in these propensity score matched cohorts should only be considered valid internally and the cancer risks were for JAKi compared to TNFi users. Of note, the setting and population characteristics of our study and the ORAL surveillance trial were different. The ORAL surveillance trial was an RCT, recruited an enriched population of high cardiovascular risk profiles, while our propensity-matched cohorts were patients from real-world routine care with heterogeneity. Population studies have shown cardiovascular disease and malignancy share a common risk profile.²² Risk of malignancy is higher in people with higher cardiovascular risk in the ORAL Surveillance trial,²¹ as well as in patients with other immune diseases.²³ Results from the ORAL Surveillance trial may not be applicable to the entire RA population in clinical practice. Two recent large trials using administrative database in real-life settings and across different JAKi have shown similar results as the current study. Data from the Korean National Health Insurance database-based study involving 4,929 RA patients did not show an increased risk of malignancy in RA patients with JAKi compared with

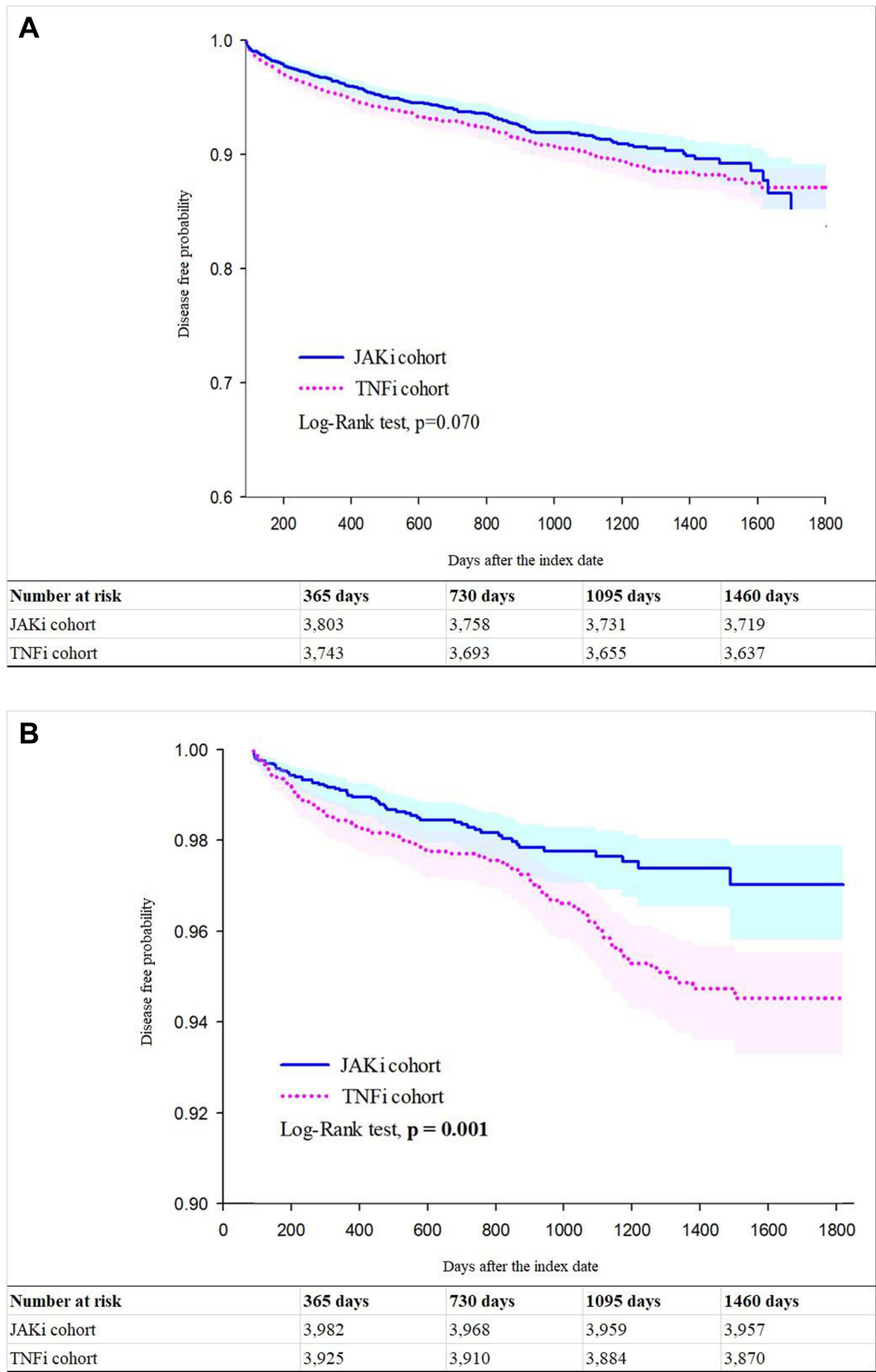


Figure 3 (A) Kaplan–Meier curve of overall cancer incidence.(B) Kaplan–Meier curve of digestive organs cancers incidence.
Abbreviations: JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor inhibitors.

those with TNFi.²⁴ Similarly, data from the Swedish rheumatology registry involving 10,447 RA patients found no increased risk of cancer other than NMSC for JAKi compared to TNFi users in clinical practice.¹⁴ Whether the risk of malignancy of JAKi could be a class effect is controversial and requires further investigations.²⁵ Phase 4 RCTs for baricitinib including RA-BRANCH and RA-BRIDGE trials are ongoing,²⁶ which will give more insight into this aspect.

Concerns have been raised about the biological plausibility of JAKi in causing solid tumors. Aberrant activation of JAK-STAT signaling pathway has been implicated in the proliferation and survival of tumor cells in head and neck squamous cell carcinoma²⁷ and ovarian tumors.²⁸ Evidence seems to suggest the contrary for digestive organs cancers. Mutation of JAK1 was found in 9.1% of patients with hepatitis B-associated hepatocellular carcinoma²⁹ and frequent amplification of the chromosomal locus containing JAK2 in gastric adenocarcinoma.³⁰ The activation of JAK-STAT pathway in these digestive organ cancers suggests that JAKi could be a potential therapeutic target. The crosstalk between JAK/STAT and extracellular signal-regulated kinase (ERK) signaling has been found in gastric cancer and pancreatic ductal adenocarcinoma cells. Tumor growth was reduced by concurrent inhibition of both the JAK/STAT and ERK pathway, but not by inhibition of each pathway alone.³¹ The role of the JAK-STAT pathway in the development and progression of malignancy is complex and may interact with other factors, ie genetic predisposition, tumor microenvironment, and interaction with other oncogenic signaling pathways.³² Further mechanistic investigations are warranted to examine the role of the JAK-STAT pathway in malignancy. Clinically, these findings suggest that JAKi may be considered preferentially over TNFi in RA patients at elevated baseline risk for digestive organ malignancies, while individual risk–benefit profiles should continue to guide therapeutic decisions.

There are several strengths of this study. First, this is based on a large cohort across multiple HCOs. This large sample size allows an adequate number of incident cancer for meaningful statistical analysis. The findings remained consistent across various subgroups, including those stratified by age, patients with newly diagnosed RA, and different follow-up durations in the analysis. Secondly, the data come from patients treated in a real-world setting and hence, the results are more generalizable to daily clinical practice. The lower methotrexate (31.0–31.6%) and higher glucocorticoid use (59.6–60.1%) in our study reflect a real-world, difficult-to-treat RA population on JAKi, often with prior csDMARD or biologic DMARD failure. Similar trends are reported among RA patients receiving JAKi in other real-world studies,^{11,12,14,33,34} emphasizing that our cohort represents patients with severe disease and complex treatment needs. Thirdly, PSM was used to adjust the possible confounding factors, including concomitant use of DMARDs and other autoimmune diseases. Approximately 4.5% of the cohort had overlap syndromes such as SLE or dermatomyositis, consistent with reported rates in RA cohorts.³⁵ These cases were propensity score matched and balanced between TNFi and JAKi groups, with the small proportion not expected to affect the overall results. Sensitivity analysis excluding them showed no material impact (data not shown). In addition, we limited the analyses to the US subnet to increase the homogeneity of the population and health system. It has been shown that cancer risk differs substantially within and outside the US.²¹ Fourthly, the follow-up time of up to 5 years should be considered adequate to reveal incident cancers. This is important as cancer incidence difference may only occur after 12–18 months as shown in the ORAL Surveillance trial.²¹ Finally, our study included all JAKi, which may provide information beyond tofacitinib.

There are some limitations of this study. First, the residual confounding effect is inherent in cohort studies that may not be able to be entirely eliminated by PSM. Second, although the absolute number of all-cancers was adequate for statistical analysis, the number of individual cancers remained small. This limits the statistical confidence in the relative risk for individual cancers. There was zero event for rare cancers (bone/articular cartilage and central nervous system malignancies) that we could provide the relative risk estimates. Similarly, caution is required in the interpretation of data of subgroup analyses due to the small sample size and absolute number of incident cancers, particularly for models for male, and American Black. Third, data on RA disease duration, disease activity, and extra-articular manifestations were not available, which may be associated with developing malignancy. For instance, high disease activity and chronic inflammation are risks for developing lymphoma.³⁶ It is unknown whether these factors are balanced between the JAKi cohort and the TNFi cohort. We had no information about the cumulative dose of TNFi and JAKi that may possibly alter the risk of cancer. Fourth, we do not know the details of malignancy in each system. Additionally, underreporting of ICD-10 codes and heterogeneity in data entry across multiple EMR users may have led to misclassification of exposures and outcomes. Fifth, our results are limited to the propensity score matched cohorts that are mainly from the academic medical center in the US with a majority of the white population. Therefore, it may not be able to extrapolate to other populations or healthcare institutions. Sixth, deaths occurring outside the healthcare organizations' systems may not be fully captured, potentially leading to missing data and underestimation of mortality in EHR-based analyses.

Conclusion

In conclusion, in this real-world RA cohort, JAKi were not associated with higher overall cancer incidence compared to TNFi, and all-cause mortality was similar at 3.2%. We observed a significantly reduced risk of incident digestive organ cancers compared with TNFi in patients with RA. Clinically, these findings suggest that JAKi may be preferentially considered over TNFi in RA patients at elevated baseline risk for digestive malignancies, while close monitoring of respiratory cancer risk in women is advised. Further studies with larger sample size and longer follow-up are warranted to ascertain these findings.

Data Sharing Statement

The datasets generated for this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

The Western Institutional Review Board has granted TriNetX a waiver of consent as it only aggregated counts and statistical summaries of de-identified data as per the de-identification standard defined in Section §164.514(a) of the Health Insurance portability and Accountability Act (HIPAA) Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. As an HCO member of TriNetX, Chung Shan Medical University Hospital (CSMUH) can access the de-identified data in the TriNetX platform. In addition, the use of TriNetX for the present study was also approved under the authority of the Institutional Review Board of CSMUH (No: CS2-21176).

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