Tumor Necrosis Factor Inhibitors and the Risk of Cancer among Older Americans with Rheumatoid Arthritis

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ABSTRACT

Background: TNF inhibitors (TNFi) effectively treat rheumatoid arthritis but may increase patient risk of some malignancies, particularly lymphomas or skin cancers.

Methods: We used Surveillance, Epidemiology, and End Results (SEER)–Medicare data to conduct a case–control study in patients with rheumatoid arthritis (2007–2015). Cases were individuals with a first cancer diagnosed in SEER registries (ages 66–99, 22 cancer sites, $N = 10{,}263$). Skin cancer cases [nonmelanoma skin cancer (NMSC, $N = 501$), basal cell carcinoma (BCC, $N = 161$), squamous cell carcinoma (SCC, $N = 150$)] and cancer-free controls ($N = 30{,}475$) were selected from Medicare beneficiaries residing in SEER areas. Cases and controls had prior Medicare claims-based evidence for rheumatoid arthritis, and TNFi exposure was ascertained from part B and part D claims. Logistic regression was used to estimate adjusted odds ratios (aOR).

Results: TNFi exposure was present in 16.2% of controls and 12.8% to 33.7% of cancer cases, varying by site. TNFi use was associated with increased risk of NMSC overall (aOR 1.32, 95% confidence interval 1.06–1.63), non-Hodgkin lymphoma (NHL) overall (1.28, 1.06–1.56) and, specifically, follicular lymphoma (2.63, 1.63–4.24). TNFi exposure was not associated with other SEER cancer sites, BCC or SCC specifically, or other common NHL subtypes.

Conclusions: Among older adults with rheumatoid arthritis, TNFi exposure was associated with elevated risk of NMSC and NHL, driven specifically by follicular lymphoma. Exposure was not associated with increased risk for other cancer sites.

Impact: Our results support a role for TNF in lymphomagenesis. Given the association with NMSC, patients initiating TNFi therapy may benefit from skin cancer screening and sun protection measures.

Introduction

Rheumatoid arthritis is an autoimmune disease that causes inflammation and pain in the joints. Globally and in the United States, approximately 0.5% of the general population has rheumatoid arthritis (1, 2). Tumor necrosis factor (TNF), an important cytokine in the inflammatory cascade, is highly expressed in rheumatoid arthritis–affected joint tissue, and TNF is thus an important therapeutic target for rheumatoid arthritis (3, 4). TNF inhibitors (TNFi) are effective in controlling active rheumatoid arthritis and preventing progressive joint damage (4). TNFis are also used to treat other autoimmune or inflammatory conditions including inflammatory bowel disease (IBD, i.e., Crohn's disease, ulcerative colitis).

Despite their utility in treating rheumatoid arthritis and other conditions, TNFis are associated with increased risk of serious infections, notably the reactivation of latent tuberculosis (5–7). Because of the apparent immunosuppressant effects of TNFis, there have also been concerns that they could increase malignancy risk, especially for cancers that have infectious or immune-related etiology. This issue is especially pertinent for lymphomas and lung cancer, because patients with rheumatoid arthritis patients already have an increased risk of these cancers compared with the general population (8–10), likely related to rheumatoid arthritis disease activity and chronic immune stimulation.

To date, studies examining the association between TNFis and cancer risk in patients with rheumatoid arthritis have been mixed. One of the earliest studies was a meta-analysis of 9 randomized, placebo-controlled trials of infliximab and adalimumab (7), which reported significantly higher overall cancer risk in the treated patients [OR, 3.3; 95% confidence interval (CI), 1.2–9.1], with an apparent excess of lymphoma cases. Notably, however, trial participants were only followed for 1 year or less, and there were only 29 cancer events. Two additional meta-analyses of randomized trials reported no association between TNFi use and overall malignancy (11, 12). However, the first of these found a two-fold increased risk for nonmelanoma skin cancer (NMSC, RR, 2.02; 95% CI, 1.11–3.95) while the other reported a nonsignificant increase in lymphoma risk (OR, 2.14; 95% CI, 0.55–8.38; refs. 11, 12). Some observational studies have also continued to observe positive associations between TNFi use and lymphoma, melanoma, or NMSC risk (13–21).

Collectively, these previous studies suggest that TNFi use may be associated with increased risk of some cancers among patients with rheumatoid arthritis. However, the studies commonly had short follow up, grouped malignancies together, or were underpowered to examine specific cancer sites or subtypes. Cancer is heterogeneous with respect to natural history and etiology. In particular, non-Hodgkin lymphoma (NHL) is comprised of etiologically distinct subtypes, and analyses of NHL overall may miss relevant associations (22). For example, some NHL subtypes [e.g., diffuse large B-cell lymphoma (DLBCL)] are greatly increased in other

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immunosuppressed populations, e.g., individuals with acquired immunodeficiency syndrome (AIDS; ref. 23).

In the present study, we examined the association between TNFi use and risk of malignancy in patients with rheumatoid arthritis over age 65 years in the United States. We utilized data from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, a large population-based resource, which allowed us to systematically assess distinct solid cancers and hematologic malignancies.

Materials and Methods

This study was considered non-human subjects research by the National Institutes of Health. We used SEER-Medicare data to perform a case–control study of cancer among individuals with rheumatoid arthritis (24). SEER-Medicare is a linkage between 18 central cancer registries covering approximately 28% of the US population and Medicare, a federally funded health insurance program for Americans aged 65 years and older or with disability (25). Approximately 93% of SEER cases over age 65 link to Medicare claims. Medicare provides hospital benefits (part A) to all enrollees, and most also receive part B benefits for outpatient and physician care. Since 2006, Medicare beneficiaries are eligible to receive medication benefits through part D. The SEER-Medicare database also includes a 5% random sample of cancer-free Medicare beneficiaries from SEER catchment areas.

We identified all SEER cases with a first cancer diagnosis at age 66 to 99 (2007–2015). Cancers diagnosed only at autopsy or on death certificate were excluded. Controls were selected for each calendar year from 2007 to 2015 from the 5% Medicare sample. They were required to be cancer-free and aged 66 to 99 years on July 1 in the calendar year of selection. Controls were selected in each calendar year they were eligible and could later become a case. We did not include individuals younger than 65, because their eligibility for Medicare due to disability may have been attributable to severe rheumatoid arthritis, making them unrepresentative of the population with rheumatoid arthritis.

To identify the subset of cases and controls who had rheumatoid arthritis, Medicare claims were assessed for each beneficiary starting at study entry, which was defined as the later of age 65 or first calendar year of Medicare claims data. All potential study participants were required to have at least 1 month of Medicare part-A, part-B, and part-D coverage outside a health maintenance organization (HMO) in the time between study entry and 365 days prior to case diagnosis/control selection (coverage in an HMO was excluded because HMOs do not provide itemized claims to Medicare for services; ref. 24). Finally, we required that included study participants have an inpatient Medicare claim with a rheumatoid arthritis diagnosis [International Classification of Diseases (ICD) 9th and 10th Revision codes, see Supplementary Table S1] or a rheumatoid arthritis diagnosis occurring in the outpatient setting from a rheumatologist at least 365 days prior to selection.

Cancer cases were classified using the SEER-site recode. Because SEER-Medicare does not allow reporting of cell sizes less than 12, we did not separately examine cancer sites for which the expected number of TNFi-exposed cases under the null hypothesis (i.e., number of site-specific cases *times* the proportion of exposed controls) was below this threshold. Instead, sites with too few cases were grouped with similar sites if possible or moved to a "miscellaneous" category. We categorized NHL cases according to SEER-recorded histology and separately evaluated the three most common subtypes [DLBCL, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)]. Hodgkin lymphoma was uncommon and was grouped with miscellaneous hematologic malignancies, but because it is a distinct entity we also examined it separately.

Cutaneous NMSC, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) diagnoses are not captured by SEER cancer registries. We therefore identified such cases using Medicare claims from the cancer-free 5% random sample of controls, requiring both a diagnosis code for the skin cancer and a procedure code indicating removal (Supplementary Table S1; ref. 26). First diagnoses in Medicare for SCC and BCC could be identified only during 2012 to 2015 when specific ICD-9/10 codes differentiating these diagnoses entered the lexicon. We assessed a first observable diagnosis of the less specific diagnosis NMSC using Medicare claims for the entire 2007 to 2015 period. NMSC, SCC, and BCC controls were selected from the full control set as described above. These controls were further required to not have a diagnosis of the respective skin cancer prior to July 1 of the selection year. See Supplementary Fig. S1 for flowchart of case and control selection.

Exposure to TNFis (etanercept, infliximab, adalimumab, golimumab, certolizumab) as well as methotrexate, other disease-modifying antirheumatic drugs (DMARD), and corticosteroids, was ascertained from part-B and part-D claims beginning at study entry and ending at cancer diagnosis/control selection [see Supplementary Table S1 for National Drug Code (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes]. Individuals with a claim for another biologic (ustekinumab, abatacept, tocilizumab, anakinra, rituximab, tofacitinib) prior to diagnosis/selection were excluded. We also used all claims between study entry and diagnosis/selection to assess potential confounding factors (Supplementary Table S2), including smoking indicators, rheumatoid arthritis severity, and history of NMSC (V code) or a diagnosis of actinic keratosis (both of which are skin cancer risk factors; refs. 2, 27). A person was classified as having a positive smoking history based on a claim for chronic obstructive pulmonary disease, smoking cessation, or history of smoking. Markers of severe rheumatoid arthritis included complications of rheumatoid arthritis, i.e., an inpatient rheumatoid arthritis diagnosis code occurring in the first position, or a claim for Sjögren syndrome, interstitial lung disease, Felty syndrome, or vasculitis. Corticosteroid or opioid use, as ascertained by the presence of a part-D claim at any time prior to diagnosis/selection, also signified severe disease. Corticosteroid use was classified as a binary variable, whereas opioid use was classified with the following levels: 0, 1–3, or 4+ part-D claims.

Logistic regression was used to estimate adjusted odds ratios (aOR) for each TNFi-cancer association, where the referent group were individuals without evidence of TNFi use. Analyses for melanoma, NMSC, BCC, and SCC were restricted to White cases and controls because there were few non-White cases. We present ORs minimally adjusted for age, sex, and race where appropriate, and cancer diagnosis/control selection year (aOR1 in **Table 2**), but our primary analyses additionally adjusted for smoking history and methotrexate use prior to diagnosis/selection (aOR2). Primary analyses for melanoma, NMSC, BCC, and SCC were further adjusted for history of NMSC and actinic keratosis. Based on prior evidence, we expected associations between TNFi and NMSC, melanoma, NHL, and Hodgkin lymphoma, so we used a P value of 0.05 to determine significance of the associations for these cancers; for other cancer sites, we used a Bonferroni correction of $0.0022 = 0.05/22$, as 22 additional cancer sites were examined. We used a robust variance calculation to account for multiple sampling of controls across calendar years and because some controls later were cases (24). For associations that were statistically significant in the primary models, we tested for an interaction between TNFi and methotrexate use, and

we further adjusted associations for markers of severe rheumatoid arthritis (complications of rheumatoid arthritis, corticosteroid use, and level of opioid use). We further conducted sensitivity analyses restricted to individuals with a claim for at least one rheumatoid arthritis medication (TNFi, methotrexate, or another DMARD) to test the robustness of associations in a population under active medical management for rheumatoid arthritis.

Additional exploratory analyses were performed to further understand primary associations. First, we examined associations separately for the most commonly used medications (infliximab and etanercept). We performed stage-specific analyses for several cancer sites with a large number of cases, to determine whether TNFi use affected how advanced the cancer was at presentation. To understand when TNFi exposure may act to alter cancer risk, we performed latency analyses for cancer sites with significant overall associations by examining associations with timing of first-observed TNFi claim (0–1, 1–2, 2–5, or 5+ years before diagnosis/selection). Finally, we performed analyses for skin cancers restricted to individuals with at least one dermatology visit more than 180 days prior to the diagnosis/selection date. Because these analyses were exploratory, we did not focus on statistical significance but on qualitative comparison to the primary associations.

Results

The study included 10,263 SEER cancer cases, 501 NMSC cases, 161 BCC cases, 150 SCC cases, and 30,475 controls with rheumatoid arthritis (**Table 1**). Because we selected all eligible controls in every calendar year, controls were selected a median of 3 times over different calendar years. Compared with controls, a lower proportion of SEER cases were female (69.4% vs. 79.9%), and a similar proportion were White (81.7% vs. 78.3%). Only 64.0% and 57.1% of SCC and BCC cases, respectively, were female. A large proportion of the study population had evidence of a history of smoking (range: 49.1%–56.0% across the case/control groups). A low proportion of cases and controls had indicators of rheumatoid arthritis complications (12.4%–18.0%), although a large fraction had prescriptions for corticosteroids (55.2%–65.2%) or opioids (63.5%–73.9%). Approximately 40% of cases and controls had a claim for methotrexate, 29.3% to 36.0% had a claim for another DMARD, and 55.5% to 68.3% received any rheumatoid arthritis medication prior to diagnosis/selection. SEER case-cancer diagnoses were classified into 26 specific sites or groupings (**Table 2**).

TNFi exposure prior to diagnosis/selection was observed in 16.5% of SEER cancer cases, 21.0% of NMSC cases generally, 15.3% of SCC cases, 26.1% of BCC cases, and 16.2% of controls (**Table 1**). TNFi use varied considerably by cancer site from 12.8% for stomach cancer to 33.7% for follicular lymphoma (**Table 2**). In the primary analyses, TNFi exposure was associated with risk of NHL overall (aOR2, 1.28; 95% CI, 1.06–1.56), follicular lymphoma (2.63, 1.63–4.24), and NMSC overall (1.32, 1.06–1.63). Exposure was not associated with Hodgkin lymphoma and miscellaneous hematologic malignancies (**Table 2**) or Hodgkin lymphoma separately ($N = 51$ cases, aOR2, 1.32; 95% CI, 0.67–2.61). Using a Bonferroni correction, we observed borderline significant inverse associations for breast cancer (aOR2, 0.85; 95% CI, 0.71–1.02) and prostate cancer (0.75, 0.57–0.99), and borderline positive associations for BCC (1.67, 1.14–2.44) and melanoma (1.33, 0.99–1.80).

Results were similar in a minimally adjusted model (aOR1, **Table 2**). The interactions between TNFi and methotrexate use were not significant for NHL overall ($P = 0.33$), follicular lymphoma ($P = 0.61$), or NMSC overall ($P = 0.99$). All statistically significant associations in **Table 2** remained significant and similar when further adjusted for markers of severe rheumatoid arthritis (Supplementary Table S3). The association between TNFi use and NMSC overall (aOR, 1.44; 95% CI, 1.12–1.85) was slightly stronger, and the association with BCC was unchanged (1.67, 1.08–2.58), when analyses were restricted to individuals with at least one dermatology visit more than 180 days prior to diagnosis/selection (Supplementary Table S4). When we restricted to individuals observed to receive at least one rheumatoid arthritis medication, results were similar, although slightly attenuated (Supplementary Table S5).

We also examined associations between infliximab or etanercept and individual cancer sites, and a few qualitative differences were suggested (**Table 3**). Notably, etanercept use was associated with greater than two-fold risk of esophageal cancer (aOR, 2.39; 95% CI, 1.17–4.86), and more than a 40% reduction in prostate cancer risk (0.55, 0.34–0.89). Infliximab and etanercept were both associated with follicular lymphoma. There were no clear patterns with respect to the associations between TNFi exposure and stage of cancer diagnosis (Supplementary Table S6).

In latency analyses (**Table 4**), the association between TNFi use and follicular lymphoma was strongest when the first TNFi claim was observed 1 to 2 years before diagnosis/selection (aOR, 4.34; 95% CI, 1.94–9.71), but the aOR was elevated for all periods at least 1 year prior to diagnosis/selection. There was an increased risk for NHL regardless of when the first TNFi claim was observed. The association between TNFi use and NMSC was elevated at all time points except in the 2 to 5 years prior to diagnosis/selection.

Discussion

In this study of TNFis and cancer risk among older adults with rheumatoid arthritis, TNFi exposure was significantly associated with an increased risk for follicular lymphoma and the broader groupings of NHL and NMSC. Notably, we did not observe significantly increased risk associated with TNFi exposure for a range of other common cancers. Because TNFi exposure is associated with an increased risk of infection and the reactivation of latent infections such as tuberculosis, there have been concerns that TNFis have immunosuppressive effects (5, 6). However, the role of TNF in cancer is complex, and TNFis may have both cancer-promoting and -limiting effects that are separate from their effects on immunity and depend on the specific cancer (28).

Although many studies have reported positive associations between TNFi use and lymphoma risk (8, 10, 12, 14, 29, 30), the evidence is still mixed with several studies reporting no association (15, 31, 32). Previous studies were generally unable to examine specific lymphoma subtypes. This could obscure results, because Hodgkin lymphoma and NHL are distinct, and NHL itself comprises a large number of subtypes which have unique etiologies (22). The significant association with NHL in our study seemed to be largely driven by follicular lymphoma. Unlike DLBCL and certain other NHL subtypes, follicular lymphoma is not elevated in immunosuppressed populations such as persons with AIDS or transplant recipients (23, 33), and to the best of our knowledge, rheumatoid arthritis itself is not associated with follicular lymphoma as it is with DLBCL (34). Furthermore, while DLBCL in immunosuppressed populations is often associated with Epstein–Barr virus (EBV), very few follicular lymphomas are EBV-positive (35).

The association between TNFi exposure and follicular lymphoma is novel. We are aware of only one prior study with data on follicular lymphoma, which evaluated a cohort of 11,931 TNFi-treated patients with rheumatoid arthritis in the United Kingdom (31). Data presented

Table 1. Demographic and clinical characteristics of cancer cases and controls with rheumatoid arthritis.

Characteristics	SEER Cases $n = 10,263$ *n* (%)	NMSC $n = 501$ *n* (%)	SCC $n = 150$ *n* (%)	BCC $n = 161$ *n* (%)	Controls $n = 30,475$ *n* (%)
Age at selection/diagnosis (years)					
65–69	1,369 (13.3)	78 (15.6)	20 (13.3)	29 (18.0)	4,536 (14.9)
70–74	2,783 (27.1)	122 (24.4)	36 (24.0)	48 (29.8)	8,223 (27.0)
75–79	2,509 (24.4)	96 (19.2)	37 (24.7)	27 (16.8)	6,861 (22.5)
80–84	1,922 (18.7)	102 (20.4)	29 (19.3)	28 (17.4)	5,571 (18.3)
85+	1,680 (16.4)	103 (20.6)	28 (18.7)	29 (18.0)	5,284 (17.3)
Sex					
Male	3,140 (30.6)	144 (28.7)	54 (36.0)	69 (42.9)	6,111 (20.1)
Female	7,123 (69.4)	357 (71.3)	96 (64.0)	92 (57.1)	24,364 (79.9)
Race					
White	8,389 (81.7)	501 (100.0)	150 (100.0)	161 (100.0)	23,860 (78.3)
Black	1,136 (11.1)	—	—	—	3,389 (11.1)
Other	738 (7.2)	—	—	—	3,226 (10.6)
Year of diagnosis/selection					
2007–2009	2,878 (28.0)	212 (42.3)	—	—	8,080 (26.5)
2010–2012	3,268 (31.8)	188 (37.5)	72 (48.0)	70 (43.5)	9,684 (31.8)
2013–2015	4,117 (40.1)	101 (20.2)	78 (52.0)	91 (56.5)	12,711 (41.7)
Smoking					
No	4,152 (40.5)	255 (50.9)	66 (44.0)	81 (50.3)	15,360 (50.4)
Yes	6,111 (59.5)	246 (49.1)	84 (56.0)	80 (49.7)	15,115 (49.6)
Complications of RA[a]					
No	8,787 (85.6)	421 (84.0)	123 (82.0)	141 (87.6)	26,248 (86.1)
Yes	1,476 (14.4)	80 (16.0)	27 (18.0)	20 (12.4)	4,227 (13.9)
Opioid use					
None	2,988 (29.1)	183 (36.5)	43 (28.7)	42 (26.1)	9,639 (31.6)
1–3 prescriptions	2,802 (27.3)	169 (33.7)	49 (32.7)	53 (32.9)	7,902 (25.9)
4+ prescriptions	4,473 (43.6)	149 (29.7)	58 (38.7)	66 (41.0)	12,934 (42.4)
Any treatment[b]					
No	4,237 (41.3)	204 (40.7)	54 (36.0)	51 (31.7)	13,564 (44.5)
Yes	6,026 (58.7)	297 (59.3)	96 (64.0)	110 (68.3)	16,911 (55.5)
Corticosteroid use					
No	4,065 (39.6)	232 (44.8)	48 (32.0)	56 (34.8)	223 (44.5)
Yes	6,198 (60.4)	286 (55.2)	102 (68.0)	105 (65.2)	278 (55.5)
Methotrexate use					
No	6,145 (59.9)	310 (61.9)	89 (59.3)	90 (55.9)	19,100 (62.7)
Yes	4,118 (40.1)	191 (38.1)	61 (40.7)	71 (44.1)	11,375 (37.3)
Other DMARD use[c]					
No	7,130 (69.5)	349 (69.7)	92 (61.3)	103 (64.0)	21,546 (70.7)
Yes	3,133 (30.5)	152 (30.3)	58 (38.7)	58 (36.0)	8,929 (29.3)
TNFi use					
No	8,571 (83.5)	396 (79.0)	127 (84.7)	119 (73.9)	25,544 (83.8)
Yes	1,692 (16.5)	105 (21.0)	23 (15.3)	42 (26.1)	4,931 (16.2)
TNFi medication					
Etanercept	508 (5.0)	30 (6.0)	NR (NR)	14 (8.7)	1,681 (5.5)
Infliximab	907 (8.8)	64 (12.8)	13 (8.7)	21 (13.0)	2,384 (7.8)
Adalimumab	368 (3.6)	16 (3.2)	NR (NR)	NR (NR)	1,199 (3.9)
Golimumab	52 (0.5)	NR (NR)	NR (NR)	NR (NR)	130 (0.4)
Certolizumab	65 (0.6)	NR (NR)	NR (NR)	NR (NR)	226 (0.7)

Abbreviations: NR, not reported because cell size < 12; RA, rheumatoid arthritis.

[a]A person is classified as having complications of RA if an RA diagnosis occurs in the first position of a hospitalization claim or if there is a diagnosis for any of the following conditions prior to cancer diagnosis/control selection: Sjogren syndrome, interstitial lung disease, Felty syndrome, or vasculitis. See Supplementary Table S2 for diagnosis codes.

[b]Any treatment is defined as methotrexate, other DMARD, or TNFi use.

[c]Other DMARDs include hydroxychloroquine, leflunomide, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, penicillamine, and minocycline. See Supplementary Table S1.

in **Table 2** of that 2015 study support an increased risk of follicular lymphoma compared with unexposed patients (incidence rate ratio 3.7), but there were only 19 cases in total and the association was not significant (χ^2 $P = 0.17$ based on our calculation). Of interest, a substantial proportion of follicular lymphomas harbor a mutation in *TNFRSF14* (a gene in the TNF receptor superfamily) that results in reduced function (36). The mechanistic implications of this mutation are uncertain, but one possibility is that TNFis may promote the

Table 2. Associations between TNFi exposure and cancer.

Controls or cancer site	Total	TNFi exposed *n* (%)	aOR1 (95% CI)	aOR2 (95% CI)
Controls	30,475	4,931 (16.2)	Reference	
Head and neck	249	41 (16.4)	0.99 (0.70–1.41)	0.96 (0.67–1.37)
Esophagus	90	19 (21.1)	1.44 (0.84–2.46)	1.55 (0.88–2.73)
Stomach	187	24 (12.8)	0.87 (0.56–1.35)	0.81 (0.52–1.28)
Colon	727	107 (14.7)	1.02 (0.82–1.27)	0.99 (0.79–1.24)
Rectosigmoid/rectum	169	27 (16.0)	1.09 (0.71–1.66)	1.02 (0.66–1.59)
Anus and genital organs	138	21 (15.1)	0.89 (0.55–1.45)	0.94 (0.58–1.54)
Liver	129	20 (15.5)	0.96 (0.59–1.58)	1.21 (0.72–2.03)
Biliary tract	137	20 (14.6)	1.00 (0.61–1.62)	0.99 (0.59–1.66)
Pancreas	392	59 (15.0)	1.02 (0.77–1.37)	1.00 (0.74–1.34)
Lung	2,167	361 (16.6)	1.01 (0.89–1.16)	0.93 (0.81–1.08)
Melanoma of skin[a]	317	73 (23.0)	**1.53 (1.15–2.03)**	1.33 (0.99–1.80)
Breast[b]	1,340	194 (14.5)	0.85 (0.72–1.01)	0.85 (0.71–1.02)
Uterus[b]	239	42 (17.6)	1.00 (0.71–1.42)	0.96 (0.68–1.37)
Ovary[b]	158	25 (15.8)	0.98 (0.64–1.52)	0.85 (0.55–1.33)
Prostate[b]	701	90 (12.8)	0.73 (0.56–0.96)	0.75 (0.57–0.99)
Urinary bladder	464	71 (15.3)	1.01 (0.77–1.33)	1.02 (0.77–1.35)
Kidney	297	55 (18.5)	1.14 (0.84–1.55)	1.15 (0.84–1.59)
Thyroid	117	23 (19.7)	1.07 (0.67–1.71)	1.16 (0.72–1.87)
Hodgkin lymphoma and miscellaneous hematologic malignancies	166	36 (21.7)	**1.46 (1.00–2.12)**	1.44 (0.96–2.17)
NHL	783	176 (22.5)	**1.49 (1.24–1.79)**	**1.28 (1.06–1.56)**
DLBCL	370	78 (21.1)	1.34 (1.03–1.74)	1.06 (0.81–1.39)
Follicular lymphoma	92	31 (33.7)	**2.56 (1.63–4.02)**	**2.63 (1.63–4.24)**
CLL/SLL	148	27 (18.2)	1.19 (0.78–1.81)	1.15 (0.74–1.78)
Myeloma	162	22 (13.6)	0.87 (0.55–1.37)	0.83 (0.52–1.31)
AML	99	17 (17.2)	1.13 (0.66–1.94)	1.16 (0.64–2.10)
NMSC[c]	501	105 (21.0)	**1.43 (1.16–1.77)**	**1.32 (1.06–1.63)**
BCC[d]	161	42 (26.1)	**1.71 (1.20–2.44)**	1.67 (1.14–2.44)
SCC[d]	150	23 (15.3)	0.89 (0.58–1.39)	0.87(0.54–1.40)
Miscellaneous	1,027	169 (16.5)	1.14 (0.95–1.37)	1.06 (0.88–1.28)

Note: Bolded values are statistically significant if $P < 0.05$ for associations with prior evidence or $P < 0.0022$ for associations without prior evidence.
Abbreviations: AML, acute myeloid leukemia; aOR1, OR is adjusted for selection year, age, and race and sex where appropriate; aOR2, OR is adjusted for selection year, age, race and sex where appropriate, methotrexate use, and smoking indicators. ORs for skin cancers are additionally adjusted for history of NMSC and actinic keratosis diagnoses.
[a]Analyses were restricted to White Medicare beneficiaries and included 23,860 controls.
[b]Analyses were restricted to males (prostate cancer cases) or females (breast, uterus, and ovary cancer cases) and, correspondingly, 6,111 male controls or 24,364 female controls.
[c]Analyses were restricted to White Medicare beneficiaries including 23,428 controls. NMSC cases were selected from the 5% random sample (2007–2015). All White Medicare controls were eligible for control selection when a NMSC diagnosis was not apparent in the years up to and including the selection year.
[d]BCC and SCC analyses (2012–2015) were restricted to White Medicare beneficiaries and included 12,511 controls for BCC cases and 12,529 controls for SCC cases.

transformation of premalignant lymphocytes to cause follicular lymphoma through a similar pathway. Follicular lymphoma cells represent the pathologic counterpart of normal germinal-center B cells and are characterized by a t(14;18) translocation between the immunoglobulin heavy-chain gene and the BCL2 oncogene (36). Although more than 70% of healthy individuals carry low levels of t(14;18)+ B cells in the blood or lymphoid tissues, the vast majority will never develop follicular lymphoma, indicating that BCL2 deregulation alone is insufficient to transform B lymphocytes.

Hodgkin lymphoma and miscellaneous hematologic malignancies were relatively uncommon in our study, and we observed only a borderline association between TNFi exposure and this malignancy. It would have been preferable to analyze Hodgkin lymphoma and the more common subtypes separately, but this study was not statistically powered for these analyses. There have been case reports of hepatosplenic T-cell lymphoma arising in children and adolescents treated for IBD with TNFis, resulting in a FDA black-box warning (37, 38). We would have liked to examine this aggressive NHL subtype, but there were no cases in our study, which is not surprising given its rarity and demographic profile (39).

Chronic ultraviolet-radiation exposure is the major cause of melanoma and NMSCs (40). Skin cancers manifest a high tumor-mutational burden caused by ultraviolet radiation, and the elevated risk in immunosuppressed populations is thought to be due to loss of immune control directed against tumor neoantigens. We observed a borderline association between TNFis and melanoma and found a significant association with NMSC generally, as has been reported by others (13). However, we did not replicate a previously reported association with SCC (19), and observed a moderately strong (albeit statistically insignificant) association with BCC. One possible explanation for these associations with skin cancers is that patients receiving TNFis may receive more frequent skin cancer screening than other patients with rheumatoid arthritis, leading to increased detection. However, when we restricted analyses to individuals with at least one dermatology visit more than 180 days prior to diagnosis/selection, the associations with BCC and NMSC overall persisted.

Table 3. Associations between exposure to TNFi, infliximab, or etanercept and cancer.

Controls or cancer site	Total	TNFi exposed *n* (%)	aOR (95% CI)	Infliximab exposed *n* (%)	aOR (95% CI)	Etanercept exposed *n* (%)	aOR (95% CI)
Controls	30,475	4,931 (16.2)	Ref	2,384 (7.8)	Ref	1,690 (5.5)	Ref
Head and neck	249	41 (16.4)	0.96 (0.67–1.37)	26 (10.4)	1.35 (0.88–2.07)	NR (NR)	0.67 (0.35–1.30)
Esophagus	90	19 (21.1)	1.55 (0.88–2.73)	NR (NR)	1.36 (0.65–2.84)	NR (NR)	**2.39 (1.17–4.86)**
Stomach	187	24 (12.8)	0.81 (0.52–1.28)	13 (7.0)	0.88 (0.49–1.57)	NR (NR)	0.52 (0.21–1.28)
Colon	727	107 (14.7)	0.99 (0.79–1.24)	61 (8.4)	1.11 (0.83–1.48)	29 (4.0)	0.82 (0.55–1.22)
Rectosigmoid/rectum	169	27 (16.0)	1.02 (0.66–1.59)	NR (NR)	0.63 (0.31–1.28)	NR (NR)	1.27 (0.67–2.40)
Anus and genital organs	138	21 (15.1)	0.94 (0.58–1.54)	NR (NR)	1.12 (0.59–2.13)	NR (NR)	0.54 (0.20–1.46)
Liver	129	20 (15.5)	1.21 (0.72–2.03)	NR (NR)	1.31 (0.66–2.62)	NR (NR)	1.17 (0.54–2.52)
Biliary tract	137	20 (14.6)	0.99 (0.59–1.66)	13 (9.5)	1.42 (0.78–2.58)	NR (NR)	1.02 (0.46–2.27)
Pancreas	392	59 (15.0)	1.00 (0.74–1.34)	27 (6.9)	0.91 (0.60–1.38)	18 (4.6)	0.91 (0.55–1.49)
Lung	2,167	361 (16.6)	0.93 (0.81–1.08)	192 (8.9)	1.00 (0.83–1.21)	104 (4.8)	0.80 (0.63–1.02)
Melanoma of skin[a]	317	73 (23.0)	1.33 (0.99–1.80)	44 (13.9)	**1.50 (1.05–2.16)**	21 (6.6)	1.11 (0.69–1.78)
Breast[b]	1,340	194 (14.5)	0.85 (0.71–1.02)	104 (7.8)	0.99 (0.79–1.25)	61 (4.6)	0.80 (0.60–1.07)
Uterus[b]	239	42 (17.6)	0.96 (0.68–1.37)	25 (10.5)	1.32 (0.86–2.04)	NR (NR)	0.50 (0.24–1.03)
Ovary[b]	158	25 (15.8)	0.85 (0.55–1.33)	NR (NR)	0.75 (0.40–1.42)	14 (8.9)	1.59 (0.89–2.83)
Prostate[b]	701	90 (12.8)	**0.75 (0.57–0.99)**	50 (7.1)	0.86 (0.60–1.24)	23 (3.3)	**0.55 (0.34–0.89)**
Urinary bladder	464	71 (15.3)	1.02 (0.77–1.35)	37 (8.0)	1.06 (0.74–1.52)	20 (4.3)	0.83 (0.51–1.34)
Kidney	297	55 (18.5)	1.15 (0.84–1.59)	32 (10.8)	1.39 (0.94–2.06)	19 (6.4)	1.13 (0.69–1.86)
Thyroid	117	23 (19.7)	1.16 (0.72–1.87)	NR (NR)	0.84 (0.40–1.76)	NR (NR)	0.95 (0.43–2.11)
Hodgkin lymphoma and miscellaneous hematologic malignancies	166	36 (21.7)	1.44 (0.96–2.17)	19 (11.4)	1.49 (0.91–2.45)	NR (NR)	1.19 (0.62–2.28)
NHL	783	176 (22.5)	**1.28 (1.06–1.56)**	97 (12.4)	**1.35 (1.06–1.72)**	60 (7.7)	1.26 (0.94–1.69)
DLBCL	370	78 (21.1)	1.06 (0.81–1.39)	41 (11.1)	1.08 (0.77–1.53)	26 (7.0)	1.05 (0.69–1.62)
Follicular lymphoma	92	31 (33.7)	**2.63 (1.63–4.24)**	18 (19.6)	**2.64 (1.51–4.62)**	NR (NR)	**2.00 (1.01–3.98)**
CLL/SLL	148	27 (18.2)	1.15 (0.74–1.78)	17 (11.5)	1.44 (0.85–2.47)	NR (NR)	1.27 (0.66–2.47)
Myeloma	162	22 (13.6)	0.83 (0.52–1.31)	NR (NR)	0.68 (0.33–1.39)	NR (NR)	0.63 (0.28–1.45)
AML	99	17 (17.2)	1.16 (0.64–2.10)	NR (NR)	1.34 (0.66–2.74)	NR (NR)	0.58 (0.18–1.88)
NMSC[a]	501	105 (21.0)	**1.32 (1.06–1.63)**	64 (12.8)	**1.37 (1.06–1.77)**	30 (6.0)	1.22 (0.85–1.75)
BCC[a]	161	42 (26.1)	**1.67 (1.14–2.44)**	21 (13.0)	1.54 (0.93–2.56)	14 (8.7)	1.52 (0.87–2.64)
SCC[a]	150	23 (15.3)	0.87 (0.54–1.40)	13 (8.7)	1.02 (0.56–1.87)	NR (NR)	1.04 (0.51–2.12)
Miscellaneous	1,027	169 (16.5)	1.06 (0.88–1.28)	89 (8.7)	1.08 (0.85–1.38)	49 (4.8)	0.92 (0.67–1.26)

Note: Bolded values signify associations where $P < 0.05$.

Abbreviations: aOR, adjusted OR; aOR is adjusted for selection year, age, race and sex where appropriate, methotrexate use, and smoking indicators; NR, not reported because cell size < 12.

[a]Analyses were restricted to White Medicare beneficiaries. See **Table 2** notes for details of control selection. ORs for skin cancers are additionally adjusted for history of NMSC and actinic keratosis diagnoses appearing in claims prior to diagnosis/selection.

[b]Analyses were restricted to males (prostate cancer cases) or females (breast, uterus, and ovary cancer cases) and, correspondingly, 6,111 male controls or 24,364 female controls.

We observed a few additional borderline significant associations, including inverse associations between TNFi exposure and prostate and breast cancers. TNF is highly expressed in some tumors including breast, prostate, ovarian, and colorectal tumors, and clinical trials have examined the treatment benefits of etanercept for breast and ovarian cancers (41, 42). It therefore may be biologically plausible that TNFis could prevent some cancers from developing. Two prior studies have suggested inverse associations with risk of breast or colorectal cancer (20, 43).

We performed latency analyses to understand how the association between TNFis and cancers varied according to when the first TNFi claim between study entry and selection was observed. There was a moderate increase in NHL risk regardless of when the first TNFi exposure occurred. Follicular lymphoma risk was increased starting more than 1 year after the first documented exposure, but the risk appeared greater in the 1- to 2-year period compared with the other intervals, suggesting that TNFi exposure may have accelerated an already-occurring carcinogenic process, e.g., by promoting expansion of t(14;18)+ B-cell clones.

Our study had several strengths. To our knowledge, it is the largest to date to evaluate the associations between TNFis and cancer risk, as can be judged by comparing the number of cancer cases in our study with those in prior cohort studies (13, 14, 17, 18, 20, 21, 29, 31, 32, 43). The large number of cases and comprehensive data in cancer registries allowed us to examine distinct cancer sites and subtypes, rather than grouping cancers as solid or hematologic malignancies. Although we made multiple comparisons, we employed a conservative Bonferroni correction to mitigate identifying spurious associations in our primary analyses. Finally, we performed several exploratory analyses to further examine the associations which we identified.

A limitation to our study is that it only included patients with rheumatoid arthritis older than age 65. However, because the incidence of most cancers increases strongly with age, our population-based sample included an important group in which to assess the effects of TNFis. Perhaps of greater salience, we lacked life-course information on rheumatoid arthritis treatment, and because RA has a median age of onset of 30 to 60 years, we could not assess

Table 4. Latency analyses for associations between TNFi exposure and selected cancers.

Cancer site	Cases *n* (%)	Controls *n* (%)	aOR (95% CI)	P_{trend}
NHL				
Never exposed	607 (77.5)	25,544 (83.8)	—	
Ever exposed	176 (22.5)	4,931 (16.2)	1.49 (1.24–1.79)	
Exposure according to earliest claim				0.53
0–1 year prior	20 (2.6)	555 (1.8)	1.54 (0.97–2.44)	
1–2 years prior	27 (3.5)	776 (2.6)	1.51 (1.01–2.26)	
2–5 years prior	75 (9.6)	1,892 (6.2)	1.71 (1.33–2.21)	
5+ years prior	54 (6.9)	1,708 (5.6)	1.32 (0.98–1.78)	
Follicular lymphoma				
Never exposed	61 (66.3)	25,544 (83.8)	—	
Ever exposed	31 (33.7)	4,931 (16.2)	2.56 (1.63–4.02)	
Exposure according to earliest claim				0.93
0–1 year prior	NR (NR)	555 (1.8)	1.58 (0.39–6.37)	
1–2 years prior	NR (NR)	776 (2.6)	4.34 (1.94–9.71)	
2–5 years prior	NR (NR)	1,892 (6.2)	2.19 (1.09–4.38)	
5+ years prior	NR (NR)	1,708 (5.6)	2.62 (1.36–5.06)	
NMSC				
Never exposed	396 (78.9)	19,541 (86.3)	—	
Ever exposed	106 (21.1)	3,905 (16.7)	1.43 (1.16–1.77)	
Exposure according to earliest claim				0.08
0–1 year prior	21 (4.2)	424 (1.8))	2.19 (1.38–3.48))	
1–2 years prior	21 (4.2)	590 (2.5)	1.90 (1.19–3.01)	
2–5 years prior	29 (5.8)	1,489 (6.4)	1.02 (0.70–1.50)	
5+ years prior	35 (7.0)	1,402 (6.0)	1.40 (0.99–1.97)	

Abbreviations: aOR, adjusted odds ratio; aOR is adjusted for selection year, age, and race and sex where appropriate. Analyses for NMSC were restricted to White Medicare beneficiaries; NR, not reported because cell size < 12.

or account for earlier therapies. Indeed, the median duration of Medicare claims data prior to cancer diagnosis among cases was only 6.7 years (interquartile range 6.1–7.3). Because of this limited window, we did not attempt a new user analysis, which would have allowed an assessment of early and cumulative effects of TNFi exposure (44, 45). Finally, we lacked detailed clinical information on rheumatoid arthritis disease severity. Although we adjusted for proxies for severe disease, some associations that we observed could have been confounded by disease severity. However, this issue may not be a major limitation, because we are not aware that severe rheumatoid arthritis by itself is associated with risk of skin cancers or follicular lymphoma, although there are reports of association with DLBCL (34, 46, 47). Finally, we had concerns that the TNFi–follicular lymphoma association could in part be attributable to detection bias, because some cases of follicular lymphoma have an indolent presentation and thus might be differentially diagnosed (48). However, CLL/SLL is also indolent, and there was no association with CLL/SLL.

A few limitations were specific to NMSC analyses. Because NMSCs are not captured in US cancer registries, we used a claims-based algorithm to identify cases (49). However, because the algorithm incorporates a surgical procedure, we expect that the algorithm is very specific which would result in minimal bias in the measured associations. Also, the identified NMSCs are unlikely to have been a person's first NMSC, since we could not identify these prior to age 65. The inability to capture and adjust for all prior skin cancer or precursor lesions might have biased the NMSC associations towards the null, if providers were reluctant to prescribe TNFis to individuals with such a history, because previous skin cancers and precursor lesions are strong risk factors for future NMSC. We were also unable to adjust for cumulative ultraviolet radiation exposure.

Reassuringly, risk of most cancers was not elevated among TNFi-exposed persons. We also did not observe an increased risk of cancers that are increased in immunosuppressed individuals such as DLBCL and human papillomavirus–associated cancers, which argues against strong immunosuppressive mechanisms. Furthermore, the associations between TNFi use and NMSC were modest. However, given the consistency with other studies, individuals initiating a TNFi should still receive regular skin cancer screenings and engage in sun protection measures, particularly if they are otherwise at elevated risk.

In conclusion, our study provides evidence for a previously unsuspected association between TNFi exposure and follicular lymphoma, which may drive the associations with lymphoma reported in other studies. Although these findings may have an immune explanation, the lack of strong immunosuppression in patients with rheumatoid arthritis treated with TNFis and the pattern of association with cancer suggest that other mechanisms could underlie this increased risk.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

M.E. D'Arcy: Conceptualization, formal analysis, methodology, writing–original draft, writing–review and editing. **D.C. Beachler:** Conceptualization, writing–review

and editing. **R.M. Pfeiffer:** Supervision, writing–review and editing. **J.R. Curtis:** Conceptualization, writing–review and editing, substantive contributions as rheumatologist. **X. Mariette:** Conceptualization, writing–review and editing, substantive contributions as rheumatologist. **R. Seror:** Conceptualization, writing–review and editing, substantive contributions as rheumatologist. **P. Mahale:** Conceptualization, writing–review and editing. **D.R. Rivera:** Conceptualization, writing–review and editing. **E.L. Yanik:** Conceptualization, writing–review and editing. **E.A. Engels:** Conceptualization, resources, supervision, writing–original draft, writing–review and editing.

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