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Risk of Cancer Recurrence Among Individuals Exposed to Anti-Tumor Necrosis Factor Therapy: A Systematic Review and Meta-Analysis of Observational Studies

Dejan Micic, MD¹, Yuga Komaki, MD¹, Aleksandar Alavanja, MD², David T. Rubin, MD¹, and Atsushi Sakuraba, MD, PhD¹

¹Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago, IL 60637 USA

²Indiana University School of Medicine, Indianapolis, IN 46202 USA

Abstract

Background—Patients with immune mediated disorders such as ankylosing spondylitis, inflammatory bowel disease, psoriasis and rheumatoid arthritis are increasingly treated with tumor necrosis factor (TNF) inhibitors. The safety of anti-TNF therapy in patients with a history of cancer requires further evaluation. We conducted a systematic review and a meta-analysis of observational studies including patients with a history of cancer exposed to anti-TNF therapy assessing for a risk of new cancer or cancer recurrence.

Materials and Methods—A computerized literature search of MEDLINE, Google scholar, and Cochrane Database of Systematic Reviews was performed through September 1, 2015. Study characteristics, quality and risk of bias was assessed. Random effects model meta-analyses were used to estimate the risk of new cancer development or cancer recurrence.

Results—Nine English-language observational studies including patients with a history of cancer and exposed to anti-TNF therapy were identified. The pooled RR of new or recurrent cancer among individuals with a history of cancer exposed to anti-TNF therapy was not significantly different compared to control therapies (Incidence Rate Ratio (IRR) 0.90; 95% CI 0.59–1.37). Subgroup analyses were performed according to disease type, underlying cancer diagnosis, time to initiation of anti-TNF therapy and study quality. Heterogeneity of study populations, heterogeneity of the included cancer subtypes and utilization of observational studies limits the study quality.

Conclusion—The risk of new cancer or cancer recurrence among patients with a history of cancer and use of anti-TNF therapy is similar to the risk with non-biologic disease modifying therapies. These results support the use of anti-TNF medications in select populations despite prior diagnosis of cancer.

Corresponding author: Atsushi Sakuraba, MD, PhD, 5841 S. Maryland Ave. MC4076, Chicago, IL 60636, asakurab@medicine.bsd.uchicago.edu.

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Keywords

tumor necrosis factor inhibitor; cancer; cancer recurrence; Inflammatory bowel disease

Introduction

Tumor necrosis factor (TNF) inhibitors are commonly utilized medications for the treatment of immune mediated conditions including ankylosing spondylitis, inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA) (1, 2). Chimeric, partly humanized, or fully human monoclonal antibodies or antibody fragments have been compared with placebo in randomized controlled trials and have demonstrated efficacy for the management of IBD (3), psoriasis (4) and RA (5). Given the efficacy of the anti-TNF biologic therapies in immune mediated disorders, studies have previously sought to quantify the risks of therapy to include cardiovascular disease (6), the development of plaque psoriasis (7), infection (3) and malignancy (8). However, randomized controlled trials of TNF inhibitors have excluded individuals with a past history of cancer, limiting the evidence for the use of anti-TNF therapy in such individuals.

There is evidence suggesting that immune suppression is associated with malignancy. This has been described in primary (congenital) immune deficiencies (9, 10), human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) (11–15) and immune suppressing medical therapies (16, 17). Studies have also assessed the role of TNF inhibitors in the development of incident cancer (8, 18–21), but its role in patients with a history of cancer has not been sufficiently reviewed (22, 23).

Current guidelines from the American College of Gastroenterology (24) and American Gastroenterological Association (25) do not provide specific recommendations for the use of anti-TNF therapy in individuals with a prior history of cancer while the European Crohn's and Colitis Organization (ECCO) consensus statement recommends delaying the resumption of immunosuppressant therapy for 2 years following the completion of cancer treatment, and extending to 5 years if the cancer is associated with an intermediate or high risk of recurrence (26). The American College of Rheumatology recommends starting or resuming biologic therapy for patients treated for a solid malignancy more than 5 years prior (27).

As patients with immune mediated conditions continue to age, the lifetime risk of cancer progressively increases due to increases in life expectancy and increased age-specific rates of various cancers (28). Combined with the improved prognosis of individuals with a history of cancer, physicians increasingly will be faced with the challenge of managing patients with a history of cancer and chronic non-communicable illnesses. In order to provide evidence for the management of immune mediated disorders in individuals with a history of cancer, we conducted a systematic review and a meta-analysis of cohort and case-control studies assessing for a risk of new cancer or cancer recurrence in individuals with a history of cancer and exposed to anti-TNF therapy.

Materials and Methods

Our meta-analysis followed the reporting recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (29). The protocol of this meta-analysis has not been published or registered to any databases.

Data Sources

We performed a computerized literature search of EMBASE (1947–September 2015), MEDLINE (1981–September 2015), Google scholar (1981–September 2015), and Cochrane Database of Systematic Reviews (2009–September 2015). For Google scholar, only the first one thousand articles were reviewed at each search, as it does not provide results beyond it. We also searched abstracts from scientific meetings: American Gastroenterology Association (2010–2015), American College of Gastroenterology (2006–2015), United European Gastroenterology, 2013–2014), American College of Rheumatology (2010–2014), European League Against Rheumatism (2002–2015), American Academy of Dermatology (2009–2015) and bibliographies of identified articles for additional references.

Search Strategy and Study Selection

To be eligible for inclusion, we only considered: 1) a study designed as case-control or cohort study, 2) evaluating the association between cancer recurrence and anti-TNF therapy, 3) including greater than 10 patients exposed to anti-TNF therapy, and 4) reporting an incidence rate ratio or hazard ratio with 95% confidence intervals (CI) utilizing a comparison group in which participants were not exposed to anti-TNF therapy. Comparator groups included those exposed to and not exposed to immunomodulatory therapy. There were no restrictions regarding age, sex, and duration of study. Case series and review articles were excluded. We imposed no geographic or language restrictions and articles in languages other than English were translated if necessary. Two authors (D.M. and A.A.) independently screened each of the potential titles, abstracts, and/or full-manuscripts to determine whether they were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus between the two authors. The corresponding authors of studies were contacted to provide additional information on studies if required.

Studies were identified in the literature review with the terms: *malignancy* or *cancer* and *recurrence*. These were combined by using the set operator AND with studies identified with the terms: *infliximab*, *Remicade*, *monoclonal antibody cA2*, *adalimumab*, *Humira*, *certolizumab pegol*, *golimumab*, *Simponi*, *etanercept*, *Enbrel*, *Cimzia*, *CDP-870*, *tumour necrosis factor*, *tumor necrosis factor*, *anti-tumour necrosis*, *anti-tumor necrosis*, *anti-TNF*, *TNF alpha antibody* (30), as free text terms.

Data Extraction and Quality Assessment

All data were independently extracted in duplicate by two authors (D.M. and A.S.) using a data extraction form. Data on the study characteristics, such as author name, year of publication, country, cohort size, mean age of patients, underlying inflammatory condition, underlying cancer, development of new cancer or cancer recurrence, follow-up and interval between cancer and anti-TNF use, were collected. Where available, the use of concomitant

immunosuppressant therapy was recorded. Studies that reported events without a comparator group were excluded from analysis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies (31). A total score of 7 or greater was defined as a high quality study and a total score of 6 or less was defined as a low quality study.

Outcome Assessment

The primary outcome assessed was the development of a new cancer or cancer recurrence while on anti-TNF therapy compared to utilization of non-biologic therapies. Where available the use of immunosuppressive therapy in the control group was recorded.

Data Synthesis and Analysis

Direct random-effects meta-analysis was performed to assess the risk of new or recurrent cancer diagnosis with anti-TNF therapies. Pooled incidence rates were compiled and an incidence rate ratio (IRR) for cancer development with 95% confidence intervals (CIs), was used to express differences in therapy.

The result of individual studies is expected to be diverse, therefore this inconsistency was quantified with a statistical test of heterogeneity. This quantity, termed I^2 , ranges from 0 to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value of 25%, accompanied by a P value of > 0.10 for the X^2 test, was arbitrarily chosen to represent low levels of heterogeneity (3). In order to address significant heterogeneity, we used a sequential approach to explore whether specific studies accounted for the observed heterogeneity (32).

To assess the potential for publication bias and small-study effect, we performed Begg's and Egger's test and constructed funnel plots to visualize possible asymmetry when three or more studies were available (33, 34).

We performed *a priori* subgroup analysis according to disease type (IBD versus RA), underlying cancer diagnosis (solid tumor malignancy, skin cancer, all cancers excluding skin cancer), time to initiation of anti-TNF therapy and study quality as assessed by the NOS score. All statistical analyses were performed with Comprehensive Meta Analysis V2 (Biostat, Englewood, NJ, USA). P values that were less than 0.05 were considered statistically significant. All statistical tests were two-sided.

Results

The search strategy identified 4,425 citations, of which 4,292 records were excluded after examining the title and abstract. Ninety-two studies were retrieved and evaluated in detail. Fifty-five studies evaluating the development of incident cancers in individuals without a history of cancer were excluded. Eight records utilizing overlapping registries (35–42), three studies evaluating the progression of premalignant conditions (43–45), fifteen case reports or case series that lacked a comparator group (46–60) and two studies including less than 10 patients exposed to anti-TNF therapy (61, 62) were excluded from the analysis (Figure 1).

Included in the meta-analysis were 9 studies (41, 63–70) reporting on 10 populations with inflammatory disorders. Six of the studies were from Europe and three were from the United States. Eight populations evaluated the risk of cancer development among individuals with a history of rheumatic disease (41, 64–70) and two evaluated the risk of new cancer or cancer recurrence among individuals with a history of IBD (63, 69). No included studies evaluated the risk of cancer recurrence in a population with psoriasis. Multicenter and registry studies included cases of all previous cancers (41, 63, 64, 70), skin cancer (melanoma and non-melanoma skin cancer (NMSC)) (41, 63–66, 69), and only solid tumor cancers: breast cancer (68) and head and neck cancer (67). The duration interval between original cancer diagnosis and initiation of anti-TNF therapy ranged from 1.2 years to 11.5 years in reported studies. The characteristics and outcomes of the included studies are summarized in Table 1.

Study quality is reported in Table 2. All studies scored well on patient selection and most studies scored well on comparability of the cohorts. Outcome assessments were more variable with poor documentation of overall follow-up.

Overall risk of new cancer or cancer recurrence with anti-TNF therapy

The nine studies included a total of 11,679 patients with a history of cancer. Of these, 3,707 individuals were exposed to anti-TNF therapy following a cancer diagnosis and 7,972 were exposed to no immunosuppression or non-biologic disease modifying therapy. In total, there were 298 new cancers or cancer recurrences among individuals exposed to anti-TNF therapy, and 625 new or recurrent cancers in the control groups. The pooled incidence rates of cancer development were 3.2/100 patient-years (95% CI 2.1–4.9) in the anti-TNF exposed group and 3.6/100 patient-years (95% CI 2.3–5.6) in the control cohort.

Two study populations included patients with a history of IBD and did not demonstrate an increased risk of new or recurrent cancer (IRR 0.68; 95% CI 0.40–1.16). Eight study populations included patients with a history of arthritis or RA without a demonstrated increased risk of new or recurrent cancer (IRR 1.06; 95% CI 0.78–1.46).

The pooled IRR of new or recurrent cancer among individuals with a history of cancer exposed to anti-TNF therapy was not significantly different compared to control therapies (IRR 0.90; 95% CI 0.59–1.37) (Figure 2). Significant heterogeneity was seen ($I^2 = 55.94\%$, $P = 0.015$) in the pooled analysis. Visual inspection of the funnel plot demonstrated no asymmetry and there was no publication bias as assessed by Begg's and Egger's test ($P = 0.86$, 0.78 , respectively). Significant heterogeneity was not observed in the subgroup of individuals with IBD ($I^2 = 0\%$, $P = 0.39$), but was observed in the subgroup with a history of arthritis or RA ($I^2 = 53.23\%$, $P = 0.036$). This heterogeneity was primarily driven by the study by Silva-Fernandez et al. (70). Exclusion of this study yielded a similar pooled IRR (0.95, 95% CI 0.52–1.73) with lower heterogeneity in the subgroup including individuals with arthritis or RA ($I^2 = 0\%$, $P = 0.59$) as well as in the pooled analysis ($I^2 = 42.47\%$, $P = 0.08$) (Appendix Figure S1).

Subgroup analysis by cancer type

Figure 3 shows the IRR for each secondary outcome with respect to the underlying cancer diagnosis (solid tumor malignancy, skin cancer, all cancers excluding skin cancer). In the a

priori subgroup analysis, the IRR of new cancer or cancer recurrence was not increased for individuals with a history of solid tumor malignancy (0.72, 95% CI 0.37–1.39) with no heterogeneity between studies ($I^2 = 9.83\%$, $P = 0.33$) and without evidence of funnel plot asymmetry (Egger test, $P = 0.77$) (63, 67, 68). Among individuals with a prior history of skin cancer, new or recurrent cancer was not increased (0.89, 95% CI 0.34–2.28) (41, 63, 65, 66, 69). Heterogeneity between studies was significant ($I^2 = 69.75\%$, $P = 0.005$) and was without evidence of funnel plot asymmetry (Egger test, $P = 0.77$). When all skin cancers were excluded in a subgroup analysis, no significant increased risk of new or recurrent cancer was demonstrated (0.80, 95% CI 0.55–1.16) with heterogeneity demonstrated between studies ($I^2 = 63.24\%$, $P = 0.018$) and without evidence of funnel plot asymmetry (Egger test, $P = 0.55$) (41, 63, 64, 67, 68, 70).

Subgroup analysis by time to anti-TNF initiation

Among studies initiating anti-TNF therapy greater than 5 years after cancer diagnosis, there was no increased risk of cancer recurrence (IRR 0.84; 95% CI 0.51–1.38) (41, 68, 70) (Figure 4). This was similar to the studies not reporting the time to anti-TNF exposure (IRR 1.11; 95% CI 0.79–1.56) (64–67, 69) and the single study reporting a median time to anti-TNF exposure of 1.2 years (IRR 0.58; 95% CI 0.28–1.23) (63). Among studies initiating anti-TNF therapy greater than 5 years after cancer diagnosis, heterogeneity was significantly increased ($I^2 = 60.45\%$, $P = 0.00$), which decreased ($I^2 = 0\%$, $P = 1.00$) when excluding the prior study by Silva-Fernandez. Visual inspection of the funnel plot did not demonstrate asymmetry and there was no publication bias as assessed by Begg's and Egger's test ($P = 1.00$; 0.37, respectively).

Subgroup analysis by NOS score

When grouping studies demonstrating high quality as critiqued by the NOS score, there was no increased risk of new cancer or cancer recurrence among studies with a NOS score of 7 (IRR 0.84; 95% CI 0.56–1.26) (63, 64, 66, 68, 70). There was no evidence of significant heterogeneity ($I^2 = 58.53\%$, $P = 0.065$) and no evidence of funnel plot asymmetry (Egger test, $P = 0.35$). This was similar to the studies with a NOS score of 6 (IRR 1.06; 95% CI 0.72–1.58) (41, 65, 67, 69), again without evidence of heterogeneity ($I^2 = 31.75\%$, $P = 0.21$) or funnel plot asymmetry (Egger test, $P = 0.45$) (Appendix Figure S2).

Discussion

We performed a systematic review and a meta-analysis of observational studies to evaluate the risk of new cancer development or cancer recurrence among individuals with a history of previous cancer and subsequently exposed to anti-TNF therapy. We found that the risk of new or recurrent cancer among individuals with a history of cancer exposed to anti-TNF therapy was not significantly different compared to control therapies. We have demonstrated that patients with a history of cancer are not at an increased risk of developing a new or recurrent cancer when exposed to anti-TNF therapy when compared to a comparator population receiving non-biologic disease modifying therapies. In terms of individual cancer types studied, there were no obvious differences in risk of new cancer development or cancer

recurrence among individuals with a history of solid tumor malignancy, skin cancer, or when examining the subgroup excluding skin cancers.

As the initial pooled analysis demonstrated significant heterogeneity, a sequential exclusion approach was used to identify studies contributing to the observed heterogeneity. Exclusion of the study by Silva-Fernandez et al. (70) led to a decrease in heterogeneity of the pooled analysis. When excluded from the subgroup analysis limited to individuals with RA and arthritis, the pooled incidence of new cancer or cancer recurrence increased in individuals exposed to anti-TNF therapy (RR: 1.27, 95% CI 1.01–1.60). While exclusion of a study demonstrating a decreased incidence of incident cancer diagnosis with anti-TNF therapy is expected to alter the results of a subgroup analysis, the study by Silva-Fernandez et al. is not an outlier with respect to methodology as a second included study from the British Society for Rheumatology Biologics Register was included in pooled analysis assessing risk of skin cancer (65).

The mechanism by which immunosuppressants promote cancer includes direct alterations of DNA in cells, reduced immunosurveillance for tumor cells, or impaired immunosurveillance for chronic infection by mutagenic viruses (71). Among individuals with IBD exposed to thiopurine therapies, increased risks of non-melanoma skin cancers, lymphoma and myeloid disorders have been demonstrated (72–74), with decreased risks of lymphoma development after drug discontinuation (72, 75).

The initial isolation of TNF in 1975 and gene cloning in 1984 stemmed from early observations of the role of bacterial extracts in necrosis of sarcoma tumors (76). Ultimately, Carswell *et al.* reported on a factor isolated in the serum of bacillus Calmette-Guerin (BCG)-infected mice made by host cells in response to endotoxin in which the term was coined “tumor necrosis factor” (77). Further studies evaluated the role of TNF in human tumors, although recombinant TNF administration was associated with severe toxicities (76). With further research into the tumor microenvironment and evidence of cancer-related inflammation and the proliferation and survival of malignant cells, the role of anti-TNF therapy has been studied in a number of active malignancies to include management of ovarian cancer (78), bladder cancer (79), advanced/metastatic solid cancer (80), cancer related cachexia (81), and in the prevention of graft-versus host disease (82) demonstrating biologic safety without significant risk of cancer progression.

Previous studies have evaluated the risk of incident cancer development among individuals exposed to anti-TNF therapy. In an early meta-analysis of data from randomized controlled trials utilizing anti-TNF therapy in individuals with RA, Bongartz *et al.*, demonstrated a dose-dependent increased risk of malignancy among individuals exposed to anti-TNF therapy (pooled OR 3.3, 95% CI 1.2–9.1) (8). However, the initial meta-analysis suggesting an increased risk of incident cancer development was critiqued citing an unexpectedly low rate of malignancy in the control arms of the meta-analysis, the use of an odds ratio to compare malignancy risk as opposed to incidence rates, therefore assuming equality of patient follow-up, as well as inclusion of malignancy diagnosed within six weeks of therapy initiation (83).

Subsequent observational registry studies evaluating incident cancer development among individuals with RA exposed to anti-TNF therapy and linked to the Swedish Cancer Registry failed to demonstrate an increased risk of incident cancer development compared to biologic-naïve comparator populations (RR 1.00, 95% CI 0.86–1.15) (20). A meta-analysis demonstrated a pooled estimate for the risk of incident cancer from seven studies without a significantly increased risk of all-site malignancy (RR 0.95, 95% CI 0.73–1.51) among patients with RA, psoriatic arthritis or ankylosing spondylitis (84). Furthermore, the risk of lymphoma was not increased (RR 1.11, 95% CI 0.70–1.51) while risks of NMSC (RR 1.45, 95% CI 1.15–1.76) and melanoma (RR 1.79, 95% CI 0.92–2.67) were increased among individuals exposed to anti-TNF therapies in four studies and two studies, respectively (84).

Although the risk of incident cancer development among individuals exposed to anti-TNF therapy does not appear to be increased compared to comparator populations, when cancers develop, previous studies have demonstrated high rates of discontinuation of anti-TNF therapy (53). When cancer develops among individuals exposed to anti-TNF therapies, a nationwide study evaluating cancer stage at diagnosis and risk of death following a diagnosis of cancer, no increased risk of death was demonstrated among individuals developing cancer while on anti-TNF therapy compared to a biologics-naïve control group (85). While the biology of cancers developing in individuals exposed to anti-TNF therapy is not more aggressive, a cancer diagnosis is a common reason for anti-TNF therapy discontinuation, with increased rates of discontinuation among the elderly.

The risk of second cancer among individuals with a history of cancer is increased compared to the general population. An analysis of the SEER Program found that cancer survivors had a 14% higher risk of developing a new malignancy that would be expected in the general population (O/E=1.14, 95% CI 1.14–1.15) (86). A more recent study from the Netherlands evaluating the development of second cancers among individuals with a history of Hodgkin's lymphoma demonstrated again a 4.6-fold increased risk of second cancer compared to the expected rate from the general population with a cumulative incidence of second cancer of 48.5% at 40 years of follow-up (87). With respect to individuals with a history of IBD, an analysis from the CESME study group identified 405 patients with a history of cancer among 17,047 patients included in a prospective observational study. Although not included in this meta-analysis as only seven patients with a history of cancer were exposed to anti-TNF therapy, the primary finding included an increased risk of cancer among those with a previous history of cancer (adjusted HR 1.9, 95% CI 1.2–3.0, $P=0.003$) (61). No significant associations were demonstrated between individuals exposed to immunosuppressant therapy and the risk of cancer development among individuals with a history of cancer.

A recent meta-analysis and systematic review combining the incidence rates of cancer recurrence among individuals with a history of cancer and immunosuppression exposure was performed demonstrating similar results to include a pooled cancer incidence rate of 33.8 per 1000 person-years among individuals receiving anti-TNF therapy and 37.5 per 1000 person-years among individuals not receiving immunosuppressive therapy (88). Our study demonstrates similar findings with the pooled incidence rates of cancer development being 3.2/100 patient-years in the anti-TNF exposed group and 3.6/100 patient-years in the control

cohort (which includes immunomodulator exposure). While both meta-analyses include several overlapping studies, our study adds to the current literature with the inclusion of several individual reports related to cancer recurrence not included in the prior meta-analysis resulting in increased power (64, 65, 67).

The strengths of our study include our ability to combine studies to include over 3,500 individuals with a history of cancer exposed to anti-TNF therapy, a sample size difficult to obtain utilizing national databases or multicenter studies. Although subgroup analyses limit the power of a conclusion, we did not find differing risks of cancer recurrence among the baseline cancer subtypes including solid tumors and skin cancers. Our meta-analysis showed no publication bias, which strengthens the results of our study.

The limitations of our meta-analysis include the inclusion of only observational studies, however, the quality of the included studies was good. Randomized controlled trials have commonly excluded patients with a history of cancer, therefore requiring the use of observational studies to assess the risk of adverse events among patients with a history of cancer. Studies of risk factors generally cannot be randomized because they relate to inherent human characteristic or practices, and exposing subjects to potential harmful risk factors is unethical (89). Limitations of use of observational studies include selection bias between the individuals selected to be exposed to anti-TNF therapy compared to those remaining on non-biologic disease modifying medications (90). A selection bias would require patients exposed to anti-TNF therapy to have a lower risk of cancer recurrence, while control populations remain at a higher risks of cancer development, therefore masking a potentially increased risk of cancer recurrence among individuals exposed to anti-TNF therapy. Secondly, short durations of follow-up can limit the detection of new or recurrent cancers, however, this was limited by including person-years of exposure in order to normalize follow-up time between anti-TNF and control groups. Lastly, different cancers have different intrinsic cancer recurrence risks based on innate biology and stage at the time of original diagnosis. We attempted to perform subgroup analysis to explore risks of cancer recurrence among differing etiologies of cancer without differences in recurrence risk dependent on anti-TNF therapy.

In conclusion, this meta-analysis including 10 study populations and over 3,500 patients with a history of anti-TNF use after cancer diagnosis demonstrates the safety of anti-TNF therapy among individuals with a history of cancer, without a demonstrated risk for the development of new or recurrent cancer compared to non-biologic disease modifying therapies. Given the prolonged interval between cancer diagnosis and anti-TNF initiation in most studies, care should still be taken with a multi-disciplinary approach to adequately discuss with the patient and treating physician risk of individual disease recurrence and the known risks and benefits of anti-TNF therapy for modifying clinical disease activity. Further large scale observational studies will be required to assess clinical factors associated with cancer recurrence in the variety of cancer subtypes in order to adequately understand factors predisposing to recurrence in patients requiring disease modifying therapy for active inflammatory disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Summary of evidence search and selection.

A.

B.

Figure 2.

Risk of new or recurrent cancer development when exposed to anti-TNF therapy. (A) Forest plot of the 10 studies. (B) Funnel plot of the overall studies included in (A).

Figure 3.
Risk of new or recurrent cancer development when exposed to anti-TNF therapy based on initial cancer type

Figure 4.
Risk of new or recurrent cancer development when exposed to anti-TNF therapy based time to anti-TNF exposure

Table 1

Characteristics of Studies Including Individuals with a History of Cancer Exposed to anti-TNF Therapy

Author	Disease	Country	Study	Years	Initial cancer type	TNF exposed, <i>n</i>	IMM exposure TNF group	No biologic therapy, <i>n</i>	IMM exposure control group	Time to initiation TNF	Definition of recurrence endpoint	Events TNF, <i>n</i>	Person years	Rate/100 pt years-TNF	Events control, <i>n</i>	Person Years	Rate/100 pt years-control	IRR	Adjustments
Phillips et al, 2010 (67)	RA	USA	Retrospective cohort	1998–2008	Head and neck cancer	40	NR	190	nbDMARD	NR	Recurrence or second head and neck cancer	7	256	2.73	35	1195	2.93	0.93 (0.41–2.10)	None
Mercer et al, 2012 (65)	RA	UK	Retrospective cohort	2001–2008	Skin cancer	177	NR	106	nbDMARD	NR	Basosquamous cell carcinoma	29	627	4.62	23	276	7.98	0.70 (0.26–1.94)	Age, sex, smoking, exposure to cyclosporine or azathioprine, NSAID and baseline characteristics
Dreyer et al, 2013 (64)	Arthritis	Denmark	Retrospective cohort	2000–2011	All cancer cases	745	NR	1965	NR	NR	Second cancer	34	2208	1.54	51	3793	1.34	1.15 (0.74–1.77)	None
Raaschou et al, 2013 (66)	RA	Sweden	Retrospective cohort	2001–2010	Melanoma	54	NR	295	NR	NR	New melanoma	3	271	1.11	10	1370	0.73	3.2 (0.8–13.1)	Age and sex
Strangfeld et al, 2013 (41)	RA	Germany	Retrospective cohort	2001–2012	Solid tumor cancer, skin cancer	109	NR	112	nbDMARD	6.8 years	Incident cancer	18	367	4.91	13	361	3.61	1.36 (0.67–2.78)	None
Raaschou et al, 2014 (68)	RA	Sweden	Retrospective case-control	1999–2010	Breast cancer	120	NR	120	NR	9.4 years	Recurrence or new primary breast cancer	9	592	1.50	9	550	1.60	1.1 (0.4–2.8)	Nodal status, type of surgery, chemotherapy
Silva-Fernandez et al, 2014 (70)	RA	UK	Retrospective cohort	2002–2013	All cancer cases, excluding NMSC and carcinoma-in-situ	243	NR	159	nbDMARD	11.5 years	Incident cancer	38	1591	2.40	40	855	4.70	0.55 (0.35–0.87)	Age and sex
Axelrad et al, 2015 (63)	IBD	USA	Retrospective cohort	1980–2014	Gastrointestinal, dermatologic, hematologic, solid tumor malignancies	106	55 combination therapy	149	No IMM	1.2 years	Incident cancer	22	699	3.15	46	852	5.40	0.58 (0.35–0.97)	None
Scott et al, 2015 (69)	RA	USA	Retrospective cohort	2006–2012	NMSC	1839	NR	4414	MTX	NR	Second NMSC	109	1465	7.44	335	4631	7.23	1.49 (1.03–2.16)	Anti-TNF before incident skin cancer diagnosis
Scott et al, 2015 (69)	IBD	USA	Retrospective cohort	2006–2012	NMSC	274	NR	462	AZA/6MP	NR	Second NMSC	26	375	6.94	63	717	8.79	0.79 (0.50–1.25)	None

AZA/6MP: azathioprine/6-mercaptopurine, IBD: inflammatory bowel disease, IMM: immunomodulator, MTX: methotrexate, nbDMARD: non-biologic disease-modifying antirheumatic drug, NMSC: non-melanoma skin cancer, NR: not reported, NSAID: non-steroidal anti-inflammatory drug, RA: Rheumatoid arthritis

Table 2

Quality Assessment of Cohort and Case-Control Studies Using the Newcastle-Ottawa Scale

Study, Year (Reference)	Selection*			Comparability**	Outcome***		
	Representativeness of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Demonstration Outcome Not Present at Study Start	Comparability of Cohorts	Follow-up Enough for Outcomes to Occur	Adequacy of Follow-up
Phillips et al, 2010 (67)	•	•	•	•	▣	▣	▣
Mercer et al, 2012 (65)	•	•	•	▣	••	▣	▣
Dreyer et al, 2013 (64)	•	•	•	•	••	▣	▣
Raaschou et al, 2013**** (66)	•	•	•	•	••	•	•
Strangfeld et al, 2013 (41)	•	•	•	•	▣	•	▣
Raaschou et al, 2014 (68)	•	•	•	•	••	•	▣
Silva-Fernandez et al, 2014 (70)	•	•	•	•	••	•	▣
Axelrad et al, 2015 (63)	•	•	•	•	••	•	▣
Scott et al, 2015 (69)	•	•	▣	•	••	▣	•
Scott et al, 2015 (69)	•	•	▣	•	••	▣	•

• = study fulfilled the listed criteria. ▣ = study did not fulfill the listed criteria.

* Representativeness of the exposed cohort: • given if representative of the average patient with cancer and an inflammatory condition in the community. ▣ given if selected from a group of volunteers or derivation of the cohort is not described.

* Selection of the non-exposed cohort: • given if drawn from the same community as the exposed cohort. ▣ given if selected from a group of volunteers or derivation of the cohort is not described.

* Ascertainment of exposure: • given if obtained by a secure record or structured interview. ▣ given if no description is given or self-report.

* Demonstration that outcome was not present at start of study: • given if demonstrated. ▣ given if not demonstrated.

** Comparability of cohorts on the basis of design or analysis: • given if study controlled for factor related to the risk of cancer recurrence. •• given if study controlled for an additional factor.

*** Assessment of outcome: • given if obtained by independent blind assessment or record linkage. ▣ given if obtained from self-report or not described.

*** Was follow-up long enough for outcomes to occur: • given if follow-up was long enough for outcome to occur (36 months of anti-TNF exposure) ▣ given if follow-up was not long enough.

*** Adequacy of follow-up of cohorts: • given if complete follow-up is provided or 90% of follow-up is provided. ▣ given if follow-up rate was < 90% or no description is provided.

*** For case-control study:

Selection: • given as the cancer diagnosis was obtained from record linkage, cases were obtained from a record (series of cases), controlled were obtained from the same record linkage and controls were not exposed to anti-TNF therapy.

Comparability: •• given as cases and controls matched based on age at cancer diagnosis, sex, year of cancer diagnosis, county of residence and cancer stage.

Exposure: • given as the ascertainment was from a secure record and the same for cases and controls. Follow-up was described for both groups.