

RESEARCH ARTICLE

Risk of Breast Cancer and Total Malignancies in Rheumatoid Arthritis Patients Undergoing TNF- α Antagonist Therapy: a Meta-analysis of Randomized Control Trials

Yang Liu^{1,3}, Wei Fan², Hao Chen², Ming-Xia Yu^{2*}

Abstract

Context: Interest exists in whether TNF-alpha antagonists increase the risk of breast cancer and total malignancies in patients with rheumatoid arthritis (RA). **Objectives:** To analyze the risk of malignancies, especially breast cancer, in patients with RA enrolled in randomized control trials (RCTs). **Methods:** A systematic literature search for RCTs from 1 January 1998 to 1 July 2013 from online databases, such as PubMed, WILEY, EMBASE, ISI web of knowledge and Cochrane Library was conducted. Studies included RCTs that compared the safety of at least one dose of the five TNF- α antagonists with placebo or methotrexate (MTX) (or TNF- α antagonists plus MTX vs placebo plus MTX) in RA patients for more than 24 weeks and imported all the references into document management software EndNote^{x6}. Two independent reviewers selected studies and extracted the data about study design, patients' characteristics and the type, number of all malignancies. **Results:** 28 RCTs from 34 records with 11,741 patients were analyzed. Of the total, 97 developed at least one malignancy during the double-blind trials, and breast cancer was observed in 17 patients (17.5% of total malignancies). However, there was no statistically significant increased risk observed in either the per protocol (PP) model (OR 0.65, 95% CI [0.22, 1.93]) or the modified intention to treat (mITT) model (OR 0.75, 95% CI [0.25, 2.21]). There were also no significant trend for increased risk of total malignancies on anti-TNF- α therapy administered at approved doses in either model (OR, 1.06, 95% CI [0.64, 1.75], and OR, 1.30, 95% CI [0.80, 2.14], respectively). As to the two models, modified intention to treat model analysis led to higher estimation than per protocol model analysis. **Conclusions:** This study did not find a significantly increased risk of breast cancer and total malignancies in adults RA patients treated with TNF- α antagonists at approved doses. However, it cannot be ignored that more patients developed malignancies with TNF- α antagonists therapy compared with patients with placebo or MTX, in spite of the lack of statistical significance, so that more strict clinical trials and long-term follow-up are needed, and both mITT and PP analyses should be used in such safety analyses.

Keywords: TNF- α antagonist therapy - rheumatoid arthritis - breast cancer - malignancies - meta analysis

Asian Pac J Cancer Prev, 15 (8), 3403-3410

Introduction

Tumor necrosis factor- α (TNF- α) is a pleiotropic cytokine. Since it reveals both pro- and anti-cancer properties (Balkwill et al., 2009), risk of malignancies in patients undergoing TNF- α antagonists therapy is always controversial. As our previous researches showed, breast cancer over-expressed TNF- α which played a vital role in the cancer's occurrence and development, and we also found transmembrane TNF- α monoclonal antibody (tmTNF- α mAb), as a TNF- α antagonist, effectively suppressed breast cancer growth (Yu et al., 2013). TNF- α antagonists seem offer therapeutic potential in solid

tumors. A phase II study had demonstrated the safety and biological activity of Etanercept in metastatic breast cancer (Madhusudan et al., 2004).

However, lots of literatures reported that patients in the duration of TNF- α antagonists therapy developed breast cancer or relapsed (Maini et al., 1999; Bathon et al., 2000; Kremer et al., 2003; Keystone et al., 2004; Maini et al., 2004; Klareskog et al., 2004; Goekoop-Ruiterman et al., 2005; Klareskog et al., 2006; Van der Heijde et al., 2006; Genta et al., 2006; Keystone et al., 2009; Emery et al., 2009; Kremer et al., 2010; Van der Heijde et al., 2010; Keystone et al., 2010; Keystone et al., 2012; Moreland et al., 2012; Weinblatt et al., 2012;

¹Center for Nanoscale Characterization & Devices (CNCD), Wuhan National Laboratory for Optoelectronics (WNLO), School of Physics, School of Optical and Electronic Information, Huazhong University of Science and Technology (HUST), ²Department of Clinical Laboratory & Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University, ³School of science, Wuhan Institute of Technology, Wuhan, China *For correspondence: dewrosy520@163.com

Emery et al., 2013; Keystone et al., 2013; Takeuchi et al., 2013; Weinblatt et al., 2013). It appears to contradiction about the interrelation between TNF- α antagonists and breast cancer. So we conduct this Meta-analysis of RCTs to define whether the risk of breast cancer is increased statistically in RA patients treated with TNF- α antagonists. And we also assess the total malignancies risk of TNF- α antagonists therapy, as the US Food and Drug Administration (FDA) has warned for thrice.

As the case stands, there has been already several meta-analyses published assessing the therapeutic safety of one or more of the five TNF- α antagonists, but the outcomes of malignancies risk are not always the same (Bongartz et al., 2006; Bongartz et al., 2009; Singh et al., 2009; Wiens et al., 2009; Aaltonen et al., 2012; Lopez-Olivo et al., 2012; Moulis et al., 2012; P et al., 2012; Wong et al., 2012). Most of the metaanalyses were conducted in modified intention to treat model (mITT) (Bongartz et al., 2009; Ni1 et al., 2012; Moulis et al., 2012), which could lead to overestimate compared with per protocol (PP). In addition to lymphoma (Wong et al., 2012) and non-melanoma skin cancers (NMSC) (P et al., 2012), there were no systematic reviews or metaanalyses assessing risk of individual cancer during TNF- α antagonists therapy in patients with RA. We conducted this Meta-analysis for the first time, to our knowledge, assessing the risk of breast cancer in which we are interested, and we used both mITT and PP models.

According to FDA, TNF- α antagonists approved for drugs included, etanercept (1998), infliximab (1998), adalimumab (2002), certolizumab pegol (2008) and golimumab (2009), and their approved doses used in RA therapy were, respectively, etanercept (subcutaneously injection (sc) 25 mg twice a week (biw), or 50 mg weekly), infliximab (adults, intravenously infusion (iv) 3 mg/kg every two months), adalimumab (sc, 40 mg every other week (eow)), certolizumab pegol (sc, 200mg eow, or 400 mg monthly for maintenance), golimumab (sc, 50 mg monthly). One or more of the five drugs were approved to treat the diseases, Rheumatoid arthritis (RA), Inflammatory bowel disease (IBD), Ankylosing spondylitis (AS), Psoriatic arthritis (PsA) and so on. This study we selected RCTs where at least one of the five TNF- α antagonists were used to RA therapy, which could be treated by all the five drugs and also the most widely used, to assess the breast cancer and total malignancies risk of TNF- α antagonists therapy in patients with RA. The main objection of this study was to assess the breast cancer and total malignancies risk in RA patients treated with TNF- α antagonists at approved doses. And we also conducted analysis to low doses and high doses compared with the approved doses to assess the possible doses-effect relation.

Materials and Methods

Study selection, evaluation of inclusion criteria, data extraction and statistical analysis were conducted based on the Cochrane handbook (Higgins et al., 2008). This article was finished on the basis of QUOROM statement (Moher et al., 1999).

Data sources and search strategy

We searched literatures from online databases including PubMed, WILEY, EMBASE, ISI Web of Knowledge and Cochrane Library, from 1 January 1998 to 1 July 2013 by terms as follow: “etanercept”, “infliximab”, “certolizumab”, “adalimumab”, “golimumab”, “Rheumatoid arthritis”, “randomized controlled trial” OR randomized OR randomly, “clinical trial”, “multicenter studies”.

To obtain the unpublished trials, we also searched the electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology to date. We referred to the references of those metaanalyses assessing the safety of TNF- α antagonists therapy published in Medline and Cochrane database to supple the possible omission. All the search process was conducted by two independent reviewers (Wei Fan and Hao Chen), and the disagreements were resolved by consensus. In addition, sponsors were contacted for the original detailed protocols.

Study selection

We included randomized, double-blind, placebo/MTX-controlled trials of the five currently licensed TNF- α antagonists. Adults patients enrolled into the trials were diagnosed as active RA according to American College of Rheumatology criteria (Arnett et al., 1989), and had to be randomly allocated to treatment group receiving at least one dose of the five TNF- α antagonists vs control group with placebo/MTX (or TNF- α antagonists plus MTX vs placebo plus MTX) for more than 24 weeks. We excluded studies as follow: 1) Juvenile idiopathic RA patients received TNF- α antagonists therapy; 2) Open-label studies, or open-label extension periods of RCTs which resulted in a possible diagnosis bias; 3) Studies with no description of adverse events (AEs) or insufficiency; 4) Duration of treatment less than 24 weeks.

Data extraction and quality assessment

Study selection and data extraction were finished by the two independent reviewers mentioned above, and the disagreements were resolved by consensus or the third reviewer, if possible. From each trial included, we extracted information about patients' characteristics, study design, type, and number of all malignancies. We merged the same RCTs or RCTs which actually were different periods of a RCT into one RCT. The quality of studies was assessed with Jadad scale ranging from 0 to 5 points (low quality study: 0-2; high quality: 3-5) (Jadad et al., 1996).

Statistical analyses

Statistical analysis was performed with Review Manager (version 5.0, Cochrane Collaboration, Oxford, UK). Based on the adverse event analysis, the number of patients developing at least one malignancy was what we needed to compared with the total patients receiving at least one dose of the study drugs. We conducted this meta-analysis in both mITT and PP models to analyze. Results were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs), and heterogeneity between

studies was calculated by I^2 and X^2 , with the significance level set at 0.05. Then we adopted fixed-effect model and calculated the pooled estimate using Mantel-Haenszel methods (M-H). Since there were null values in some studies without any malignancies developed, continuity correction estimate of the OR was used (J Sweeting et al., 2004), namely, a constant value of 0.5 was added to each number.

Results

Search results

We imported all the records into EndNotex6, and 720 records were left after auto-deduplicated. By reading the titles and abstracts, 559 records were excluded, 161 records left to find the full-text for eligibility. Of the 161 articles, 34 containing 28 trials met our inclusion criterion (Figure 1). Ten trials were excluded because of the duration of treatment less than 24 weeks. In five trials, malignancies were unclear and only one trial that we got the details by sending emails to the authors. Twenty three open-label trials were excluded, and we also excluded the open-label periods following up the double-blind trials in case of diagnosis bias. Eleven trials were excluded, because the control groups were not placebo or MTX. Other exclusion reasons included subanalysis or review (n=20), no adverse event (n=33), unblind or juvenile RA (n=26).

Studies characteristics

Twenty-eight RCTs with 11741 patients were included, and the drugs were etanercept in 6 trials, infliximab in 5 trials, certolizumab pegol in 4 trials, adalimumab in 8 trials, and golimumab in 5 trials (Table 1).

Dosages for each drug in each trial were multiple. Dosages in etanercept were 10 mg and 25mg biw, or 50mg

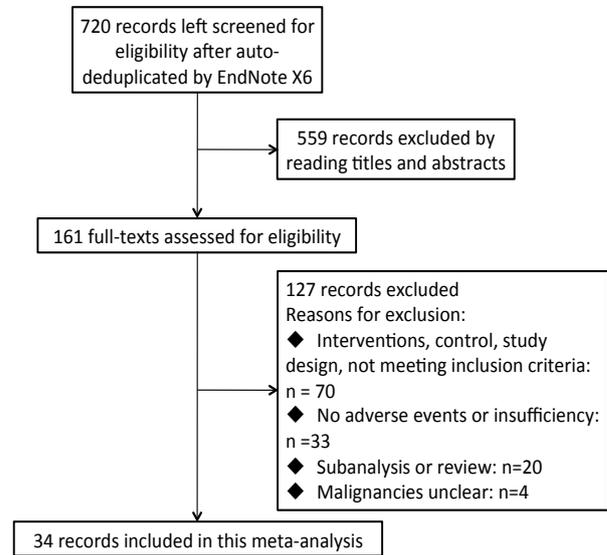


Figure 1. Flow Chart Illustrating the Process of Studies Selection

Table 1. Risk of Total Malignancies in Each Trial Per Protocol Model

First author	Year	Country	Type of TNF- α antagonists	No. of malignancies/ No. of participants randomized		Odds Ratio (95%CI)	Continuity correction* OR (95%CI)
				Treatment	Control		
Moreland	1999	USA	ETA	1/59	0/26	1.36(0.05,34.47)	1.35(0.05,34.19)
Weinblatt	1999	USA	ETA	0/57	0/24	NE	0.43(0.01,21.98)
Bathon	2000	USA	ETA	3/193	2/202	1.58(0.26,9.55)	1.40(0.27,7.18)
Van der Heijde	2007	Netherlands	ETA	9/301	2/119	1.80(0.38,8.47)	1.53(0.37,6.25)
Emery	2008	UK	ETA	4/221	4/189	0.85(0.21,3.46)	0.85(0.35,2.08)
Takeuchi	2013	Japan	ETA	2/151	2/123	0.81(0.11,5.85)	0.81(0.14,4.77)
Maini	1998	UK	INF	0/21	0/6	NE	0.30(0.01,16.78)
Maini	2004	UK	INF	1/47	1/14	0.28(0.02,4.83)	0.29(0.03,3.02)
St Clair	2004	USA	INF	0/323	0/245	NE	0.76(0.01,38.40)
Quinn	2005	UK	INF	0/9	0/10	NE	1.11(0.02,61.37)
Schiff	2008	USA	INF	2/141	1/104	1.48(0.13,16.57)	1.24(0.16,9.52)
Keystone	2008	Canada	CZP	7/255	1/43	1.19(0.14,9.88)	0.86(0.14,5.08)
Fleischmann	2009	USA	CZP	0a/76	0/28	NE	0.37(0.01,19.26)
Smolen	2009	Austria	CZP	1/174	1/17	0.09(0.01,1.55)	0.10(0.01,1.02)
Choy	2012	UK	CZP	0/98	0/65	NE	0.67(0.01,33.92)
Weinblatt	2003	USA	ADA	0/50	0/18	NE	0.37(0.01,16.13)
Furst	2003	USA	ADA	1/290	0/288	2.90(0.12,73.69)	2.99(0.12,73.70)
Breedveld	2006	Netherlands	ADA	6/370	4/169	0.68(0.19,2.44)	0.66(0.19,2.21)
Kim	2007	USA	ADA	0/51	0/40	NE	0.79(0.02,40.49)
Miyasaka	2008	Japan	ADA	0/75	2/80	0.21(0.01,4.40)	0.23(0.01,5.03)
Bejarano	2008	UK	ADA	0/50	0/36	NE	0.72(0.01,37.30)
Detert	2013	Germany	ADA	0/82	3/73	0.12(0.01,2.40)	0.12(0.01,2.36)
Kavanaugh	2013	USA	ADA	2/466	0/460	4.96(0.24,103.53)	4.96(0.24,103.54)
Kay	2008	USA	GLM	1/29	0/21	2.26(0.09,58.32)	2.30(0.10,58.21)
Emery	2009	UK	GLM	1/150	2/150	0.50(0.04,5.54)	0.61(0.04,4.99)
Keystone	2010	Canada	GLM	1/109	1/84	0.77(0.05,12.47)	.80(0.05,12.60)
Tanaka	2012	Japan	GLM	0b/81	0/84	NE	1.04(0.02,52.88)
Hagashi	2013	Japan	GLM	0/8	0/6	NE	0.77(0.01,43.95)

Abbreviations: ETA, etanercept; INF, infliximab; CZP, certolizumab pegol; ADA, adalimumab; GLM, golimumab; NE, negative; CI, confidence interval; OR, Odds Ratio; No., number. *Continuity correction was conducted by adding a constant 0.5 to each cell; a. Two benign neoplasm (1 uterine fibroids and 1 benign parathyroid tumor) were not included; b. One neoplasm (thoracic vertebra tumor) was not included, because it was considered as "borderline" or low malignancy potential

weekly, since 25 mg biw or 50 mg weekly were approved doses, we considered 10 mg biw as low doses, and no high doses were administered; infliximab, dosages were 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, every 4 weeks (q4wk) or every 8 weeks (q8wk), as 3 mg/kg q8wk was approved doses, we considered 1 mg/kg q4wk as low doses and 3 mg/kg q4wk, 6 mg/kg q8wk, 10 mg/kg q4 or q8wks as high doses; certolizumab pegol, dosages were 200 mg, 400 mg, q2wk or q4wk, 400 mg q4wk and 200 mg q2wk were approved, so we considered 400 mg q2wk as high doses, and no low doses were administered; adalimumab, dosages were 20 mg, 40 mg, 80 mg, eow, 40mg eow was approved, so 20 mg eow and 80 mg eow were low and high doses, respectively; golimumab, dosages were 50 mg, 100 mg, q2wk or q4wk, as 50 q4wk was approved, 50 or 100 mg q2wk and 100 mg q4wk were considered as high doses, and no low doses were administered. In one trial (Weinblatt et al., 2013), patients treated with golimumab were administered intravenously 2 mg/kg every 8 weeks, which were excluded from the analysis for irregular route of administration; in this trial, 1 breast cancer was developed in treatment group.

Of the total 11741 patients, treatment groups including different doses were 7780, and 6252 completed the double-blind trials, on the other hands, control groups were 3961, with 2721 completion. No matter of doses, 71 malignancies were developed on TNF-α antagonists and 26 on placebo, and breast cancer was 10 vs 7.

Total malignancies and breast cancer

In PP analysis, there were no statistically significant increased risk of breast cancer (OR 0.65, 95%CI [0.22, 1.93]) and total malignancies (1.06[0.64, 1.75]) in RA patients with TNF-α antagonists therapy at approved doses (Table 1 and Table 3), the same as at low doses (OR 0.54, 95%CI [0.09, 3.13], OR 0.46, 95%CI [0.13, 1.56], respectively) and high doses (OR 1.61, 95%CI [0.30, 8.78], OR 1.88, 95%CI [0.89, 3.99], respectively) (Table 3). In mITT analysis, the risk of total malignancies at high doses seems to be increased (OR 2.39, 95%CI [1.13, 5.05]) (Table 3), while the breast cancer risk stills no significance (OR 1.74, 95%CI [0.32, 9.44]). Our outcome of total malignancies risk with high doses in mITT analysis is similar with Bongartz et al, (2009) (OR 4.3, 95%CI [1.6, 11.8]), but different with Moulis et al (Moulis et al., 2012)

Table 3. Risk of Breast Cancer and Total Malignancies at Different Doses in Both Models

Doses	Model	Total malignancies	Breast cancer
Low doses	mITT	0.53(0.16,1.80)	0.64(0.11,3.71)
	PP	0.46(0.13,1.56)	0.54(0.09,3.13)
Doses approved	mITT	1.30(0.80,2.14)	0.75(0.25,2.21)
	PP	1.06(0.64,1.75)	0.65(0.22,1.93)
High doses	mITT	2.39(1.13,5.05)	1.74(0.32,9.44)
	PP	1.88(0.89,3.99)	1.61(0.30,8.78)
All doses	mITT	1.37(0.87,2.17)	0.70(0.27,1.82)
	PP	1.12(0.70,1.78)	0.61(0.24,1.59)

Table 2. Risk of Total Malignancies in Each Trial in Modified Intention to Treat Model

First author	Year	Country	Type of TNF-α antagonists	No. of malignancies/No. of participants randomized		Odds Ratio (95%CI)	Continuity correction* OR (95%CI)
				Treatment	Control		
Moreland	1999	USA	ETA	1/78	0/80	3.12(0.13,77.66)	3.12(0.13,77.71)
Weinblatt	1999	USA	ETA	0/59	0/30	NE	0.51(0.01,26.50)
Bathon	2000	USA	ETA	3/207	2/217	1.58(0.26,9.56)	1.48(0.29,7.54)
Van der Heijde	2007	Netherlands	ETA	9/454	2/228	2.29(0.49,10.67)	1.93(0.48,7.85)
Emery	2008	UK	ETA	4/274	4/268	0.98(0.24,3.95)	0.98(0.26,3.64)
Takeuchi	2013	Japan	ETA	2/182	2/176	0.97(0.13,6.94)	0.97(0.17,5.65)
Maini	1998	UK	INF	0/29	0/14	NE	0.49(0.01,20.08)
Maini	2004	UK	INF	1/86	1/88	1.02(0.06,16.63)	1.02(0.10,10.03)
St Clair	2004	USA	INF	0/373	0/298	NE	0.80(0.02,40.41)
Quinn	2005	UK	INF	0/10	0/10	NE	1(0.02,55.26)
Schiff	2008	USA	INF	2/165	1/110	1.34(0.12,14.93)	1.12(0.15,8.58)
Keystone	2008	Canada	CZP	7/393	1/199	4.17(0.51,34.18)	2.57(0.44,14.94)
Fleischmann	2009	USA	CZP	0/111	0/109	NE	0.98(0.02,49.95)
Smolen	2009	Austria	CZP	1/246	1/127	0.51(0.03,8.29)	0.52(0.05,5.00)
Choy	2012	UK	CZP	0/126	0/121	NE	0.96(0.02,48.76)
Weinblatt	2003	USA	ADA	0/67	0/62	NE	0.93(0.02,47.37)
Furst D E	2003	USA	ADA	1/318	0/318	3.01(0.12,74.15)	3.01(0.12,74.14)
Breedveld	2006	Netherlands	ADA	6/541	4/257	0.71(0.20,2.54)	0.68(0.20,2.30)
Kim H Y	2007	USA	ADA	0/65	0/63	NE	0.97(0.02,49.60)
Miyasaka	2008	Japan	ADA	0/91	2/87	0.19(0.01,3.95)	0.18(0.01,3.95)
Bejarano	2008	UK	ADA	0/75	0/73	NE	0.97(0.02,49.75)
Detert	2013	Germany	ADA	0/87	3/85	0.13(0.01,2.65)	0.14(0.01,2.75)
Kavanaugh	2013	USA	ADA	2/525	0/517	4.94(0.24,103.20)	4.94(0.24,103.23)
Kay	2008	USA	GLM	1/35	0/35	3.09(0.12,78.41)	3.09(0.12,78.41)
Emery	2009	UK	GLM	1/159	2/160	0.50(0.04,5.57)	0.60(0.08,4.60)
Keystone	2010	Canada	GLM	1/89	1/133	1.50(0.09,24.30)	1.50(0.15,14.61)
Tanaka	2012	Japan	GLM	0/86	0/88	NE	1.02(0.02,52.14)
Hagashi	2013	Japan	GLM	0/6	0/8	NE	1.31(0.02,75.11)

Abbreviations: ETA, etanercept; INF, infliximab; CZP, certolizumab pegol; ADA, adalimumab; GLM, golimumab; NE, negative; CI, confidence interval; OR, Odds Ratio; No., number. *Continuity correction was conducted by adding a constant 0.5 to each cell; a. Two benign neoplasm (1 uterine fibroids and 1 benign parathyroid tumor) were not included; b. One neoplasm(thoracic vertebra tumor) was not included, because it was considered as "borderline" or low malignancy potential

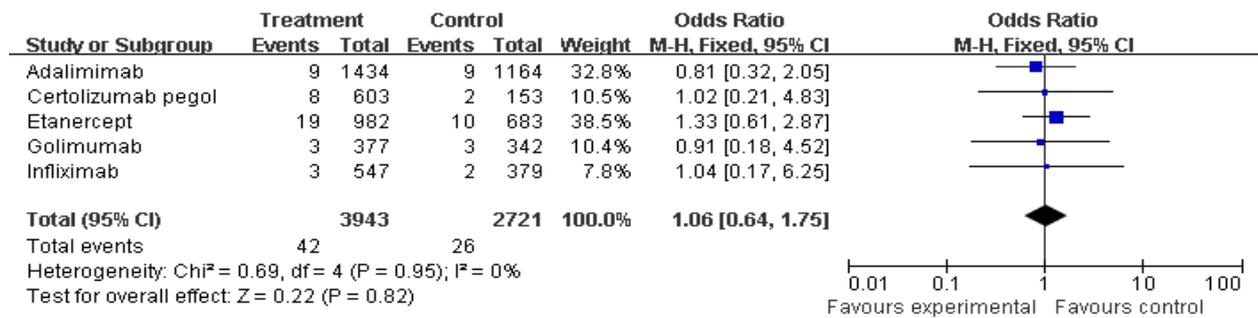


Figure 2. Per Protocol Meta-Analysis of Total Malignancies Risk of TNF- α Antagonists Therapy Used at Doses Approved in RA Patients

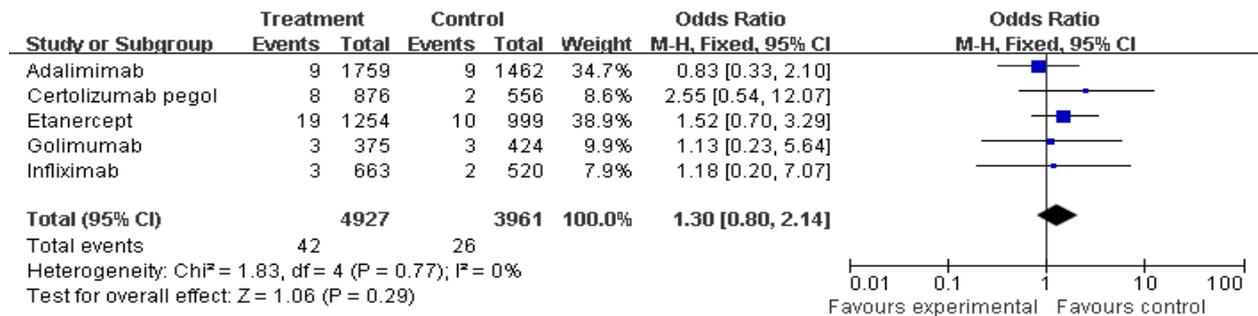


Figure 3. Modified Intention to Treat Meta-Analysis of Total Malignancies Risk of TNF- α Antagonists Therapy Used at Doses Approved in RA Patients

(OR 1.56, 95%CI [0.78, 3.12]). As to the two models, modified intention to treat model analysis led to higher estimation than per protocol model analysis. Egger's test did not show a publication bias, and no heterogeneity was found ($I^2 = 0$) (Figure 2 and Figure 3).

There were no significant differences among the five drugs at approved doses about risk of malignancies ($p=0.82$ in PP, $p=0.29$ in mITT) and breast cancer ($p=0.30$, $p=0.60$, respectively).

Discussion

A recent study (Tripsianis et al., 2013) demonstrated that patients with primary breast cancer over-expressed TNF- α and anti-TNF- α might be effective. However, the safety of anti-TNF- α therapy was seldom investigated. We conducted this meta-analysis with both mITT and PP models to assess the breast cancer and total malignancies risk of the five TNF- α antagonists therapy in RA patients at different doses. We pooled the results from 28 RCTs with 11741 patients for therapy duration for more than 24 weeks. There was no statistically significant increased risk of breast cancer in both models by means of different doses of TNF- α antagonists vs placebo or MTX. In PP analysis, increased risk of total malignancies was not significant, but in mITT analysis, risk of malignancies with high doses TNF- α antagonists therapy notably increased.

There were several previously published reports reviewing the risk of malignancies, including one for lymphoma and one for non-melanoma skin cancer, in RA patients with TNF- α antagonists therapy. However, there was only one meta-analysis (Moulis et al., 2012), to our knowledge, conducting the per protocol analysis which was considered as more eligible for safety analyses for all the patients included to analysis exposing to the

drugs all the study times. In that meta-analysis, they included 33 RCTs to assess the cancer risk of the five TNF- α antagonists therapy with RA patients in PP model comparing with mITT. Of the 33 RCTs, 4 were excluded during our study selection, because 3 RCTs' (Abe et al., 2006; Weisman et al., 2007; Chen et al., 2009) double-blind periods less than 24 weeks, and 1 RCT (Taylor et al., 2004) did not mention adverse events, in which they considered the cancer as 0. Our outcomes of total malignancies risk were similar to their in PP model, but in mITT model, we found a significant increased risk of total malignancies at high drugs doses, while their analysis showed no significance. It may result from the different inclusion criterion and deviation of data extraction. And the malignancies we considered not included the benign neoplasm developed in two RCTs (Fleischmann et al., 2009; Tanaka et al., 2012).

To avoid the diagnosis bias, we excluded open-label trials or periods of open-label extension following up double-blind, in which many patients developed breast cancer after therapy (Kremer et al., 2003; Klareskog et al., 2006; Van der Heijde et al., 2010; Weinblatt et al., 2011; Keystone et al., 2012; Emery et al., 2013; Keystone et al., 2013; Keystone et al., 2013), and patients in one trial excluded developed breast cancer, of which we could not obtain the details. For those reason, it may result in underestimation of the risk of breast cancer.

Our study has several limitations. Four trials were excluded grudgingly for the publications not providing enough details in their reports. AS the language limited, we included records only in English, which led to underestimation in our results. But no evidence of publications bias was detected in our analysis. Some studies conducted open-label trials immediately after patients completed the double-blind periods, we did not

include the malignancies developed in the follow-up open-label trials. It was annoying that sometimes data from RCTs were not always generalizable, dosages of the drugs administered were always mutative during the studies, which led to the comparison irrisoruous and deviation of data extraction.

Overall, we do not find a increased risk of total malignancies and breast cancer in RA patients undergoing TNF- α antagonists at approved doses for at least 24 weeks. It seems safe for RA patients to receive the TNF- α antagonists therapy at doses in line with New Drug Approval. However, it can't be ignored that more patients developed malignancies with TNF- α antagonists therapy compared with patients with placebo or MTX, in spite of no statistical significance. More strait clinical trials and long-term follow-up are needed, and both models should be applied.

Acknowledgements

We appreciate the financial support by the National Natural Science Funds (no. 30901308), Wuhan key scientific and technological project (2014060101010045), the Dawn Project for Young Scientists of Wuhan City (no. 20105023106), and the Hubei Province Natural Science Funds of (no. 2013CFB233 and no. 2013CFB235). In addition, We deeply thank to all the people who gave us good suggestions and help.

References

Arnett FC (1989). Revised criteria for the classification of rheumatoid arthritis. *Bull Rheum Dis*, **38**, 1-6.

Abe T, Takeuchi T, Miyasaka N, et al (2006). A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol*, **33**, 37-44.

Aaltonen KJ, Virkki LM, Malmivaara A, et al (2012). Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PLoS One*, **7**, 30275.

Bathon JM, Martin RW, Fleischmann RM, et al (2000). A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *New Engl J Med*, **343**, 1586-93.

Breedveld FC, Weisman MH, Kavanaugh AF, et al (2006). The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*, **54**, 26-37.

Bongartz T, Sutton AJ, Sweeting MJ, et al (2006). Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*, **295**, 2275-85.

Bejarano V, Quinn M, Conaghan PG, et al (2008). Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. *Arthritis Rheum*, **59**, 1467-74.

Bongartz T, Warren FC, Mines D, et al (2009). Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Ann Rheum Dis*, **68**, 1177-83.

Balkwill F (2009). Tumour necrosis factor and cancer. *Nat Rev Cancer*, **9**, 361-71.

Chen DY, Chou SJ, Hsieh TY, et al (2009). Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. *J Formos Med Assoc*, **108**, 310-9.

Choy E, McKenna F, Vencovsky J, et al (2012). Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford, England)*, **51**, 1226-34.

Detert J, Bastian H, Listing J, et al (2013). Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis*, **72**, 844-50.

Emery P, Breedveld FC, Hall S, et al (2008). Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet*, **372**, 375-82.

Emery P, Fleischmann RM, Moreland LW, et al (2009). Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum*, **60**, 2272-83.

Emery P, Fleischmann RM, Doyle MK, et al (2013). Golimumab, a human anti-TNF monoclonal antibody, injected subcutaneously every 4 weeks in MTX-naive patients with active rheumatoid arthritis: 1-year and 2-year clinical, radiological, and physical function findings of a Phase 3, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Care Res*.

Furst DE, Schiff MH, Fleischmann RM, et al (2003). Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*, **30**, 2563-71.

Fleischmann R, Vencovsky J, van Vollenhoven RF, et al (2009). Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis*, **68**, 805-11.

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al (2005). Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*, **52**, 3381-90.

Genta M S, Kardes H, Gabay C (2006). Clinical evaluation of a cohort of patients with rheumatoid arthritis treated with anti-TNF-alpha in the community. *Joint Bone Spine*, **73**, 51-6.

Higgins JPT, Green S, Collaboration C (2008). *Cochrane Handbook for Systematic Reviews of interventions*. Wiley Online Library.

Hayashi M, Kobayakawa T, Takanashi T, et al (2013). Golimumab reduces disease activity of rheumatoid arthritis for 1 year and strongly inhibits radiographic progression in Japanese patients: partial but detailed results of the GO-FORTH and GO-MONO studies. *Clin Rheumatol*, **32**, 961-7.

Jadad AR, Moore RA, Carroll D, et al (1996). Assessing the

- quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*, **17**, 1-12.
- J Sweeting M, J Sutton A, C Lambert P (2004). What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*, **23**, 1351-75.
- Kremer JM, Weinblatt ME, Bankhurst AD, et al (2003). Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. *Arthritis Rheum*, **48**, 1493-9.
- Klareskog L, van der Heijde D, de Jager JP, et al (2004). Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet*, **363**, 675-81.
- Keystone EC, Kavanaugh AF, Sharp JT, et al (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum*, **50**, 1400-11.
- Klareskog L, Gaubitz M, Rodriguez-Valverde V, et al (2006). A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs. *Ann Rheum Dis*, **65**, 1578-84.
- Kim H Y, Lee S K, Song Y W, et al (2007). A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR J Rheumatol*, **10**, 9-16.
- Kay J, Matteson EL, Dasgupta B, et al (2008). Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum*, **58**, 964-75.
- Keystone E, Heijde D, Mason D Jr, et al (2008). Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum*, **58**, 3319-29.
- Keystone EC, Genovese MC, Klareskog L, et al (2009). Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Arthritis Rheum*, **68**, 789-96.
- Keystone E, Genovese MC, Klareskog L, et al (2010). Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Arthritis Rheum*, **69**, 1129-35.
- Kremer J, Ritchlin C, Mendelsohn A, et al (2010). Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum*, **62**, 917-28.
- Keystone EC, Combe B, Smolen J, et al (2012). Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. *Rheumatology (Oxford, England)*, **51**, 1628-38.
- Keystone EC, Genovese MC, Hall S, et al (2013). Golimumab in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: Results Through 2 Years of the GO-FORWARD Study Extension. *J Rheumatol*, **40**, 1097-103.
- Kavanaugh A, Fleischmann RM, Emery P, et al (2013). Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis*, **72**, 64-71.
- Keystone EC, van der Heijde D, Kavanaugh A, et al (2013). Clinical, Functional, and Radiographic Benefits of Longterm Adalimumab Plus Methotrexate: Final 10-year Data in Longstanding Rheumatoid Arthritis. *J Rheumatol*, **40**, 1487-97.
- Lipsky PE, van der Heijde DM, St Clair EW, et al (2000). Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *The New England J Med*, **343**, 1594-602.
- Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al (2012). Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA*, **308**, 898-908.
- Moreland LW, Schiff MH, Baumgartner SW, et al (1999). Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med*, **130**, 478-86.
- Maini RN, Breedveld FC, Kalden JR, et al (1998). Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*, **41**, 1552-63.
- Moher D, Cook Dj, Eastwood S, et al (1999). Improving the quality of reports of meta-analysis of randomised controlled trial: the QUOROM statement. Quality of Reporting of Meta-analysis. *Lancet*, **354**, 1896-900.
- Maini R, St Clair EW, Breedveld F, et al (1999). Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*, **354**, 1932-39.
- Madhusudan S, Foster M, Muthuramalingam S R, et al (2004). A phase II study of etanercept (Enbrel), a tumor necrosis factor α inhibitor in patients with metastatic breast cancer. *Clin Cancer Res*, **10**, 6528-34.
- Maini RN, Breedveld FC, Kalden JR, et al (2004). Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*, **50**, 1051-65.
- Miyasaka N (2008). Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. *Mod Rheumatol*, **18**, 252-62.
- Moreland LW, O'Dell JR, Paulus HE, et al (2012). A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum*, **64**, 2824-35.
- Moulis G, Sommet A, Bene J, et al (2012). Cancer risk of anti-TNF-alpha at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. *PLoS One*, **7**, 48991.
- Ni XJ, Xia TS, Zhao YC, et al (2012). Postmenopausal Hormone Therapy is Associated with in Situ Breast Cancer Risk. *Asian Pac J Cancer Prev*, **13**, 3917-25.
- P LEB, Mouterde G, Barnetche T, Morel J, Combe B (2012). Short-term risk of total malignancy and nonmelanoma skin cancers with certolizumab and golimumab in patients with rheumatoid arthritis: metaanalysis of randomized controlled trials. *J Rheumatol*, **39**, 712-5.
- Quinn MA, Conaghan PG, O'Connor PJ, et al (2005). Very early

- treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*, **52**, 27-35.
- St Clair EW, van der Heijde DM, Smolen JS, et al (2004). Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum*, **50**, 3432-43.
- Schiff M, Keiserman M, Codding C, et al (2008). Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis*, **67**, 1096-103.
- Smolen J, Landewe RB, Mease P, et al (2009). Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis*, **68**, 797-804.
- Singh JA, Christensen R, Wells GA, et al (2009). A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ*, **181**, 787-96.
- Taylor PC, Steuer A, Gruber J, et al (2004). Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum*, **50**, 1107-16.
- Tanaka Y, Harigai M, Takeuchi T, et al (2012). Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Ann Rheum Dis*, **71**, 817-24.
- Takeuchi T, Miyasaka N, Zang C, et al (2013). A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. *Mod Rheumatol*, **23**, 623-33.
- Tripsianis G, Papadopoulou E, Romanidis K, et al (2013). overall survival and clinicopathological characteristics of patients with breast cancer in relation to the expression pattern of HER-2, IL-6, TNF- α and TGF- β 1. *Asian Pac J Cancer Prev*, **14**, 6813-20.
- Van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al (2006). Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum*, **54**, 1063-74.
- Van der Heijde D, Klareskog L, Landewe R, et al (2007). Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum*, **56**, 3928-39.
- Van der Heijde D, Breedveld FC, Kavanaugh A, et al (2010). Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. *J Rheumatol*, **37**, 2237-46.
- Weinblatt ME, Kremer JM, Bankhurst AD, et al (1999). A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *New Engl J Med*, **340**, 253-9.
- Weinblatt ME, Keystone EC, Furst DE, et al (2003). Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*, **48**, 35-45.
- Weisman MH, Paulus HE, Burch FX, et al (2007). A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology (Oxford, England)*, **46**, 1122-5.
- Weinblatt ME, Bathon JM, Kremer JM, et al (2011). Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. *Arthritis Care Res*, **63**, 373-82.
- Wiens A, Correr CJ, Venson R, et al (2009). A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. *Clin Rheumatol*, **28**, 1365-73.
- Wong AK, Kerkoutian S, Said J, Rashidi H, Pullarkat ST (2012). Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. *Clin Rheumatol*, **31**, 631-6.
- Weinblatt ME, Fleischmann R, Huizinga TW, et al (2012). Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology*, **51**, 2204-14.
- Weinblatt ME, Bingham CO, Mendelsohn AM, et al (2013). Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. *Ann Rheum Dis*, **72**, 381-9.
- Yu M, Zhou X, Niu L, et al (2013). Targeting Transmembrane TNF- α Suppresses Breast Cancer Growth. *Cancer Res*, **73**, 4061-74.