Safety of long-term anti-TNF use, with respect to malignancy, in a national cohort of people with rheumatoid arthritis

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

2012

Louise Kate Mercer

School of Medicine

Contents

List of tables

List of figures

Abstract

The University of Manchester

Louise Kate Mercer

Doctor of Philosophy

Safety of long-term anti-TNF use, with respect to malignancy, in a national cohort of people with rheumatoid arthritis

November 2012

Aim

The broad aim of this thesis was to explore the risk of malignancy in people with rheumatoid arthritis (RA), treated with anti-tumour necrosis factor (TNF) drugs.

Methods

This thesis used data from patients with RA registered with the British Society of Rheumatology Biologics Register-RA. The risk of cancer in biologic-naive patients treated with traditional disease modifying drugs (nbDMARD) was compared to that in the general population by calculating standardised incidence ratios (SIR). The influence of anti-TNF on cancer risk was then explored by comparing the risk in the anti-TNF cohort to that in the nbDMARD cohort using Cox proportional hazard models.

Results

The risk of cancer was increased in the nbDMARD cohort by 28% compared to the general population (SIR 1.28, 95% confidence interval (CI) 1.10, 1.48). Risks of lung cancer (SIR 2.39, 95% CI 1.75, 3.19), Hodgkin lymphoma (SIR 12.82, 95% CI 4.16, 29.92) and Non-Hodgkin Lymphoma (SIR 3.12, 95% CI 1.79, 5.07) were increased compared to the general population and both prostate cancer and cancers of the female genital organs reduced; SIRs 0.35 (95% CI 0.11, 0.82) and 0.35 (95% CI 0.10, 0.90) respectively. There was no difference in the risk of cancer in patients treated with anti-TNF compared to nbDMARD, after adjusting for differences in baseline characteristics; Hazard ratio for lymphoma: 1.00 (95% CI 0.49, 2.05); cancers of the solid organs: 0.83 (95% CI 0.64, 1.07); and keratinocyte skin cancer: basal cell carcinoma 1.06 (95% CI 0.64, 1.75), squamous cell carcinoma 1.62 (95% CI 0.44, 5.90).

Conclusions

Subjects with RA, treated with nbDMARD were at increased risk of cancer compared to the general population. In particular, lung cancer, lymphoma and KSC were increased. Treatment with the TNF inhibitors ETA, INF or ADA was not associated with a difference in relative risk of lymphoma, solid cancer or skin cancers when compared to nbDMARD.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this university of any other university or other institute of learning.

Copyright Statement

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and she has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made **only** in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://www.campus.manchester.ac.uk/medicalibrary/policies/intellectual-property.pdf), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations (see http://www.manchester.ac.uk/library/ aboutus/regulations) and in The University's policy on Presentation of Theses.

Acknowledgements

Thank you to the Medical Research Council for funding this PhD.

I am very grateful to Dr Kimme Hyrich and Professor Deborah Symmons for their wisdom, guidance and dedicated supervision of this PhD. Thank you to Dr Richard Byers for his enthusiastic help with the lymphoma histology work and to Professor Chris Griffiths for his advice and support as advisor. I would like to thank all members of the BSRBR team in Manchester. Special thanks go to Lesley Albutt, Yvonne King and Ursula Pattinson for helping me to collect additional data for the analysis of lymphoma histology. Thank you to Katy Mowbray and Kath Watson for their help with the amendment to the ethical approval of the BSRBR study, necessary for the lymphoma analysis. Many thanks to Mark Lunt, without whom I would not have developed the skills to perform the statistical analyses included in this thesis. Thank you to Will Dixon for his ideas and encouragement. Special thanks go to my colleagues James Galloway and Audrey Low for their friendship and for generously sharing their knowledge and ideas about the analyses in this thesis. Thank you to all the patients and Rheumatology teams who have participated in the study.

Finally, I would like to thank my family, who have grown in size during the course of this PhD, for their endless support. I thank Mark and George, in particular, for their love and patience.

Preface

I graduated from the University of Liverpool with an MBChB with honours in 2001. I was appointed as a Specialist Registrar in Rheumatology in Manchester in 2005 and my first post was working at Hope Hospital alongside Kimme Hyrich, sparking my interest in the British Society for Rheumatology Biologics Register. That year I enrolled in an MSc in Clinical Rheumatology, which I completed in 2007. In 2008 I was awarded a three-year clinical training fellowship from the Medical Research Council to develop skills in epidemiological research whilst studying the influence of anti-TNF on risk of cancer within the BSRBR. The work in this thesis is the result of that fellowship.

Role of the candidate in this PhD

I took a leading role in all aspects of the work described in this thesis. Specifically, in

- Establishing the research questions
- Applying for funding
- Designing the Events of Special Interest forms to collect data on cancer and lymphoproliferative malignancies
- Planning the analyses
- Inputting and extracting data
- Data cleaning
- Validation of outcomes
- Performing the statistical analyses
- Applying for ethical approval for the histology work included in the lymphoma chapter
- Writing the letters and patient information leaflet for the lymphoma histology sub-study
- Working with Rheumatology and Pathology departments to facilitate the loan of lymphoma tissue blocks
- Interpreting the study findings
- Presenting the findings at international conferences and writing papers
- Writing of this thesis

Publications

The publications in the following list have arisen as a result of this fellowship.

Mercer LK, Davies, R, Galloway JB, Low, A, Lunt M, Dixon WG, Watson KD, Symmons DPM and Hyrich KL on behalf of the British Society for Rheumatology Biologics Register Control Centre Consortium (2013). Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the general population. *Rheumatology*, 52(1), 91-98.

Galloway JB , **Mercer LK**, Moseley A, Dixon WG, Ustianowski A, Helbert M, Watson KD, Lunt M, BSRBR Control Centre Consortium, Hyrich, KL and Symmons, DPM on behalf of the BSRBR (2012). Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*, [Epub ahead of print].

Mercer LK, Low ASL, Galloway JB, Watson KD, Lunt M, BSRBR Control Centre Consortium, Symmons DPM and Hyrich KL on behalf of the BSRBR (2012). *Ann Rheum Dis*, [Epub ahead of print].

Mercer LK, Green A, Galloway JB, Davies R, Lunt M, Dixon WG, Watson KD, BSRBR Control Centre Consortium, Symmons DPM and Hyrich KL on behalf of the BSRBR (2012). The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*, 71(6), 869-874.

Mercer LK, Dixon WG (2011). Looking beyond incidence in the relationship between anti-TNF therapy and malignancy. *Arthritis Rheum*, 63(7), 1773-1775.

Galloway JB, Hyrich KL, **Mercer LK**, Dixon WG, Watson KD, Lunt M, BSRBR Control Centre Consortium and Symmons DPM on behalf of the BSRBR (2011). The risk of serious infections in patients receiving anakinra for rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology*, 50(7), 1341-1342.

Galloway JB, Hyrich KL, **Mercer LK**, Dixon WG, Ustianowski AP, Helbert M, Watson KD, Lunt M, BSRBR Control Centre Consortium and Symmons DPM on behalf of the BSRBR (2011). Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*, 70(10), 1810-1814.

Galloway JB, Hyrich KL, **Mercer LK**, Dixon WG, Ustianowski AP, Watson KD, Lunt M, BSRBR Control Centre Consortium, Symmons DPM on behalf of the BSRBR (2011). Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)*, 50(1), 124-131.

Dixon WG, Watson KD, Lunt M, **Mercer LK**, BSRBR Control Centre Consortium, Hyrich KL and Symmons DPM on behalf of the BSRBR (2010). Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: Results from the British Society for Rheumatology Biologics Register. *Arthritis Care Res (Hoboken)*, 62(6), 755-63.

Hyrich KL and **Mercer LK**. Rheumatoid arthritis and malignancy. CML Rheumatology 2009; 28(2): 25-34

List of abbreviations

ACR	American College for Rheumatology
ADA	Adalimumab
AIDS	Acquired immune deficiency syndrome
ARTIS	Anti-Rheumatic Therapies in Sweden
ATTRACT	Anti-TNFα trial in RA with concomitant therapy
AZA	Azathioprine
BCC	Basal cell carcinoma
BSR	British Society for Rheumatology
BSRBR-RA	British Society for Rheumatology Biologics Register Rheumatoid Arthritis Study
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CLL	Chronic lymphocytic leukaemia
CSA	Ciclosporin
CYC	Cyclophosphamide
DAS28	Disease activity score
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DP	Deciles of propensity score
EBV	Epstein-Barr virus
ERA	Early rheumatoid arthritis
ESI	Events of special interest
ETA	Etanercept
EULAR	European League Against Rheumatism
FDA	United States Food and Drug Administration
FL	Follicular lymphoma
HAQ	Health Assessment Questionnaire
HL	Hodgkin lymphoma
HR	Hazard ratio
ICD	International Classification of Diseases
INF	Infliximab
IP	Inflammatory polyarthritis

IPTW	Inverse probability of treatment weighting
IQR	Inter-quartile range
IRR	Incidence rate ratio
KSC	Keratinocyte skin cancer
LOS	Longitudinal observational study
LPM	Lymphoproliferative malignancy
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
MNAR	Missing not at random
MPM	Myeloproliferative malignancy
MTX	Methotrexate
nbDMARD	Non-biologic disease-modifying anti-rheumatic drug
NDB	National Data Bank
NICE	National Institute for Health and Clinical Excellence
NHL	Non-Hodgkin lymphoma
NHS IC	NHS Information Centre
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
ONS	Office for National Statistics
PH	Proportional hazards
PS	Propensity score
Pyrs	Person years
RA	Rheumatoid arthritis
RABBIT	Rheumatoid Arthritis – Observation of Biologic Therapy
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
SE	Shared epitope
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SSATG	South Swedish Arthritis Treatment Group

SLE	Systemic lupus erythematosus
TNF	Tumour necrosis factor alpha
VAS	Visual analogue scale
WHO	World Health Organisation

1. Introduction

This chapter will give an overview of the treatment of rheumatoid arthritis and the risk of cancer associated with the disease. In addition, a systematic literature review on the influence of anti-TNF, if any, on the incidence of cancer in rheumatoid arthritis will be presented.

1 Introduction

1.1 Rheumatoid arthritis and its treatment in the pre-biologic era

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterised by the involvement of synovial joints. Synovial inflammation leads to pain, swelling and stiffness in the joints. This, along with extra-articular manifestations of the disease can lead to significant functional disability [1], work disability [2, 3] and mortality [4]. The aim of treating RA is to both resolve the symptoms of pain and stiffness and to prevent RA-related morbidity and mortality in the longer term. No specific treatments were available prior to the 20th century. Since then therapies that suppress disease activity, termed disease modifying anti-rheumatic drugs, have been discovered and used (Table 1-1) [5].

Table 1-1 History of nbDMARD use in the management of RA [5]

nbDMARD	Mechanism of action	Date first used for RA
Gold	Uncertain	1935
Antimalarials e.g. hydroxychloroquine	Uncertain	1951
Penicillamine	Uncertain	1960s
Sulphasalazine	Uncertain; Sulphapyridine (rather than 5-aminosalicyclic acid) is the active metabolite.	1970s
Azathioprine	Synthetic purine analogue	1970s
Cyclophosphamide	Mainly used in extra-articular RA; little effect in synovium	1970s
Methotrexate	Uncertain; Dihydrofolate reductase inhibitor	1980s
Ciclosporin	Suppresses T cells	1990s
Leflunomide	Dihydro-orotate dehydrogenase inhibitor (involved in pyrimidine synthesis)	1998

Although the mechanism of action of most of these drugs in RA remains unknown, many of them function through general suppression of the immune system. In this thesis, such drugs will be referred to as non-biologic disease modifying anti-rheumatic drugs (nbDMARD) to distinguish them from the newer biologic agents. In addition, corticosteroids

were first used in the treatment of RA in the mid-20th century, and remain an important treatment option for patients with RA. Each of the nbDMARDs take at least 1-3 months to work after starting treatment and efficacy for each is unpredictable and frequently sub-optimal. Most are also associated with a range of potential toxicities. However, methotrexate (MTX) is considered currently to be the gold-standard nbDMARD and is typically used first, with or without other nbDMARDs, in the management of newly diagnosed RA [6].

1.2 Tumour necrosis factor

In the mid 1990's the treatment options for RA underwent a fundamental shift, away from general immunosuppressive agents towards an approach which targeted specific components of the inflammatory pathway. The first treatments against RA in this class of drugs, known collectively as biologic agents, were the inhibitors of tumour necrosis factor-alpha (TNF) [7-9]. Tumour necrosis factor is an important cytokine, with roles in inflammation, immunity and tumour surveillance. It is predominantly produced by macrophages. It has a pivotal role in the inflammation associated with RA by co-ordinating the release of a number of pro-inflammatory cytokines including IL-1, IL-6, IL-8 and GM-CSF [10]. The result of this is synoviocyte proliferation, recruitment and activation of inflammatory cells (neutrophils, macrophages and lymphocytes), neoangiogenesis, and joint destruction [11]. During the acute phase response TNF also acts on distant sites, such as the brain, inducing hyperthermia [11]. The effects of TNF can be both beneficial, for example in preventing intracellular infection [12], and harmful in the case of profound sepsis [11].

1.2.1 Anti-TNF therapy in the treatment of RA

Etanercept (ETA) was the first anti-TNF drug to be approved by the US Food and Drug Administration (FDA) in 1998, closely followed by infliximab (INF) in 1999 [13, 14]. This followed randomised controlled trials (RCT) that showed these drugs to be highly effective in treating patients in combination with nbDMARD [15, 16]. Anti-TNF drugs were approved in Britain by the National Institute for Health and Clinical Excellence (NICE) for treating severe RA in 2002 [17]. Five drugs are currently approved; the monoclonal antibodies against TNF: INF, adalimumab (ADA) and golimumab; a pegylated Fab' fragment of a

monoclonal antibody: certolizumab pegol; as well as the soluble TNF receptor fusion protein: ETA. All five drugs bind to TNF but ETA also neutralises lymphotoxin α. This thesis will focus on the first three of these drugs to be approved for use in the UK, namely ETA, INF and ADA, for which the most clinical experience exists.

1.2.2 Role of TNF in tumour surveillance

Tumour necrosis factor has paradoxical roles in the development and progression of malignancy. The potential for TNF to treat cancer was first utilised more than a century ago by William Coley, who had some success using a mixture of *Streptococcus pyogenes* and *Serratia marescens* to treat patients with sarcoma, carcinoma and lymphoma [18]. TNF has subsequently been isolated as the key mediator of this effect, and hence the name 'tumour necrosis factor' [19]. Indeed high dose, locally administered TNF has been shown to have a powerful anti-neoplastic effect against melanoma and sarcoma [20-22].

Conversely, chronic TNF production, a characteristic of chronic inflammatory diseases including RA, can promote tumour growth [23]. Evidence for the tumour promoting potential of TNF comes from mouse models in which mice lacking TNF or its receptors have shown resistance to skin and liver cancers [24, 25]. Furthermore, *in* vivo mouse studies of mice with pancreatic cancer have demonstrated reduced tumour growth and liver metastases following treatment with the anti-TNF drugs INF and ETA [26]. In humans, TNF acts as a tumour promoter in a number of ways; by up-regulating production of nitric oxide leading to deoxyribonucleic acid (DNA) mutations [27]; acting as an autocrine growth signal [28]; promoting angiogenesis [29]; increasing tumour cell invasion via induction of matrix metalloproteinases [30]; and inducing resistance to cytotoxic therapy [31].

Human studies using TNF blockers to treat malignancies have been conducted. Two phase II trials of INF in renal cell carcinoma, that were reported together, demonstrated that high circulating levels of TNF and other cytokines were associated with survival less than 12 months and that a proportion of patients achieved partial response or stable disease in response to INF [32]. Following administration of INF to 41 patients with locally advanced metastatic solid cancer, disease was stabilised in seven patients and none had accelerated

progression [33]. Interestingly, none of the seven patients whose disease stabilised had detectable plasma levels of plasma TNF at baseline where as 17 of the 34 patients who progressed did have detectable levels of TNF [33]. The effect of anti-TNF on progression of haematological malignancies has not been widely studied and remains uncertain. Twenty-five patients (9 with myelofibrosis, 8 with chronic lymphocytic leukaemia (CLL), 5 with Philadelphia negative myeloproliferative disease and 3 with hairy cell leukaemia) treated with ETA had no response [34] where as in a phase I/II study ETN has been shown to be a promising adjuvant to rituximab in the treatment of certain types of CLL [35].

Based on our current knowledge, the relationship between TNF inhibitors and cancers (both existing tumours and the risk of future malignancy) remains unknown. The use of TNF inhibitors in RA has been coupled with concerns they may cause cancer, by blocking the protective effect of TNF [36-38]. Conversely, since subjects with RA carry an increased risk of certain malignancies, including lymphoma and lung cancer (see sections 1.3.3 and 1.3.6.1), it is plausible that through suppressing inflammation anti-TNF may reduce the risk of cancer. The influence of anti-TNF on cancer risk might differ between the drugs and in particular for ETA, since lymphotoxin α plays a part in tumour surveillance independent of TNF [39]. There may also be a differential effect between certain cancers. For example, one may expect to see an increase in cancers associated with immunosuppression, such as Keratinocyte skin cancers (KSC), but a reduction in lymphomas that are related to chronic inflammation.

1.3 Malignancies in rheumatoid arthritis

Prior to studying the risk of a new treatment on cancer risk in a chronic condition, such as RA, it is important to understand the background risk of cancer prior to the introduction of therapy. This next section provides an overview of the literature of cancer and rheumatoid arthritis in patients who have not received treatment with biologic therapies.

1.3.1 Overall risk (all cancer sites)

Following conflicting reports of cancer risk in RA, Isomaki *et al.* published a retrospective study of cancer risk in 46,101 patients with RA compared to non-RA controls, identified from the Finnish Social Insurance Institution's Population Data Register, in 1978 [40]. They found a very small increased incidence of malignancy when looking at all subtypes of cancer together as well as an increase in respiratory cancers in men [40]. Subsequently several studies from around the world have examined the association between RA and cancer (Table 1-2). Eight of these studies were based on population databases and eight were clinic-based cohorts of patients with RA. All studies excluded cancers occurring prior to the diagnosis of RA from the analysis. Gridley also excluded cancers and follow up during the first 60 days of the study [41], Thomas during the first three months [42], and Askling, Cibere and Mellemkjaer during the first year [43-45].

In these studies the standardised incidence ratio (SIR) varied, with some studies showing a modest increased risk of cancer compared to the general population of around 10 to 30% for all cancers [43, 45-50], but others showing no increase [41, 44, 51-54]. Although the magnitude of increased risk appears to be greatest for lymphoma and leukaemia (reviewed in section 1.3.6), these cancers are uncommon and there were no consistent differences in overall cancer risk between studies that included or excluded these cancers. A meta-analysis of sixteen observational cohorts published in 2008 reported a modest increased risk of cancer in people with RA (SIR 1.05, 95% confidence interval [CI] 1.01, 1.09) [55]. This meta-analysis did include two cohorts of patients treated with anti-TNF drugs.

The disadvantage of looking at all malignancies as a combined end-point is that there appears to be considerable variability in risk between different subtypes of cancer. Several studies have shown an increased risk in skin cancer [43, 45, 47, 50] and lung cancer [40, 42, 43, 45, 47, 49, 50, 52]. Conversely, a reduced risk of breast [41, 43, 45] and colorectal cancers has repeatedly been reported [40-45, 47, 50]. The 2008 meta-analysis of observational studies confirmed the divergent directions of risk; SIR for lung cancer 1.63 (95% CI 1.43, 1.87); breast cancer 0.84 (95% CI 0.79, 0.90) and colorectal cancer 0.77 (95% CI 0.65, 0.90) [55].

Table 1-2 SIR of solid tumours in biologic naïve RA patients

Study	No of subjects (person years)	Methodology	SIR all cancer sites (95% CI)	SIR lung (95% CI)	SIR breast (95% CI)	SIR prostate (95% CI)	SIR colorectal (95% CI)	SIR KSC (95% CI)
Population-based studies								
Isomäki, Finland 1978 [40][1]	46101 (213,991)	Population based	1.06 (1.0-1.1)	1.25 (1.1-1.4)[2]	1.03 (0.9-1.2)	-	0.75 (0.6-0.9)	1.07 NS[3]
Gridley, Sweden 1993 [41]	11683 (101,000)	Hospital admissions database for RA	0.95 (0.9-1.0)	1.31 (1.0-1.7)	0.79 (0.6-1.0)	1.2 (0.9-1.4)	0.63 (0.5-0.9)	1.17 (0.8-1.7)
Mellemkjaer, Denmark 1996 [45]	20699 (144,421)	Hospital discharges database for RA/ JIA	1.08 (1.03-1.13)	1.5 (1.3-1.7)	0.8 (0.7-0.9)	1.2 (0.9-1.4)	0.8 (0.7-0.9)	1.3 (1.1-1.4)
Thomas, Scotland 2000 [42]	M: 7080 (38654) F: 19543 (113333)	Hospital in patient records	M: 1.10 (1.0-1.2) F: 0.97 (0.9-1.0)	M: 1.32 (1.2-1.5) F: 1.44 (1.27-1.6)[4]	0.95 (0.8-1.1)	1.26 (1.00-1.56)	M: 0.87 (0.7-1.1) F: 0.71 (0.59-0.9)	M: 0.97 (0.8-1.2) F: 1.06 (0.92-1.2)
Askling, Sweden 2005 [43]	55067 (297,102)	Hospital discharge records	1.05 (1.0-1.1)	1.48 (1.3-1.7)[2]	0.83 (0.8-0.9)	1.0 (0.9-1.1)	0.74 (0.7-0.8)	1.66 (1.5-1.8)[5]
Hemminki, Sweden 2008 [47]	42262	Hospital discharge records	1.23 (1.19, 1.27)	1.73 (1.57, 1.89)	0.97 (0.90, 1.05)	1.44 91.33, 1.57)	Colon: 0.77 (0.68, 0.88) Rectum: 0.68 (0.56, 0.82)	1.89 (1.68, 2.12)[5]

Study	No of subjects (person years)	Methodology	SIR all cancer sites (95% CI)	SIR lung (95% CI)	SIR breast (95% CI)	SIR prostate (95% CI)	SIR colorectal (95% CI)	SIR KSC (95% CI)
Parikh-Patel, California 2009 [48]	84,475 (405,540)	Retrospective hospital admission records	Not stated	M: 1.7 (1.5-1.8) F: 1.3 (1.2-1.4)	0.6 (0.6-0.7)	0.7 (0.6-0.7)	M: 0.7 (0.6-0.8) F: 0.8 (0.7-0.8)	-
Chen, Taiwan 2011 [49]	23644 (139555)	National health insurance database	1.23 (1.22, 1.23)	1.36 (1.34, 1.38)[6]	1.21 (1.19, 1.23)	1.31 (1.25, 1.36)	0.94 (0.86, 1.02)	0.87 (0.83, 0.91)
Clinic based studies								
Katusic, USA 1985 [51]	521 (7389)	Hospital based incident cohort	M: 0.96 (0.6-1.5) F: 0.99 (0.7-1.3)	1.4 (0.6-2.9)	1.0 (0.5-1.8)	-	1.2 (0.5-2.2)	-
Prior, England 1985 [46]	489	In and out patient hospital based cohort	1.3 p<0.05	1.1 NS[2]	0.9 NS	-	-	-
Cibere, Canada 1997 [44]	862 (14,998)	Hospital based cohort	0.80 (0.7-1.0)	1.08 (0.6-1.8)	0.90 (0.5-1.2)	1.0 (0.5-1.7)	0.52 (0.3-1.0)	0.83 (0.6-1.2)[3]
Askling, Sweden 2005 [43]	3703 (13,292)	Inception out patient cohort	1.1 (0.9-1.3)	2.4 (1.5-3.6)[2]	0.6 (0.3-?)	1.6 (1.1-2.3)	1.1 (0.7-1.8)	0.7 (0.2-1.6)[5]
Franklin, England 2007 [53]	IP: 2105 (15547), of whom 1237 RA	Inception primary care cohort	0.9 (0.7, 1.1)	1.1 (0.7, 1,8)[7]	0.8 (0.6, 1.3)	0.6 (0.3, 1.2)	0.9 (0.5, 1.4)	-

Study	No of subjects (person years)	Methodology	SIR all cancer sites (95% CI)	SIR lung (95% CI)	SIR breast (95% CI)	SIR prostate (95% CI)	SIR colorectal (95% CI)	SIR KSC (95% CI)
Abasolo, Spain 2008 [52]	789 (2269)	Prospective out patient cohort from 34 hospitals of prevalent RA	1.2 (0.8-1.9)	3.5 (1.4-7.1)	0.9 (0.1-3.2)	-	0.3 (0.0-1.9)	-
Yamada, Japan 2011 [50]	7566 (25567)	Single hospital based cohort	1.18 (1.02, 1.37)	2.29 (1.57, 3.21)	1.05 (0.64, 1.62)	3.20 (1.38, 6.31)	0.49 (0.26, 0.83)	2.34 (0.64, 6.00)[3]
Kim, Korea 2012 [54]	1534 (6493)	Single hospital based cohort	0.86 (0.58, 1.23)	-	-	-	-	-

[1] Relative risk and confidence intervals from Macfarlane 1996 [56]; [2] Respiratory; [3] Skin; [4] Lung, bronchus and pleura; [5] Excludes BCC; [6] Lung and mediastinum; [7] Lung, bronchus and trachea

M males; F females; NS not significant; JIA juvenile idiopathic arthritis

1.3.2 Skin cancer

1.3.2.1 Keratinocyte skin cancer

Keratinocyte skin cancers, also referred to as non-melanoma skin cancers, are the most commonly occurring cancers in the UK general population [57]. At least 75% of KSC are BCC [58], the next most common subtype being squamous cell carcinoma (SCC). The true incidence of KSC is difficult to estimate accurately, since registration of these malignancies with regional cancer registries is poor both in the UK and worldwide [57, 59]. This is particularly true for BCC which are often treated without histological confirmation. Keratinocyte skin cancers most frequently occur on sun exposed skin and Ultraviolet B light plays a role in the pathogenesis of both BCC and SCC [60]. Age, male gender and fair skin are risk factors for KSC and more than 99% of individuals developing BCC are white [58]. Smoking may be a risk factor for SCC, but not BCC [61]. Differences exist in the epidemiology of BCC and SCC. Chronic immunosuppression, due to e.g. organ transplantation or HIV, is a risk factor for KSC, but especially SCC. The ratio of BCC to SCC is reversed [62], with rates of SCC up to 250-fold higher than in the general population reported following transplantation [63]. The risk increases with cumulative exposure to immunosuppression [62, 64]. Sun exposure remains an important risk factor for SCC in immunosuppressed patients. It has been reported that approximately 45% of organ transplant recipients in Australia are diagnosed with SCC within 10 years of transplant [65], compared to 10% in the Netherlands [63] and 14% in Northern England [66].

Studies investigating the risk of skin cancer in RA have produced inconsistent results. Askling *et al.* did not report on BCC but found a 70% increase in risk of cutaneous SCC in their prevalent cohort of RA patients, but not in their incident cohort [43]. Mellemkjaer *et al.* found an overall increased risk of KSC of 30%, with an SIR of 1.3 for BCC and 1.4 for SCC [45]. They found the increased risk of BCC was present both early on and late in follow up, but the increased risk for SCC only occurred with prolonged follow up [45]. An increased risk of skin cancer has been demonstrated in Japan. Yamada *et al.* reported a more than doubling in risk of skin cancer (all types) in patients with RA (SIR 2.34, 95% CI 0.64, 6.00) [50]. The wide confidence interval reflects the fact that this study followed a relatively small cohort of patients from a single institution. A study in Taiwan [49], as well as several Western studies [40-42, 44], have not demonstrated an association. These conflicting results may, in part, reflect both differing definitions of skin cancer and incomplete registration of these neoplasia with cancer registries, as well as a possible true difference.

1.3.2.2 Malignant melanoma

Buchbinder *et al.* conducted a study of 459 patients with RA (4145 patient years follow up) attending community-based private Rheumatology practices in Australia [67]. All patients were taking MTX at the time of entry to the study. They found a three-fold increased risk of melanoma (SIR 3.0, 95% CI 1.2, 6.2) that was not seen in other studies of biologic naïve patients [40, 42, 47, 51, 52, 67]. This may in part be due to the increased incidence of melanoma in Australia increasing the power of the study to detect a difference in risk. The number of melanomas in the other studies was small, suggesting that they were not adequately powered to look at this outcome individually.

1.3.3 Lung cancer

Excluding keratinocyte skin cancer (KSC), lung cancer is the second most commonly reported cancer in the UK [57]. A large case-control study in US veterans demonstrated an association between RA and subsequent diagnosis with lung cancer (odds ratio [OR] 1.43, 95% CI 1.23, 1.65) [68], in keeping with the findings from the cohort studies discussed above. The study of veterans found that other known risk factors for lung cancer were more likely to be present in people diagnosed with cancer, namely increasing age, male gender, exposure to asbestos and smoking. The reasons why RA is associated with lung cancer are uncertain. This association may be partly explained by smoking, a shared risk factor for RA and lung cancer [69]. Second, interstitial lung disease is common in patients with RA and itself is a risk factor for lung cancer, independent of smoking [70, 71]. Third, elevated C-reactive protein has been shown to be risk factor for lung cancer, even after a latent period of five years, with a hazard ratio (HR) of 2.8 (95% CI 1.6, 4.9), supporting the hypothesis that systemic inflammation may be a risk factor in the development of lung cancers [72].

1.3.4 Colorectal cancer

Excluding KSC, colorectal cancers are the third most commonly reported cancers in the UK [57]. The risk of colorectal cancer appears to be reduced in people with RA [55]. Cibere *et al.* performed a Canadian hospital-based prospective study to collect information on possible predictors of cancer risk [44]. Ninety-seven percent of their study participants received non-steroidal anti-inflammatory drugs (NSAID) [44]. Since a meta-analysis of aspirin and NSAID use has shown them to be associated with a reduced risk of colorectal cancer [73], the high proportion of NSAID use amongst people with RA might account for the reduction in colorectal cancer seen in this study.

1.3.5 Breast cancer

Breast cancer is the most common cancer in women, excluding KSC, with 40260 cancers reported to the English cancer registry in 2009 [57]. Several large population based cohort studies have demonstrated a reduced incidence of breast cancer in women with RA [41, 43, 45, 48]. This may be due to a protective effect of NSAIDs or an unknown confounder, perhaps related to oestrogen, influencing the risk of both RA and breast cancer in women [74].

1.3.6 Lympho- and myeloproliferative malignancies

Several cohort studies have reported the incidence of lymphoproliferative malignancy (LPM) and myeloproliferative malignancy (MPM) in RA compared to the general population (Table 1-3). The settings of these studies are outlined in Table 1-2, with the exception of the study by Franklin *et al.* that looked at the incidence of lymphoma in a British cohort of 2105 patients with new onset inflammatory polyarthritis (IP) [75]. Subjects were followed annually and cases of lymphoma identified from the region's hospital electronic records system and verified by case note and histology review [75]. Fifty nine percent of subjects fulfilled the 1987 American College for Rheumatology (ACR) criteria for RA by their fifth annual assessment [75, 76].

Table 1-3 SIR of lymphoma, leukaemia and myeloma in biologic naïve RA patients

Study	No of subjects (patient years)	SIR all lymphoma (95% CI)	SIR NHL (95% CI)	SIR Hodgkin (95% CI)	SIR leukaemia (95% CI)	SIR myeloma (95% CI)
Hospital discharges or insurance claims linked to cancer registries						
Isomäki, Finland 1978 [40][1]	46,101 (213,991)	-	2.68 (1.9-3.7)	2.79 (1.7-4.4)	1.74 (1.3-2.3)	2.2 (1.5-2.2)
Gridley, Sweden 1993 [41]	11,683 (101,000)	1.98 (1.5-2.6)	1.88 (1.3-2.6)	2.34 (1.2-4.1)	1.23 (0.8-1.8)	-
Mellemkjaer, Denmark 1996 [45]	20,699 (144,421)	-	2.4 (1.9-2.9)	3.4 (1.8-5.6)	1.3 (0.9-1.7)	1.1 (0.7-1.7)
Thomas, Scotland 2000 [42]	7080	-	M: 2.39 (1.61-3.41) F: 2.04 (1.60-2.58)	M: 5.49 (2.36-10.8) F: 3.04 (1.39-5.78)	M: 2.01 (1.26-3.05) F: 1.07 (0.69-1.59)	M: 1.07 (0.43-2.21) F: 1.90 (1.29-2.69)
Parikh-Patel, California 2009 [48]	84,475 (405,540)	-	M: 2.1 (1.7-2.5) F: 1.4 (1.2-1.6)	M: 2.8 (1.3-5.1) F: 1.6 (0.9-2.7)	M: 1.7 (1.3-2.1) F: 1.3 (1.0-1.5)	M: 1.2 (0.8-1.8) F: 0.8 (0.6-1.1)
Chen, Taiwan 2011 [49]	23644 (139555)	2.74 (2.68, 2.81)[2]	3.54 (3.45, 3.63)	1.76 (1.45, 2.17)	1.48 (1.41, 1.56)	-
Clinic based studies						
Katusic, USA 1985 [51]	521 (7389)	1.2 (0.2-3.4)	-	-	1.9 (0.4-5.5)	5.0 (1.4-12.8)
Prior, England 1985 [46]	489	-	24.1 p<0.001	12.5 p<0.05	4.3 NS	-
Cibere, Canada 1997 [44]	862 (14,998)	-	0.55 (0.11-1.60)	0.00 (0.00-8.53)	2.47 (1.12-4.69)	-

Study	No of subjects (patient years)	SIR all lymphoma (95% CI)	SIR NHL (95% CI)	SIR Hodgkin (95% CI)	SIR leukaemia (95% CI)	SIR myeloma (95% CI)
Franklin, England 2006 [75]	2105 (15,548) IP 1237 RA	IP 2.34 (1.18-4.24) RA 2.94 (1.34-5.57)	-	-	-	-
Abasolo, Spain 2008 [52]	789 (2269)	-	5.4 (1.1-15.7)	-	8.8 (2.4-22.6)	-
Yamada, Japan 2011 [50]	7566 (25567)	6.07 (3.71, 9.37)	-	-	-	-

[1] Relative risk and CI from Macfarlane 1996 [56] [2]Haematological malignancies
IP inflammatory polyarthritis; M males; F females; NS not significant

1.3.6.1 Lymphoma

Lymphomas comprise a heterogeneous group of malignancies involving the lymphoid tissues and are classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) [77]. Around 85% of lymphomas are NHL, with an annual incidence rate in the UK general population of 17.9 per 100,000 men in 2009 and 12.7 per 100,000 women [57]. Although these cancers are uncommon, there is an association with autoimmune diseases [78-81] including RA [55]. The incidence of diffuse large B-cell lymphoma (DLBCL), in particular, appears to be increased in people with RA [82]. In a review of lymphoma tissue in 35 patients with RA in Sweden, two-thirds of NHL were found to be DLBCL compared with 30-40% in the general population [82]. All but one of the studies reported in Table 1-3 reported an increased risk of lymphoma in RA cohorts. The SIR varied considerably in these studies (between 1.88 and 24.1). A meta-analysis of nine observational studies, two of which included patients exposed to anti-TNF, reported an overall relative risk of 2.08 (1.80, 2.39) [55]. Although HL is less common than NHL the relative risk in RA populations is higher; SIR 3.29 (95% CI 2.56, 4.22) for HL versus 1.95 (95% CI 1.70, 2.24) for NHL [55]. Gridley *et al.* drew attention to the fact that miscoding between NHL and HL was not uncommon in Sweden during the period of their study, which may have affected the classification of their 12 cases of Hodgkin's and 36 NHL [41]. Cibere *et al.*'s finding of a reduction in lymphoma risk, all be it not statistically significant, is at odds with the other studies. This study used a relatively small hospital cohort and the actual numbers of events were small with three NHL and no HL, resulting in very wide confidence intervals for the estimates.

Whilst there is a clear association between autoimmune diseases, including RA, and lymphomagenesis, the relative contributions of shared genetic or environmental risk factors in lymphoma risk versus the direct effect of RA and its treatment are uncertain. Genome-wide association studies have identified risk loci for NHL and autoimmune diseases, particularly in the major histocompatability complex on chromosome 6, supporting a shared genetic susceptibility to the diseases [83]. A case-control study from Scandinavia looked at the OR of personal history of RA and family history of RA in people with NHL to test for shared susceptibility [84]. Whilst the OR for personal history of RA was increased (1.6, 95% CI 1.4, 1.8), no increase was seen in relation to family history (OR 1.1, 95% CI 0.96, 1.3). Furthermore, Hellgren *et al* matched 6745 subjects registered in the Swedish Early Arthritis Registry with 5 general population controls for sex, year of birth, marital status and county of residence [85]. After linking participants with the national cancer registry, they

found no increased risk of lymphoma in the ten years prior to RA diagnosis and a 75% increased risk during the first ten tears following diagnosis. These studies do not exclude the possibility of a shared genetic risk for a number of reasons. First, the median age for RA onset is less than that of lymphoma. Second, lymphoma may be fatal and so patients that would have subsequently been diagnosed with RA would be missed. Third, treatment for lymphomas, including steroids and rituximab, may mask the future development of RA symptoms. Finally, lymphomas are a heterogeneous group of cancers, many of which are very rare. To facilitate analysis sub-groups of lymphoma are lumped together and so possible associations between RA and particular subtypes of lymphoma may be missed.

Evidence for the pathogenic effect of chronic immune stimulation / chronic inflammation in lymphomagenesis comes from a large Swedish nested case-control study [86]. Baecklund *et al.* matched 378 consecutive RA patients diagnosed with lymphoma between 1964 and 1995 to 378 RA controls [86]. The lymphoma pathological specimen was reviewed in 343 patients and 165 (48%) were classified as diffuse large B-cell lymphomas (DLBCL). Thirty seven (12%) of 304 were Epstein Barr virus (EBV) positive. Disease activity was calculated at each hospital visit from RA diagnosis to lymphoma diagnosis or dummy date of diagnosis using clinical and laboratory markers. Cumulative disease activity was estimated as the cumulative duration of four levels of RA activity: inactive, low, medium and high. Cumulative disease activity was split into deciles for analysis, with the first decile indicating lowest activity used as the referent group. Marginal increases in lymphoma risk were seen up to the seventh decile after which the risk rose steeply and for the tenth decile the OR was 61.6 (95% CI 21.0 to 181.1) [86]. A separate study from Sweden reported a reduced lymphoma risk associated with exposure to corticosteroids, after adjusting for RA disease severity (adjusted OR for steroids 0.58 (95% CI 0.38, 0.90) [87]. When subtypes of lymphoma were considered separately, there was a negative association with DLBCL (unadjusted OR 0.59, 95% CI 0.37, 0.94). They hypothesised that the reduced risk associated with steroids might be due to reduced inflammation following treatment or due to other mechanisms such as apoptosis of emerging populations of clonal B-cells.

The association between EBV and the development of lymphoma in the absence of RA is well known [88], and lymphoma in the presence of EBV infection is a well-recognised complication of organ

transplantation [89]. An overall role for EBV in lymphoma development in RA above that in the underlying population has not been supported. A case-control study comparing 42 cases of NHL in patients with RA to 49 cases in patients without RA found no difference in the rates of EBV genes in the lymphoma specimens from the two samples [90]. Having said that, there have been numerous case reports of EBV-related lymphoma occurring in people treated with MTX for RA and other diseases (for example [91-94]). Georgescu *et al.* published a report of two cases of B-cell lymphoma, occurring in patients treated with MTX for RA [95]. They also reviewed the literature and found a further 23 case reports. Most of the cases had large or polymorphous B-cell lymphoma, in common with other immunosuppressed subjects [96]. Seventeen of the cases were assayed for EBV and seven (41%) found to be positive. Interestingly, eight of the cases went into remission on stopping MTX without further treatment for their cancer, four of whom were positive for EBV. There have been other reported cases where lymphomas which have developed on MTX have regressed on discontinuing MTX, without any further specific treatment, although it appears that the majority of LPM occurring during MTX treatment do not spontaneously regress [97].

1.3.6.2 Other lympho- and myeloproliferative malignancies

Leukaemias are a collection of uncommon malignancies of haemopoietic stem cells derived from bone marrow. The annual incidence rate is the general population is around 16 per 100,000 men and 11 per 100,000 women [57]. Most studies in Table 1-3 reported a 1.5 to 2 fold increase in RA, with Abasolo *et al.* finding a much greater risk with a SIR of 8.8 (95% CI 2.4, 22.6) based on four leukaemias [52].

Plasma cell myeloma is a bone-marrow based plasma cell neoplasm with an M-protein found in serum and/or urine [77]. It comprises 10-15% of haematopoietic malignancies [77]. The RR of myeloma in RA varies between studies from 0.8 to 5.0 (Table 1-3). The variability in these findings may in part be due to real differences in the underlying background rates in the countries where studies were conducted. Diversity in study sources, for example inception versus in patient cohorts, may also influence findings. Additionally, the wide confidence intervals of several of the estimates suggest the possibility that these studies may be underpowered to detect an increase, due to the relative rarity of the events in question.

1.3.7 Premalignant conditions

Given the association between RA and certain cancers, one might expect to find an increase in premalignant conditions, such as cervical intraepithelial neoplasia (CIN) and Barrett's oesophagus, in RA. However, data regarding this are sparse. A recently published Mexican cross-sectional study compared the prevalence of cervical human papillomavirus and Papanicolaou changes in 43 women with RA and 146 healthy controls [98]. They found that the proportion of women with human papillomavirus was similar between the groups (28% versus 31%), as was the proportion of women with Papanicolaou changes (Pap II 67% versus 85%; Pap III 12% versus 8%). It has been widely reported that women with systemic lupus erythematosus (SLE), another systemic inflammatory autoimmune disease, are more likely to have human papillomavirus and CIN detected on smear testing [99-101]. Whilst one retrospective review found an increased prevalence of CIN in patients with SLE exposed to cyclophosphamide (CYC) compared to unexposed patients [102] , no association with immunosuppressant drugs was observed in a cross-sectional study [99].

1.3.8 Factors influencing the risk of malignancy in RA

1.3.8.1 Study setting and design

Each study design has its own strengths and limitations that may influence the observed risk of cancer. The diagnosis of RA varied between the studies discussed above. Results from cohorts assembled several decades ago, such as those analysed by Isomaki [40] and Katusic [51], may not apply to contemporary RA patients due to changes in RA diagnostic criteria, management of RA and introduction of cancer screening programs. Mellemkjaer *et al.* included palindromic rheumatism and juvenile idiopathic arthritis in their definition of RA [45]. Single hospital based studies, such as those by Prior [46] and Katusic [51] were able to apply stricter diagnostic criteria to their RA patients, but were unable to detect modest differences in risk due to the small size of their cohorts. Population-based studies were unable to formally verify the diagnosis of RA. Furthermore, studies that were based solely on hospital in-patient episodes were susceptible to selection bias with only patients with more severe RA being admitted to hospital. Bias may also have resulted from subjects being admitted to hospital with symptoms of an undiagnosed cancer that were first attributed to RA, with the diagnosis of cancer being made later.

The duration of follow up varied between studies and may have influenced the observed RR of cancer. Thomas *et al.* linked hospital discharge records to the Scottish cancer registry and found a six-fold increase in men and four-fold increase in women of cancers occurring within the first three months of hospitalisation, whether or not the admission was principally related to RA [42]. In women, a three-fold increase in colorectal cancer was seen in the first three months and thereafter the SIR dropped below one [42]. This study was based on hospitalisations so this increase in cancers within the first three months may be explained by protopathic bias, or reverse causality, resulting from symptoms of an undiagnosed malignancy being interpreted as active RA leading to hospitalisation. Hemminki *et al.* calculated the SIR for different periods of follow up in their study that linked the Swedish hospital discharge register with the national cancer register [47]. The SIR for all cancer sites was highest in the first year (2.51, 95% CI 2.28, 2.76) versus 1.23 (95% CI 1.19, 1.27) for all follow up and 1.17 (95% CI 1.19, 1.27) for ≥10 years follow up. A Taiwanese study that reported a 23% increased risk of cancer compared to the general population overall also demonstrated that that the SIR decreased with duration of follow up; SIR 58.96 (95% CI 58.13, 59.96) in the first year versus 0.31 (95% CI 0.31, 0.32) ≥ 8 years [49]. Katusic and Gridley analysed hospital based cohorts in the USA and Sweden respectively and found no trend in SIR for cancer relating to duration of follow up [41, 51]. Hemminki *et al.* proposed that the early observed increased risk in their study was due to earlier diagnosis of cancers, due to investigations performed for RA, which would have otherwise been detected later.

Most of the earliest studies were European, and in particular from the Nordic countries. Recent publications from the Far-East and California have examined the cancer risk in Asian and Hispanic populations respectively [48-50, 54]. Whilst the results from these studies are broadly similar to those from European studies, none of the studies from the Far-East has demonstrated a reduction in breast or prostate cancer risk.

1.3.8.2 Genetic risk factors

Recent studies have highlighted potential genetic risk factors for early mortality due to malignancy in RA. The HLA-DRB1 shared epitope (SE) genotype was found to be associated with cancer-related mortality in RA in the UK Early Rheumatoid Arthritis Study [103]. This inception cohort study followed 767 patients with RA for up to 18 years, 46 of whom died of cancer. An association

between the SE, particularly *0101 genotypes, was observed (HR for SE+/SE+ 2.18, 95% CI 1.17, 4.08; HR for DRB1*0101/*0401 and *0101/*0404 both >6). A Spanish single centre out-patient cohort of patients with RA that looked at risk factors for incident and fatal cancer was published in the same year [104]. Eighty-seven participants (49%) carried the HLA-DRB1*04 shared epitope; 53 of which were the HLA-DB01*0401 phenotype and 16 HLA-DB01*0404. They reported an association between cancer incidence with the *0404 phenotype (HR 3.24, 95% CI 1.00, 10.49) but not *0401 (HR 0.86, 95% CI 0.27, 2.64). They reported an association between both *0401 and *0404 and cancer mortality, that did not reach statistical significance. All patients were registered for this study in 1996, but follow up time started at the time of diagnosis with RA, which could be several years earlier, introducing the possibility of immortal time bias in this analysis. Immortal time bias occurs when follow up time is included in a study during which the outcome of interest cannot occur. Another susceptibility locus for RA, TRAF1/C5 has also been found to be associated with mortality due to malignancy in RA [105]. Interestingly, TRAF1 has also been found to be over expressed in both NHL and CLL [106].

1.3.8.3 Surveillance bias

Surveillance bias has been investigated as a potential reason for the observed increased diagnosis of certain malignancies in RA, since it is plausible that patients attending regular medical appointments may also be more likely to be screened for cancer. For example, one might expect lung cancers to be diagnosed earlier in people with RA due to the routine request for a chest radiograph at presentation and prior to starting MTX.

Reports on the uptake of national screening programmes for malignancy in subjects with RA have been conflicting. A study of 1355 patients with RA reported a low uptake for mammography and cervical screening using the Papanicolaou test [107], whereas another found an increased uptake of mammography but not pelvic bimanual examination in RA [108]. This study comprised female nurses and one might hypothesise that uptake for screening would be higher in healthcare professionals compared to the general population, regardless of co-morbidities. A further recent study from North America of 13,314 patients with RA found uptake of screening using mammography, Papanicolaou smear and colonoscopy to be similar to those without RA [109].

Interestingly, uptake of screening for cervical cancer has been found to be reduced in patients with SLE compared with general population, despite the known association between SLE and CIN [110].

1.3.8.4 Inflammation

Virchow reported in 1858 that malignancies are frequently seen at the site of chronic inflammation [111, 112]. He hypothesised that inflammation could play a role in cellular proliferation and tumourigenesis. This hypothesis is supported by an increased risk of cancer in patients with chronic inflammatory conditions, development of cancers at the site of chronic inflammation, reduction in risk of certain cancers following long-term treatment with NSAIDs and the presence of inflammatory mediators within cancer cells that promote tumour growth [113]. Whilst chronic inflammation may induce malignancy, acute inflammation can have anti-tumour properties. Direct application of a live attenuated form of *Mycobacterium bovis* is an effective intra-vesicular treatment for carcinoma in situ (CIS) of the bladder [114].

As discussed above in section 1.3.6.1, there is an association between chronic burden of inflammation and lymphomagenesis in RA [86]. The effect of chronic inflammation on risk of other cancers has not been addressed directly in a well conducted study. Llorca *et al.* registered consecutive patients with RA attending their out-patient department in 1996 [104]. They looked at risk factors within the cohort for incidence of cancer and found an association between inflammation measured by CRP (HR for each mg/L 1.13, 95% CI 1.05, 1.22) or ESR (HR for each mm per hour 1.04 95% CI 1.01, 1.07). They did not find an association with rheumatoid factor positivity or presence of extra-articular disease. Although this paper prompts further research, the results should be interpreted cautiously since they included follow up time retrospectively from time of RA diagnosis, introducing the possibility of immortal time bias. Abasolo *et al.* did find an incidence rate ratio (IRR) of 1.68 (95% CI 1.13, 2.49) for every five years since RA diagnosis [52], in keeping with the notion that chronic inflammation is a predictor of cancer.

1.3.8.5 Non-steroidal anti-inflammatory drugs

Aspirin and NSAIDs have been associated with a reduced risk of numerous cancers, most notably colorectal and breast cancer [73, 115, 116] but also bladder [117], prostate [118], melanoma [119]

and lung cancer [120]. They are thought to exert their anti-cancer properties through inhibition of COX-2 which promotes angiogenesis in tumours and increases resistance to apoptosis [121]. A review and meta-analysis of the effect of aspirin and NSAIDs on risk of colorectal cancer found a pooled OR of exposure of 0.80 (95% CI 0.73, 0.87) in cases indicating a protective effect of these drugs [73]. Similarly, a meta-analysis of observational studies investigating the association between NSAIDs and breast cancer reported a combined RR of 0.82 (95% CI 0.75, 0.89) [116].

In contrast to this, in North America both a large prospective study linked to the Surveillance Epidemiology and End Results (SEER) cancer database [122], and a case control study [123] have shown a positive association between the use of aspirin or NSAIDS and non-Hodgkin's lymphoma. The prospective study followed up 27,290 post-menopausal women for seven years and found a SIR of 1.7 (95% CI 0.9, 3.1) for aspirin and 2.4 (1.2, 4.8) for other NSAIDs [122]. Other risk factors for NHL in this cohort included RA, age, marital status, farm residence, blood transfusion, hormone replacement therapy, diabetes, red meat and fruit intake, alcohol and smoking [122]. The association between NSAIDs and NHL persisted even after adjusting for confounders in multivariate analysis [122]. The case control study compared 376 patients with lymphoma to 473 controls and used telephone interviews to collect information on prior medication use [123]. They found prolonged NSAID use to be associated with NHL [123]. A weakness of this study was potential inaccuracy in collected information since 25% of cases had died at the time of the study so relatives were asked to provide information. Recall bias may also be a problem since the median time from NHL diagnosis to telephone interview was 1.2 years. Finally, within the group of participants taking NSAIDs, patients using them for rheumatological reasons, such as RA, tended to have an increased risk suggesting that the risk may in part be due to the confounding by underlying condition.

1.3.8.6 Disease-modifying anti-rheumatic drugs

The influence, if any, of nbDMARDs on the association between RA and cancer has been difficult to determine. Other immunosuppressed populations, namely transplant recipients and subjects with acquired immune deficiency syndrome (AIDS), are at increased risk of cancer, particularly those cancers that are associated with viruses such as EBV associated large B-cell lymphoma [96]. Treatment with azathioprine (AZA) was first shown to be associated with malignancy in transplant recipients [124] and later in RA [52, 125-127]. Asten *et al.* followed up 1773 patients starting

immunosuppressive nbDMARDs for rheumatic diseases for ten years [125]. The aim of this European-wide study was to determine the influence of duration of exposure to nbDMARDs on the risk of malignancy [125]. Seventy nine percent of patients had RA and 51% received AZA. Other nbDMARDs included MTX, CYC, chlorambucil and proresid, a microtubulin antagonist used in Sweden [125]. Duration of exposure to immunosuppressive nbDMARDs was categorised as <1 year, 1-<3 years, 3-<6 years and 6+ years, with the <1 year category used as the referent group [125]. Patients with the highest cumulative exposure to nbDMARDs had an IRR of 1.68 (95% CI 0.94, 2.93) for developing cancer [125]. When just cancers of the immune system, skin cancers and bladder cancers were analysed, the IRR rose to 4.45 (95% CI 1.43, 13.86) [125]. Patients with rheumatic disease and exposure only to AZA were analysed separately and found to have a similar increase in risk [125]. In contrast, in an Australian cohort of patients with RA, of whom a third were exposed to AZA, patients taking AZA had a reduced risk of malignancy compared to non-users (HR 0.5, 95% CI 0.3, 1.0) [67].

Abasolo *et al.* looked at previous use of AZA, chlorambucil or CYC collectively and found them to be significant predictors with an IRR of 14.3 [52]. A novel finding was that patients with low haemoglobin or high white cell count also had an increased rate of malignancy and they suggested that these factors may reflect active RA [52]. Interestingly no association was seen with other markers of severe disease such as rheumatoid factor or extra-articular disease [52]. Ciclosporin (CSA) has been associated with increased cancer risk in transplant recipients [128], but in RA the evidence is conflicting [52, 129, 130]. These studies did not adjust for disease activity or severity and so it is not clear how much of the increased risk can be attributable to the disease and the drug.

An association between CYC and malignancy has been reported in RA. Radis *et al.* matched a cohort of 119 patients with RA treated with oral CYC to 119 control patients with RA, matched for age, sex, disease duration and functional class [131]. Subjects requiring CYC for extra-articular RA were excluded. The RR for cancer was 1.5 (95% CI 0.93, 5.5). Nine of the 50 cancers in CYC cohort were bladder cancers, occurring up to 17 years after stopping the drug, versus none in the control group. There were 19 skin cancers in the CYC group compared to 6 in the controls. Information about exposures and outcomes for this study was collected via telephone survey at baseline in 1985 and at the end of the study in 1992-3, introducing the possibility of recall bias. Hospital records, pathology

reports and death certificates were used to verify presence or absence of malignancy, where available. Furthermore, confounding by indication cannot be excluded since in this study group, CYC was initiated in people with active RA that had failed to respond to conventional nbDMARDs.

Few studies have looked at site-specific cancer risk in patients exposed to nbDMARD. Bernatsky *et al.* conducted a nested case-control study of 960 patients with lung cancer each matched to 10 controls from a cohort of 23,810 patients with RA, identified from a Canadian claims database [132]. Prior exposure to nbDMARDs was similar in cases and controls, indicating no increased risk of lung cancer following exposure; rate ratio for MTX 1.12 (95% CI 0.97, 1.29), AZA 0.89 (95% CI 0.65, 1.22), CYC 1.09 (95% CI 0.76, 1.28) and antimalarials 1.11 (95% CI 0.96, 1.28).

Whilst there have been reports of lymphomas in people treated with MTX that regress on stopping treatment (see section 1.3.6.1), large cohort studies of MTX-treated patients have not consistently found the overall risk of malignancy to be increased. A retrospective French study of 426 RA patients treated with MTX found no increase in malignancies compared to either a control population of patients with RA or the general population [133]. Similarly, a large study from the US National Data Bank long-term study of the outcomes of RA and OA (NDB) did not identify an association between MTX and lymphoma (OR 1.3 (95% CI 0.6, 2.7)) [134]. Mariette *et al.* conducted a prospective study set in 61 rheumatology departments in France in which information was collected on all new cases of lymphoma occurring in RA patients receiving MTX [135]. They did not find an increase in NHL, however, the standardised mortality ratio (SMR) for Hodgkin's disease was found to be 7.4 (95% CI 3.0, 15.3) [135]. Buchbinder *et al.* also found an increase in both NHL and Hodgkin's disease in their cohort of MTX treated patients with RA, with SIRs of 5.1 (95% CI 2.2, 10.0) and 8.9 (95% CI 0.2, 49.8) [67].

Bernatsky *et al.* conducted a nested-case control study to investigate the association between nbDMARD exposure and haematological cancer risk using the methods outlined above for their lung cancer study [132, 136]. Haematological cancers occurred in 619 participants. The adjusted rate ratio was increased in subjects with previous exposure to CYC (1.84, 95% CI 1.24, 2.73) but not for other nbDMARDs including MTX (rate ratio 1.12, 95% CI 0.93, 1.34).

1.4 Malignancies and anti-TNF drugs

1.4.1 Measuring the risk

The risk of malignancy with the anti-TNF drugs can be assessed in three main ways; in RCTs; in pharmacovigilance services; and in systematic observational studies, such as the British Society for Rheumatology Biologics Register (BSRBR). The key difference between RCTs and observational studies is that observational studies do not randomise subjects as to whether or not they will receive the intervention. There are inherent strengths and weaknesses to each study design, as discussed below.

1.4.1.1 Randomised controlled trials

When a drug is granted a licence, the main source of data concerning its potential to cause adverse events in humans is RCTs. The primary aim of a RCT is to demonstrate efficacy of a drug under ideal conditions and so patients who may not survive to meet the primary endpoint, for example those with significant co-morbidities such as cancer, are frequently excluded. This may influence the rates of malignancies observed in RCT of anti-TNF since the excluded subjects may be those with the highest risk of developing cancer. In addition, the detailed work up of subjects prior to entering a RCT may lead to detection of early cancers, prohibiting them from entering the trial. These trials are conducted under strict conditions and with precise inclusion and exclusion criteria. Their short duration of follow up (typically 6 months to a year) along with the strict entry criteria limit the ability to draw conclusions about the effect of anti-TNF on uncommon and latent events such as cancer.

Several studies have demonstrated that patients recruited to RCTs of anti-TNF were not representative of the underlying RA population [137-139], diminishing the external validity of their results. Sokka and Pincus [137] applied the inclusion criteria for the early RA trial of ETA versus MTX (ERA) to a cohort of 232 patients with early RA. They also applied the criteria for the anti-TNF trial in RA with concomitant therapy (ATTRACT) of INF with MTX versus MTX alone to 152 patients with established RA [137], 138 of whom had a joint count recorded in the case notes. Just 37 of the 232 (16%) patients with early RA met the criteria for ERA and 7 of the 138 (5%) with late RA met the criteria for ATTRACT [137]. Zink *et al.* reported that only 21-33% of patients receiving anti-TNF in the German register RABBIT would have been eligible for the major RCTs [138]. The main reasons for exclusion were lower disease activity, more comorbidities and lower functional status. They found

that fewer ineligible patients achieved a 20 or 50% improvement in their disease activity but that absolute improvement was similar to that in eligible patients. Kievit *et al.* reported similar results from the Dutch biologics register, with 34-79% of patients fulfilling inclusion criteria for RCTs and lower response rates to anti-TNF among ineligible subjects [139].

With respect to cancer, early trials of INF excluded patients with prior lymphoproliferative malignancy (LPM) or any cancer within five years [7, 140] where as trials for ADA [8, 141] and ETA [9, 142] excluded patients with any history of cancer. Certain studies specified that fully excised KSC did not preclude entry to the trial [140, 141]. In other studies the precise inclusion criteria with respect to cancer are difficult to determine from the published report [8, 15, 143-148].

A key strength of RCTs is the fact that randomisation should balance confounders between the groups and so make rates of adverse events internally comparable within each trial. Individually RCTs lack power to detect a difference in risk of cancer between treatment groups and so a number of researchers have attempted to combine results from several studies by performing a meta-analysis (Table 1-4). All studies used fixed-effect models, which usually produce narrower confidence intervals with rare outcomes, on the grounds that they didn't want to miss a safety signal.

Table 1-4 Summary of findings from meta-analyses of cancer risk in randomised controlled trials of anti-TNF for rheumatoid arthritis

Study	Anti-TNF	Methods	No. of studies	No of cancers in each treatment arm (% of participants or rate per 100,000 pyrs)		Findings (95% CI)
				Anti-TNF	Control	
Bongartz, 2006 [149]	INF; ADA	Pooled OR; fixed effects	9	All: 29 (0.8%) Excl KSC: 19 (0.5%)	All: 3 (0.2%) Excl KSC: 1 (0.1%)	All: OR 3.3 (1.2, 9.1) Excl KSC: 3.7 (1.0, 13.2)
Bongartz, 2008 [150]	ETA	Survival analysis; fixed effects	9	All: 26 (1047) Excl KSC: 17 (684)	All: 7 (666) Excl KSC: 4 (381)	All: HR 1.84 (0.79, 4.28) Excl KSC: 1.86 (0.62, 5.59)
Leombruno, 2009 [151]	ETA; INF; ADA	Rate ratio adjusted for unequal follow up; fixed effects; recommend dose of anti-TNF	17	Excl KSC: 36 (667) Lymphoma: 5 (92) KSC: 12 (253)	Excl KSC: 10 (617) Lymphoma: 1 (62) KSC: 3 (226)	Excl KSC: RR 1.21 (0.63, 2.32) Lymphoma: 1.26 (0.53, 3.01) KSC: 1.01 (0.42, 2.44)
Askling, 2010 [152]	ETA; INF; ADA	Bayesian; fixed effects;	59, of which 31 were RA	All: 103(8088) Excl KSC: 52 (8111) KSC:53 (8094)	All: 34 (3608) Excl KSC: 22 (3614) KSC: 12 (3613)	All sites: HR 1.30 (0.89, 1.95) Excl KSC: 0.99 (0.61, 1.68) KSC: 2.02 (1.11, 3.95)
Thompson, 2011 [153]	ETA; INF; ADA	Early RA; MTX control group; Pooled OR; fixed effects	6	19 (0.87%)	10 (0.81%)	OR 1.08 (0.50, 2.32)

Pyrs person years
CI = 95% confidence interval for frequentist analyses and 95% credible interval for Bayesian analyses
Primary use condition = rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or ulcerative colitis

The earliest meta-analysis of anti-TNF RCTs looked at the risk of cancer in patients treated with anti-TNF monoclonal antibodies compared to controls [149]. This analysis found an increased risk of malignancy in the anti-TNF group and that this risk was greatest when anti-TNF drugs were used in high doses [149]. The OR for all malignancies was 3.3 (95% CI 1.2, 9.1). A commentary by Dixon and Silman highlighted sources of potential inaccuracy in the findings of this analysis [154]. In particular the calculation of ORs did not allow for differences in follow-up duration between groups. Since open-label extensions were included in the meta-analysis this may have biased the meta-analysis towards detecting more cancers in patients who received anti-TNF. Dixon and Silman also identified an important issue when applying these findings to the British population [154]. The doses of anti-TNF used in clinical trials at which malignancies occurred were often higher than those used in routine clinical practice, for example INF 10mg/kg compared to the approved dose of 3mg/kg [154]. Costenbader *et al.* [155] used identical methodology and added data from the PREMIER randomised controlled trial of ADA [148]. They calculated a revised OR of 2.02 (95% CI 0.95, 4.29) [155].

In 2008 Bongartz *et al.* performed a meta-analysis of nine RCTs of ETA [150]. The findings suggested a trend towards increased risk of cancer in the ETA arm; HR 1.84 (95% CI 0.79, 4.28). No difference in incidence of cancer was seen between different periods of follow up, nor was a dose effect observed [150]. A strength of this analysis was its compensation for the doubling in dropout rate of patients receiving placebo compared to ETA by performing a time-to-event analysis. Bongartz *et al.* did note that the power was only 39% to detect a doubling in risk of malignancy between the two groups [150].

Leombruno *et al.* published a pooled analysis of malignancies occurring in seventeen RCTs of INF, ETA or ADA [151]. Exposure adjusted meta-analyses were performed to account for differential dropout rates between patients and controls. The analysis looked at three outcomes; non-cutaneous cancers with melanoma; lymphoma; and KSC. No difference in cancer risk was detected for any of the outcomes when anti-TNF was given at a recommend dose (Table 1-4). Eight RCT included patients receiving above recommended doses of INF and ADA, but not ETA. Meta-analysis of subjects receiving high dose anti-TNF versus controls showed a trend towards increased risk of non-cutaneous cancers and melanoma, with a risk ratio of 3.04 (95% CI 0.95, 9.68).

The most carefully conducted meta-analysis to date was performed by Askling *et al.* [152]. They used patient-level data from 74 RCT of ETA, INF or ADA. They classified 59 of these trials as being for a primary condition: RA, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or ulcerative colitis. In these 59 trials there were 103 cancers in the anti-TNF groups (1273 per 100,000 person years [pyrs]) and 34 in the control groups (942 per 100,000 pyrs). They used Bayesian methodology to compare the rates between the two cohorts, yielding a 95% credible interval which means that there was a 95% probability that the true value lay in that range. They used three outcome definitions; A) all cancers during the study period; B) excluded cancers that were definitely prevalent i.e. first sign or symptom recorded before the start of the study; and C) excluded events from B that were judged to be prevalent by the oncologists verifying the cancers, based on the natural history of the cancer. Using definitions A, B and C respectively, the HRs for cancers at all sites as a combined end-point were 1.30 (95% CI 0.89, 1.95), 1.21 (95% CI 0.77, 1.90) and 1.75 (95% CI 0.90, 3.63) [152]. Whilst the HR was higher for INF (1.56 95% CI 0.61, 4.67) than ETA (1.15 (95% CI 0.60, 2.29) or ADA 1.40 (95% CI 0.78, 2.61), the authors drew attention to the fact that there were uneven cancer rates in the comparator arms for the three drugs; 769 per 100,000 pyrs for INF versus 937 for ETA and 1024 for ADA.

Askling *et al.* also looked at two other outcomes; all cancers excluding KSC, and KSC only. When KSC were excluded, there was no difference in overall risk of cancer in the anti-TNF and comparator arms using outcomes A, B or C [152]. There was a trend towards an increased cancer risk for INF but not for ETA and ADA. However, the crude rate of cancer was lowest for INF of the three anti-TNF agents and the number of cancers in the comparator arm for INF was very low (one cancer using outcome A and none using outcomes B or C). The authors discussed the fact that it is difficult to determine whether apparent differences in cancer risk among the three drugs were related to (i) real differences between the drugs; (ii) differences in the comparator arms; (iii) study-specific differences in the reporting of cancers; or (iv) chance. Drug-specific differences in risk are biologically plausible due to differences in the type of drug (monoclonal antibody or receptor fusion protein), mode of delivery (subcutaneous or intravenous) and other factors (fully humanised or not). The risk of KSC-only was increased in the anti-TNF arm compared to the comparator arm; outcome A HR 2.02 (95% CI 1.11, 3.95); B 2.18 (95% CI 1.03, 4.92); C 4.96 (95% CI 1.21, 41.06). There was around a two-fold increased risk for ETA and ADA but not for INF. There were, again, indicators of heterogeneity in comparator group risk across the three drugs.

The background risk of cancer needs to be borne in mind when considering whether or not anti-TNF influences this risk. All the above analyses in this meta-analysis included patients treated for conditions other than RA, in whom the risk of cancer may differ. There were 31 RCT of RA patients in the meta-analysis [152]. In these trials, there were 75 cancers in the anti-TNF arm (1230 per 100,000 pyrs) and 22 (851 per 100,000 pyrs) in the comparator arm. The crude rate ratio was 1.45 (95% CI 0.90, 2.32). Since the background risk of cancer may be different in people with early compared to established RA, a meta-analysis that only included patients with early RA is included in Table 1-4 [153] This analysis reported no difference in the risk of cancer between subjects exposed to anti-TNF and the biologic naïve comparator arm (OR 1.08, 95% CI 0.50, 2.32).

The results from these meta-analyses should be interpreted with caution since there are limitations of combining data from several sources. The trial design, subject group and method of defining and reporting malignancies may vary between studies. In addition, significant results from a small, well conducted study may be masked by results from larger studies.

1.4.1.2 Spontaneous pharmacovigilance

Pharmacovigilance programmes include programmes such as the United Kingdom's 'yellow card' reporting system and the United States Food and Drug Administration's (FDA) MedWatch program. The yellow card scheme was introduced in 1964 in response to the thalidomide tragedy. These systems are particularly useful for signal generation of a possible causal association between an adverse event and a drug. The main drawback of such programmes is the fact that it is not always possible to accurately estimate the number of people exposed to a particular drug, information that is required to calculate the rate of an adverse event. Incomplete ascertainment of adverse events also occurs since reporting of events to the yellow card scheme is voluntary for UK health professionals and patients. A further drawback of such schemes is the lack of a control group or comparator cohort.

Brown *et al.* published a series of 26 cases of lymphoma reported to MedWatch, occurring in patients treated with ETA or INF between May 1999 and December 2000 [156]. Eighteen (69%) of the patients had RA, five (19%) Crohn's disease, two (8%) psoriatic arthritis and one (4%) was not

specified [156]. They used the manufacturers' estimates of ETA and INF users of 95,500 and 121,000 respectively to calculate crude incidence rates. They estimated the rate of lymphoma as 19/100,000 in ETA treated patients (18 cases) and 6.6/100,000 in INF treated patients (eight cases) [156]. The time from starting biologic therapy to lymphoma diagnosis was recorded in 17 cases for ETA and seven for INF. Interestingly, ten cases (59%) were diagnosed within eight weeks of commencing ETA and four (57%) within eight weeks of starting INF, suggesting protopathic bias. However, in two patients the lymphoma regressed on stopping the biologic drug, neither of whom were concurrently taking MTX, suggesting a potential role of the anti-TNF drug in tumourigenesis. Four patients died; two deaths occurred in patients who were in remission from a prior NHL and relapsed after starting ETA; one occurred in a patient with ETA diagnosed with nodular sclerosing HL; and one death occurred in a patient with NHL receiving INF [156]. Brown *et al*. acknowledged the limitations of their work, namely the lack of control group and incomplete ascertainment of cases, preventing the authors from concluding that there is a causal association between anti-TNF and cancer.

Meyboon *et al.* reported on 121 cases of leukaemia in patients using anti-TNF drugs that were collected by the international pharmacovigilance program of the World Health Organisation (WHO) [157]. These patients did not exclusively have RA and they found no characteristic patterns in regards duration of treatment, age or type of leukaemia. With no denominator and the possibility of under reporting, this study was unable to determine whether the anti-TNF drugs are associated with increased risk of leukaemia.

The FDA have issued a black box warning for cancer when prescribing anti-TNF. In particular, they highlighted concerns about the risk of hepatosplenic T-cell lymphoma in children and adolescents in their last review, updated in 2011 [158]. This is a very rare, aggressive cancer that is usually fatal. The majority of the cases reported to the FDA were in children treated with anti-TNF for inflammatory bowel disease whilst only two had RA. Many of the patients were co-prescribed thiopurines (AZA or 6-mercaptopurine) which is not usual practice in Rheumatology. There have also been case reports of hepatosplenic T-cell lymphoma occurring in biologic-naïve subjects with inflammatory bowel disease treated with thiopurines [159].

1.4.1.3 Observational studies

The strength of observational studies lies in their evaluation of large, real-life groups of patients. They have greater external validity than RCTs which use highly selected patient groups. Rare outcomes can be addressed, either in case-control studies, or in cohort studies observing patients over several years. In cohort studies, the analysis tends to focus on comparing current disease status in patients to controls whereas in RCTs change in disease status, for example the number of participants improving by 20%, is frequently the primary outcome. Arguably current disease status is more important to the patient and their treating physician [160, 161]. Observational studies are often cheaper to run than RCTs. As patients are not randomly assigned to treatment or control groups in cohort studies confounding by indication, or channelling bias, may compromise the validity of results, as illustrated later on in this review.

1.4.2 Systematic review of cancers in observational studies of anti-TNF in RA

The purpose of this search was to review all cancers in observational studies of anti-TNF drugs in RA. The literature review utilised the Medline database and was accessed via Ovid. Medline is produced in the United States by the National Library for Medicine and covers more than 3000 medical, dentistry and nursing journals [162]. The search strategy can be found in Appendix 1. The search was last updated on 3rd August 2012. The search was limited to publications in the last 20 years since the first RCTs of anti-TNF drugs took place in the late 1990s. The titles and abstracts of these publications were reviewed and full text retrieved if they fulfilled all of the following criteria:

a) Studies in Rheumatoid arthritis
b) Studies primarily assessing malignancy as an outcome
c) Observational study design, with or without a control group
d) The latest published results from a cohort if data have been analysed more than once, with one exception (ARTIS; see below)

Case reports were not included. Only full text articles were retrieved for this review, but on-line only publications were included. The bibliography of each retrieved publication was screened to detect other relevant articles. Publications arising from the work presented in this thesis were excluded.

Sixteen studies met the above criteria; eight studies included cancer risk at all sites and/or solid organs; three studies addressed skin cancer risk; five studies of lympho- and myeloproliferative cancer risk; and two that were limited to people with previous cancer (Table 1-5). There were no studies including patients treated with either golimumab or certolizumab. The Swedish biologics register named Anti-Rheumatic Therapies in Sweden (ARTIS) published results on solid cancer and lympho- and myeloproliferative cancers in 2005 and 2009 [43, 163-165]. The earlier studies were included as well as the later studies since they included additional information about site-specific risks. Although Wolfe *et al* were the first to address the risk of lymphoma in anti-TNF treated patients in 2004 using the NDB [166], they added to this analysis in 2007 by including a larger cohort, adding ADA, and extending follow up [134]. For this reason the 2004 paper was excluded from detailed analysis.

There are difference in the setting, design and analysis of the studies included in this review that need to be borne in mind when interpreting the findings. The biologic cohorts differed in their composition, with some studies including anakinra as well as anti-TNF. Few studies addressed the risk of each anti-TNF agent separately. Although pooling data from each drug may increase the power of a study to detect a different risk, it may disguise diverging effects on malignancy between them since they work via different mechanisms.

Table 1-5 Characteristics of observational studies of cancer risk in anti-TNF treated patients

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed model				
All-sites							
Askling, ARTIS Sweden 2005 [43]	National inception cohort; starting ETA, INF, ADA; registration 1999-2003	Excluded 1st year from inpatient registry	Yes	General population. Inpatient registry and early RA cohort also compared to the general population	Prospective; linkage to the Swedish Cause of Death Register and the Population and Emigrations Register	Linkage to the Swedish cancer register; BCC excluded from the register; Lymph- and myeloproliferative cancers excluded	SIR calculated; Expected cancers calculated by multiplying age-, sex- calendar period-specific pyrs with national rates
Askling, ARTIS Sweden 2009 [164]	National inception cohort; starting ETA, INF, ADA; registration 1998-2006	None	Yes	Rheumatoid arthritis from 3 national registers; Inpatient Register; Outpatient Register; and Early RA Register	Prospective; linkage to the Swedish Cause of Death Register and the Population and Emigrations Register	Linkage to the Swedish cancer register; BCC excluded from the register	Cox model adjusted for sex, age, county of residence, marital status, time-dependent co-morbidity.
Bernatsky, Canada 2008 [132]	Quebec administrative database; RA defined from one billing code plus one nbDMARD prescription; ETA and INF; recruitment 1980-2003	None	Yes	Participants in the same database, not taking anti-TNF	Drug exposure from Quebec pharmacy claims database	ICD code for lung cancer recorded at out patient visit or hospitalisation	Excluded people with prior cancer Nested-case control study. Each person with lung cancer matched to 10 controls for age, sex, cohort entry; Adjusted for steroid use, number of physician visits and extra-articular RA features

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed				
Geborek, SSATG Sweden 2005 [167]	Regional cohort of RA patients treated with ETA or INF; recruitment 1999-2002	None	Yes	Community based cohort from one city hospital and 4 private rheumatologists 98% fulfilled 1987 ACR criteria; recruitment 1997-2002	Linkage with the southern Swedish Census Registry	Linkage to Southern Swedish cancer registry	Excluded people with prior cancer Cancers grouped; lymphoma; blood (leukaemia, myeloma); smoking related (UGI, airway, urinary tract); other. SIR compared to South Swedish healthcare region Cox proportional hazards adjusted for HAQ, age, sex
Pallavicini, LORHEN Italy 2009 [168]	Inception cohort in 4 centres; starting ETA, INF, ADA; registration since 1999	No	Yes	General population	For 3 years; 6 monthly questionnaires and assessments	6 monthly questionnaires	SIR calculated; Expected cancers calculated by multiplying age- and sex- specific pyrs follow up with regional rates (Milan and Varese)
Strangfeld, RABBIT Germany 2010 [169]	National inception cohort; starting ETA, INF or ADA; registration 2001-2006	No	Yes	RA; starting a nbDMARD; previously failed ≥1 nbDMARD	Assessments and questionnaires at 3, 6,18, 24, 30, 36, 48, 60 months	Excluded BCC; Questionnaires at all follow up time points	Excluded people with prior cancer Versus general population: SIR calculated Versus nbDMARD: (1) Cox regression used to compare rates, adjusted for age, sex, disease duration, Rh factor, functional capacity, co-morbidity, previous use of CSA or AZA; (2)Nested case-control study matched 1:1 on smoking, sex, co-morbidity, age, DAS28, fup time

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed				
Setoguchi, North America 2006 [170]	Retrospective cohort from 2 US Medicare databases (1994-2004) and all residents of British Colombia (1996-2003) aged ≥65; RA diagnosis based on a claim for RA and prescription for nbDMARD /steroid; Prevalent users of INF, ETA or anakinra;	180 days in sensitivity analysis	Yes	MTX users from the same cohorts – biologic v controls differentiated by prescriptions	Drug exposure from prescriptions; follow up censored at end of study, or diagnosis of first cancer	Cancers diagnosed from procedure codes	Excluded people with prior cancer and HIV Cox regression adjusted for 'demographic factors, risk factors for cancer, RA severity factors, health care utilisation, other co-morbidities'
Wolfe, USA 2007 [171]	Participants in NDB; subjects received ADA, INF, ETA or anakinra; registration 1998-2005	180 days	Yes	Biologic-naïve participants with RA from NDB; registration 1998-2005	nbDMARD/anti-TNF data collected by semi-annual patient questionnaire	From semi-annual patient questionnaire; cancer verified by hospital record or death certificate; Excluded KSC	Excluded people with prior cancer Conditional logistic regression adjusted for time of entry/exit to study, age, sex, education, smoking, disease activity, prednisolone use

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed				
Skin cancer							
Amari, USA 2011 [172]	Participants in a Veterans' administrative database with a code for RA, prescription for RA and ≥2 clinic visits; ETA, INF or ADA; recruitment 1998-2008	No	No	Controls from the same database without prescription for anti-TNF	Drug exposure from the Veterans' pharmacy database; follow until first KSC, last clinic visit, last nbDMARD or 2008	ICD code for KSC in database; verification at a single centre found a positive predictive value of 60% and negative predictive value of 95%	People with prior KSC excluded; Cox regression adjusted for medication changes over time, age, sex, race, co-morbidity, RA disease severity
Chakravarty, USA 2005 [173]	Participants with physician-diagnosed RA in the NDB who returned at least 2 semi-annual questionnaires; registration 1999-2003; subjects received 'TNF inhibitors'	No	Yes	Controls with RA from NDB	Patients completed semi-annual questionnaires with drug exposure details, HAQ and co-morbidities	KSC reported on patient questionnaires. A proportion were verified by interviewing the patient and accepted on the basis of a physician's diagnosis	Cox regression adjusted for nbDMARDs, age, gender, race, disease duration, education, marital status, prior KSC
Wolfe, USA 2007 [171]	Participants in NDB; subjects received ADA, INF, ETA or anakinra; registration 1998-2005	180 days	Yes	Biologic-naïve participants with RA from NDB; registration 1998-2005	nbDMARD/anti-TNF data collected by semi-annual patient questionnaire	From semi-annual patient questionnaire; cancer verified by hospital record or death certificate	Excluded people with prior cancer Conditional logistic regression adjusted for time of entry/exit to study, age, sex, education, smoking, disease activity, prednisolone use

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed				
Lympho- and myeloproliferative malignancies							
Askling ARTIS, Sweden 2005 [163]	National inception cohort; starting ETA, INF, ADA; registration 1998-2003	None	Yes	From the Swedish national in patient register with a diagnosis of RA, recruited 1990-2003	Prospective; linkage to the Swedish Cause of Death Register and the Population and Emigrations Register	Linkage to the Swedish cancer register used to capture all haematopoietic cancers	Lymphoma- Poisson regression used to compare groups adjusted for sex, age at entry, duration of RA Other haematological- SIR using age-, sex- calendar period-specific pyrs follow up
Askling ARTIS, Sweden 2009 [165]	National inception cohort; starting ETA, INF, ADA; registration 1998-2006	None	Yes	From 2 national registers; Inpatient Register, recruited 1964-2005 and Early RA Register, recruited 1995-2005	Prospective; linkage to the Swedish Cause of Death Register and the Population and Emigrations Register	Linkage to the Swedish cancer register used to capture lymphomas	Cox regression adjusted for sex, civil status, region, year of birth, co-morbidities and hospitalisations
Bernatsky, Canada 2008 [136]	Quebec administrative database; RA defined from one billing code plus one nbDMARD prescription; ETA and INF; recruitment 1980-2003	None	Yes	Participants in the same database, not taking anti-TNF	Drug exposure from Quebec pharmacy claims database	Any haematological malignancy recorded as the primary diagnosis at an out patient visit or hospital discharge	Excluded people with prior haematological cancer Nested-case control study. Each person with haematological cancer matched to 10 controls for age, sex, cohort entry; Adjusted for steroid use, number of physician visits and extra-articular RA features

Study	Anti-TNF group	Exposure definition		Controls	Follow up	Outcome	Analysis
		Lag period	Ever exposed				
Mariette, RATIO France 2010 [174]	National registry collecting adverse events in patients exposed to ETA, INF or ADA; Patients with RA, PsA, Ps, AS, Crohn's, UC	None	No	Biologic-naïve controls from RATIO centres matched 2:1 on age, sex and disease	Exposure time on anti-TNF estimated from number of doses of anti-TNF sold by the pharmaceutical companies	Events reported 2004-2007; Physician-reported events, centrally validated	Versus general population: SIR calculated; population lymphoma rates taken from the national France-Cancer-Incidence et Mortalité registry (2005) Versus nbDMARD: Case control study Sub-group analysis for RA-only
Wolfe, USA 2007 [134]	Questionnaire based US NDB linked to SEER national database for malignancies	None	Yes	Participants in NDB who completed 2+ semi-annual questionnaires 1998-2005 Subjects received ADA, INF or ETA. Patients with prior lymphoma excluded	Controls with RA from NDB Anti-TNF use prior to registration in controls and anti-TNF group ignored		Conditional logistic regression used to compare between groups -variables inc year of entry/exit to study, RA duration, baseline nbDMARDs, prednisolone use and HAQ
Prior malignancy							
Dixon, BSRBR UK 2010 [175]	National inception cohort; starting ETA, INF, ADA; registration 2001-2007	No	Yes	RA; active RA (guideline DAS28 ≥4.2); on nbDMARD	Questionnaires 6 monthly; flagging with the national deaths registry	Excluded CIS and KSC; 6 monthly questionnaires; flagging with the national cancer registry	Cox regression adjusted for age, sex, DAS28, HAQ, disease duration, entry year, smoking
Strangfeld, RABBIT Germany 2010 [169]	National inception cohort; starting ETA, INF or ADA; registration 2001-2006	No	Yes	RA; starting a nbDMARD; previously failed ≥1 nbDMARD	Questionnaires at 3, 6,18, 24, 30, 36, 48, 60 months	Excluded BCC; Questionnaires at all follow up time points	crude IRR calculated

AS Ankylosing spondylitis; HAQ Health Assessment Questionnaire; LOHREN Lombardy Rheumatoid Arthritis Network; Ps psoriasis; PsA psoriatic arthritis; RATIO Research Axed on Tolerance to bIOtherapies; UC ulcerative colitis; UGI upper gastrointestinal tract

The statistical analysis varied between the studies; some compared cancer rates to the general population by calculating SIR [43, 167]; some calculated the relative risk between anti-TNF treated and untreated RA patients [171, 173]; and others used both methods to assess risk [134, 163, 165, 170]. Adjusted analyses differed between studies since information that was collected on potential confounders varied. For example ARTIS did not collect data on smoking status which is known to be a risk factor for some cancers. In addition, the way in which data about the outcome were collected differed; ARTIS linked their database with the national cancer registry guaranteeing near complete capture of cancer cases with a high degree of accuracy. Other studies relied on patient-reported outcomes, for example the Veterans study in which misclassification was demonstrated to have occurred [172]. Several studies excluded a period of follow up time immediately after recruitment to the study before including them in the analysis (a lag period; Table 1-5). Up to a year of follow up was excluded in this manner. All studies, except the Veterans study included follow up time and events after stopping anti-TNF in the analysis (ever exposed model). The reason for including this additional follow up time is that inhibition of TNF may have long-lasting effects on a person's subsequent risk of cancer.

1.4.3 All sites and solid organ cancers

Eight observational studies addressed the risk of solid organ or skin cancers and the results are shown in Table 1-6. Three studies were conducted in Sweden; two within ARTIS; and one within the South Swedish Arthritis Treatment Group (SSATG). A large degree of overlap between the anti-TNF treated subjects in these studies is likely, since patients may be enrolled in both studies [176].

Table 1-6 Findings of observational studies of solid malignancy including skin cancers in anti-TNF treated patients

Study	No of subjects (pyrs)	No of cancers	SIR cancer for anti-TNF cohort (95 % CI)	Anti-TNF versus no anti-TNF (95% CI)	Site-specific increased risk	Site-specific reduced risk
Askling, 2005 [43]	Anti-TNF: 4160 (9715)	Anti-TNF: 67	0.9 (0.7-1.2)	Not assessed	None	Breast: SIR 0.4 (0.2-0.9)
Askling, 2009 [164]	Anti-TNF: 6366 (25693) nbDMARD: 61160 (330,498)	Anti-TNF: 240 nbDMARD: 4244	1.14 (1.00, 1.3)	RR 1.00 (0.87, 1.17) ETA: 0.78 (0.61, 1.00) INF: 1.09 (0.91, 1.30) ADA 1.32 (0.87, 1.98)	Not assessed	Not assessed
Bernatsky, 2008 [132]	All: 23810 (157,204)	All: 960 Anti-TNF: 2	Not assessed	Not assessed	Not assessed	Lung: IRR 0.84 (0.19, 3.73)
Geborek, 2005 [167]	Anti-TNF: 757 (1603)	Anti-TNF: 16	1.1 (0.6, 1.8) Excl lymphoma: 0.8 (0.4, 1.4) Smoking related cancer: 2.2 (0.7-5.1) Other solid cancer: 0.5 (0.2-1.2)	Included in methods but result not reported	Not assessed	Not assessed
Pallavicini, 2010 [168]	Anti-TNF: 1064 (2068)	Anti-TNF: 18	All: Milan 0.94 (0.55, 1.48); Varese 1.09 (0.64, 1.72) Solid: Milan 0.72 (0.38, 1.24); Varese 0.85 (0.45, 1.45)	Not assessed	Not assessed	Not assessed

Study	No of subjects (pyrs)	No of cancers	SIR cancer for anti-TNF cohort (95 % CI)	Anti-TNF versus no anti-TNF (95% CI)	Site-specific increased risk	Site-specific reduced risk
Strangfeld, 2010 [169]	Anti-TNF: 3651 (8558) nbDMARD: 1684 (3561)	Anti-TNF: 44 nbDMARD: 30	0.75 (0,54, 1.01)	HR 0.70 (0.44, 1.12) Nested case control study p=0.70	Lung: SIR 1.23 (no CI)	Breast: SIR 0.58 (no CI) Male reproductive organs: SIR 0.61 (no CI) Female reproductive organs: SIR 0.5 (no CI)
Setoguchi, 2006 [170]	Biologic: 1152 (approx 3000); 2% anakinra MTX: 7306 (approx 30000)	Biologic: 57 nbDMARD: 646	Not assessed	All: HR 0.98 (0.73, 1.31); excl first 180 days 0.99 (0.71, 1.36) Solid: HR 0.91 (0.65-1.26); excl first 180 days 0.98 (0.69, 1.38)	Not assessed	Not assessed
Wolfe, 2007 [171]	Biologic: 6282; 1% anakinra nbDMARD:6634	All: 537	Not assessed	OR 1.0 (0.8-1.2)	None	None

None of the studies showed a difference in the risk of cancers at all sites combined in patients with RA treated with anti-TNF compared to the general population. The SIR varied from 0.75 (95% CI 0.54, 1.01) in the German register (Rheumatoid Arthritis – Observation of Biologic Therapy; RABBIT) [169], to 1.14 (95% CI 1.00, 1.3) in ARTIS 2009 [164]. Four studies compared the risk of cancer in the anti-TNF treated cohort to the risk in a biologic-naïve population with RA. None of these studies demonstrated a difference in overall cancer risk following treatment with anti-TNF. Askling *et al.* looked at the risk of cancer for each anti-TNF drug separately compared to a cohort of biologic-naïve patients with prevalent RA [164]. They found no significant increase or decrease in the RR for ETA, INF or ADA but the point estimate was below one for ETA and above one for the monoclonal antibodies; ETA RR 0.78 (95% CI 0.61, 1.00); INF 1.09 (95% CI 0.91, 1.30); and ADA 1.32 (95% CI 0.87, 1.98).

Three studies looked at site-specific risk of solid cancer; ARTIS 2005; RABBIT and the US NDB [43, 169, 171]. Each of these studies had low numbers of outcomes, particularly in the anti-TNF arms, limiting their ability to detect a clinically important difference in risk. ARTIS and RABBIT both reported a reduced risk of breast cancer in participants exposed to anti-TNF compared to the general population. They both also reported a reduced SIR for breast cancer in their biologic-naive cohorts, in keeping with findings from other studies of biologic-naïve subjects [41, 45, 48]. A reduced risk of cancers of the male and female reproductive organs was reported by RABBIT. The NDB study did not find a statistically significantly difference in risk for any solid cancer in patients exposed to biologic therapy compared to those who were biologic-naive. The OR was reduced, with wide confidence intervals, for bladder, liver, pancreatic, soft tissue and vaginal cancers and increased for kidney and ovarian cancers. Further follow up in larger cohorts is required to determine whether site-specific differences in the influence of anti-TNF on cancer risk exist.

Three studies attempted to address the effect of duration of anti-TNF therapy on cancer risk and found no association [164, 170, 171]. The analyses from North America (Setoguchi *et al.* and Wolfe *et al.*) were limited by the fact that their studies used prevalent users of anti-TNF rather than following patients from the time that they initiated therapy. This meant that they were unable to calculate the total time each patient was exposed. Furthermore, these patients may have taken an alternative biologic prior to study entry. The Swedish study ARTIS (2009) found no difference in

relative risk of cancer in anti-TNF exposed versus anti-TNF naïve patients for different strata of time since starting anti-TNF, for example RR for <1 year 1.04 (95% CI 0.77, 1.39) and for ≥6 years 0.96 (95% CI 0.50, 1.86) [164]. There was also no association with cumulative dose of anti-TNF, for example RR <2 years 1.00 (95% CI 0.83, 1.22) and ≥6 years 0.96 (0.50, 1.86). This study also looked at whether the risk varied depending on the year of starting anti-TNF, since patients who started anti-TNF in their early years had more severe disease than those initiating therapy more recently. The relative risk of cancer was not different in patients starting anti-TNF 1999-2001, 2002-2003 or 2004-2006.

1.4.4 Skin cancer

1.4.4.1 Keratinocyte skin cancer

The four studies that addressed the risk of KSC in anti-TNF treated patients consistently reported an increased risk (Table 1-7) [43, 171-173]. In ARTIS 2005 the risk of cutaneous SCC was increased 3.6-fold in the anti-TNF cohort compared to the general population; SIR 3.6 (95% CI 1.8-6.5) [43]. Whilst one cannot directly compare SIR derived from different periods of follow up, it is noteworthy that this is higher than the SIR they reported in their biologic-naïve cohorts: SIR for prevalent cohort 1.66 (95% CI 1.50, 1.84); incident cohort 0.7 (95% CI 0.2, 1.6) [43].

Table 1-7 Findings of observational studies of skin cancers in anti-TNF treated patients

Study	No of subjects (pyrs)	No of cancers	SIR cancer for anti-TNF cohort (95 % CI)	Anti-TNF versus no anti-TNF (95% CI)
Amari 2011 [172]	Anti-TNF: 4088 (11084) nbDMARD: 18396 (82291)	KSC: Anti-TNF 283; nbDMARD 1043	Not assessed	KSC: HR 1.42 (1.24, 1.63) ADA v ETA: 92 in 2583 pyrs v 145 in 6827 (p<0.0001) INF v ETA: 47 in 1674 pyrs v 145 in 6827 (p=0.260)
Askling, 2005 [43]	Anti-TNF: 4160 (9715)	Anti-TNF: Cutaneous SCC 11; melanoma 1	SCC 3.6 (1.8-6.5) Melanoma 0.3 (0.0, 1.8)	Not assessed
Chakravarty, 2005 [173]	All RA: 15789 (40125)	All RA: KSC 738	Not assessed	KSC: anti-TNF without MTX HR 1.24 (0.97-1.58) Anti-TNF with MTX HR 1.97 (1.51-2.58)
Wolfe, 2007 [171]	Biologics: Melanoma 1394; KSC 6597 All: Melanoma 3260 (48795); KSC 13584 (46494)	Melanoma: 32 KSC: 623	Not assessed	Melanoma: OR 2.3 (0.9-5.4) KSC: OR 1.5 (1.2-1.8)

The other three studies compared anti-TNF users to biologic-naïve subjects with RA. Wolfe *et al.* found an increased risk of KSC in their biologics treated cohort with an odds ratio of 1.5 (95% CI 1.2-1.8) [171]. They excluded the first six months of follow up to avoid including prevalent cancers, but in doing so may have missed any increased risk of early cancers. Chakravarty *et al.* used the same cohort as Wolfe *et al.* (the NDB) and using multivariate modelling found a hazard ratio (HR) of 1.24 (95% CI 0.97-1.58) for anti-TNF and 1.97 (95% CI 1.51-2.58) for anti-TNF with MTX, compared to biologic naïve controls [173]. This increased risk with combination therapy may reflect more severe underlying RA, or greater immunosuppression. Chakravarty *et al.* looked at other known risk factors for KSC and found the greatest risks were previous KSC, with a HR of 6.7 (95% CI 5.3-8.5) and Caucasian race, HR 5.58 (95% CI 2.1, 15) [173]. Most recently Amari *et al.* studied a cohort of Veterans in which 90% of participants were men [172], unlike most studies of RA. This study reported a 40% increased hazard for KSC following anti-TNF; HR 1.42 (95% CI 1.24, 1.63). Other risk factors for KSC in this study were older age, male gender, use of NSAID or steroids and previous cancer. Sun exposure was not included in this analysis and may have been a confounder. The increased risk of KSC in male veterans could, in part, reflect greater sun exposure compared to female veterans who may have been more likely to be working in administrative or nursing roles. It is not known whether there is an association between RA disease severity and lifetime sun exposure, although inverse associations between vitamin D status and RA disease activity and disability have been demonstrated [177].

These observational data are in line with results from the RCTs of TNF inhibitors [152]. An increased risk of KSC has been observed in other immunosuppressed populations, in whom it is predominantly SCC rather than BCC that are increased [62]. A limitation of the studies in RA is that none of the North American studies were able to differentiate between BCC and SCC and ARTIS only included SCC. Whilst the consistent finding of an increased risk of KSC from RCT and observational data supports a causal association, another explanation may be surveillance bias. One might expect that, due to concerns regarding anti-TNF and cancer risk, patients starting anti-TNF and their physicians may be particularly vigilant in looking for KSC. In neither of the NDB US studies were KSCs validated and so they may represent benign skin lesions excised due to heightened concern. Amari *et al.* did look at the accuracy of KSC diagnosis in a single medical centre. The medical records of 71 study participants with an ICD code for KSC were reviewed along with records from 198 subjects without a code for KSC. Reports of probable or definite KSC were accepted, whereas possible or questionable

diagnoses were rejected. Pathology reports were also reviewed, where available. Only reports within 90 days of the ICD code were accepted. Only 43 of the 71 KSC recorded in the Veterans database were validated, yielding a positive predictive value of 60%. Nine of the 198 subjects without a code for KSC were found to have one during the review; negative predictive value 95%. The authors attempted to address the misclassification in their outcome in a sensitivity analysis. They simulated 100 datasets and assigning subjects with KSC a probability of 0.4 of no KSC. In each dataset they found the adjusted risk to be increased for anti-TNF; median HR 1.32 (95% CI 1.21, 1.42). However, this sensitivity analysis would not have eliminated bias caused by differential misclassification in the exposed and unexposed subjects. Whether or not such a difference was noted in the verification cohort was not reported.

1.4.4.2 Melanoma

There have been concerns that anti-TNF may increase the risk of melanoma since it became available for the treatment of RA. These concerns are due to both the efficacy of TNF in the treatment of melanoma [20, 178] and more recently case reports of late recurrences [38]. Two studies looked at the risk of melanoma following treatment with anti-TNF (Table 1-7). In ARTIS 2005 there was one melanoma in 9715 pyrs of follow up in the anti-TNF cohort, suggesting a reduced risk compared to the general population; SIR 0.3 (95% CI 0.0, 1.8) [43]. They reported an SIR of 1.19 (95% CI 0.99, 1.42) in their prevalent cohort and 0.9 (95% CI 0.2, 2.2) in their incident early RA cohort, with overlapping confidence intervals [43]. Wolfe *et al.* reported 32 melanomas in 3260 patients in the NDB, of whom 1394 were exposed to biologics during follow up (99% anti-TNF) [171]. They calculated an adjusted OR of 2.3 for biologic therapy, but the 95% CI crossed unity (0.9, 5.4). Patients with prior melanoma were excluded from this analysis and so the influence of anti-TNF on reactivation or recurrence of melanoma could not be addressed. Follow up in the biologic cohort of both studies was of short duration meaning late cancers would not be captured. Furthermore, the absolute numbers of melanomas were very small, suggesting that the studies were not sufficiently powered to detect a change in risk.

1.4.5 Lymphoproliferative and myeloproliferative malignancies

Ten observational studies addressed the risk of lympho- and myeloproliferative malignancies. The characteristics of these studies are summarised in Table 1-5 and their results in Table 1-8.

Table 1-8 Findings of observational studies of lympho- and myeloproliferative malignancies in anti-TNF treated patients

Study	No of subjects (pyrs)	No of cancers	SIR cancer for anti-TNF cohort (95 % CI)	Anti-TNF versus no anti-TNF (95% CI)
Askling 2005 [163]	Anti-TNF: 4160 (9715) nbDMARD: 53067 (297102)	Anti-TNF: Lymphoma 9; Leukaemia 2; myeloma 0 nbDMARD: Lymphoma 319	All: 2.1 (1.1, 3.8) Lymphoma: 2.9 (1.3, 5.5) Leukaemia: 2.0 (0.2-7.3) Myeloma: 0.0 (0.0-4.2)	Lymphoma: RR 1.1 (0.6-2.1)
Askling 2009 [165]	Anti-TNF: 6604 (29981) nbDMARD: 67743 (365,026)	Lymphoma: Anti-TNF 26; nbDMARD 336	Lymphoma: 2.72 (1.82, 4.08)	Lymphoma: RR 1.35 (0.82, 2.11)
Bernatsky 2008 [136]	All: 23810 (157,204)	All: Lymphoma 346; Leukaemia 178; Myeloma 95 Anti-TNF 3 in total	Not assessed	Haematologic cancers: IRR 1.92 (0.49, 7.50)
Geborek 2005 [167]	Anti-TNF: 757 (1603) nbDMARD: 800 (3948)	Anti-TNF: Lymphoma:5; Leukaemia and myeloma 1 nbDMARD: Lymphoma 2; Leukaemia and myeloma 2	Lymphoma: 11.5 (3.7, 26.9) Leukaemia or myeloma: 0 (0 to 9.2)	Lymphoma: HR 5.0 (0.9, 27.6)
Mariette 2010 [174]	Anti-TNF: ? (57711)	Lymphoma: 37 (27 in RA)	Anti-TNF in RA: 2.3 (1.6, 3.3)	Lymphoma: INF or ADA v ETA OR 6.68 (1.90, 23.54)
Pallavicini, 2010 [168]	Anti-TNF 1064 (2068)	Lymphoma 4	Lymphoma: Milan 5.99 (1.61-15.35); Varese 4.98 (1.34, 12.74)	Not assessed

Study	No of subjects (pyrs)	No of cancers	SIR cancer for anti-TNF cohort (95 % CI)	Anti-TNF versus no anti-TNF (95% CI)
Setoguchi 2006 [170]	Biologic: 1152 (approx 3000); 2% anakinra MTX: 7306 (approx 30000)	Anti-TNF: NHL 4; Myeloma 4; Leukaemia 3 nbDMARD: NHL 54; Myeloma 15; Leukaemia 19	Not assessed	NHL, CLL and myeloma: HR 1.11 (0.51, 2.37) Leukaemia, lymphoma and myeloma: 1.37 (0.71, 2.65)
Strangfeld, 2010 [169]	Total: Anti-TNF; 3651 (8558) nbDMARD; 1684 (3561)	NHL: Anti-TNF 5; nbDMARD 1	NHL 2.63 (no CI)	Nested case control study for NHL p=0.38
Wolfe 2007 (all cancer sites) [171]	HL: Biologic 264; All 696 NHL: Biologic 2080; All: 5589 Leukaemia: Biologic: 1367; All: 3348	All: HL 4; NHL 42; Leukaemia 24	Not assessed	HL: OR >100 (0-) NHL: 0.7 (0.3, 1.5) Leukaemia: 1.2 (0.5, 3.1)
Wolfe 2007 (lymphoma study) [134]	All: 19591 (89710) of which 55.3% received biologic during the study	Lymphoma: 95	Not assessed	Lymphoma: OR 1.0 (0.6, 1.8) Versus all other treatments: ETA 0.7 (0.3, 1.6) INF 1.2 (0.6, 2.2) ADA 4.5 (0.9, 23.1)

1.4.5.1 Lymphoma

Each of the studies addressing the risk of lymphoma found there to be an increase in anti-TNF treated patients compared to the underlying population [163, 165, 167, 174]. Geborek *et al.* calculated a relative risk compared to the South Swedish population that was much higher than in other studies; SIR 11.5 (95% CI 3.7-26.9) [167]. This estimate was based on five lymphomas in their cohort of 757 anti-TNF treated patients and the wide confidence intervals reflect the statistical uncertainty around the result.

Four studies looked at the risk of all lymphomas in anti-TNF versus biologic-naïve patients with RA two of which were from the same group (ARTIS 2005 and 2009). No association was seen in the ARTIS studies, nor the NDB study [134, 163, 165]. The SSATG was the only study to find a differential risk between anti-TNF patients and controls when the two groups were directly compared. They calculated a relative risk of 5.0, although the 95% CI did cross one (0.9-27.9) [167]. Whilst the authors did attempt to account for disease activity by adjusting for differences in the baseline HAQ, confounding by indication may have persisted due to differences in cumulative disease activity. Other factors contributing to the risk were outlined in the editorial by Franklin *et al.* including the low rate of lymphoma seen in the control cohort (SIR 1.3) and the fact that lymphomas diagnosed soon after starting biologic therapy could be latent malignancies, present prior to starting therapy [179] . Additionally, the possibility of protopathic bias, or reverse causality, was raised since lymphoma can cause arthralgia that may be mistaken for RA disease activity leading to initiation of anti-TNF therapy [179]. Finally, concern amongst the patients or their physicians may lead to surveillance bias and earlier diagnosis of lymphoma in the anti-TNF cohort. This effect may be magnified by the fact that the mean follow up time was shorter at 2.1 years in anti-TNF treated patients than controls at 5.5 years [179].

Two studies investigated whether the risk of lymphoma varied with time. Wolfe *et al.* found no difference in lymphoma risk in the first year of treatment [134]. In their most recent publication, the ARTIS group noted that the risk of lymphoma was increased in their anti-TNF cohort recruited 1998-2001; SIR 3.50 (95% CI 2.09, 5.36); RR compared to biologic- naïve 1.61 (95% CI 0.96, 2.71) [165]. The risk compared to the biologic-naïve cohort was not increased in patients starting treatment 2002-2003 or 2004-2006. They didn't find an association between lymphoma and time since start of anti-

TNF or accumulated time on anti-TNF. The authors acknowledged that the secular differences in risk of lymphoma likely resulted from incomplete control for confounding due to RA disease severity. The early patients had higher disease activity measured by DAS28, higher HAQ scores and had accrued more hospitalisations, suggestive of more severe, active disease that is itself a risk factor for lymphoma [86].

Three studies presented results on the risk of lymphoma for individual anti-TNF agents. Askling *et al.* found no difference in lymphoma incidence between the anti-TNF drugs, nor in patients who had received two or more biologics, but did comment that their estimates were imprecise [165]. Wolfe *et al.* presented twenty different drug combinations in total and found a higher OR for anti-TNF with MTX than anti-TNF alone that was not statistically significant [134]. They found an OR for ADA with MTX of 5.6 (95% CI 1.1-29.0) versus all other treatments, based on just two lymphomas [134]. This analysis excluded patients who had received another anti-TNF drug prior to ADA and when these patients were included the OR was 1.2 (95% CI 0.3-5.1) [134]. Together with the fact that no correction was made for multiple comparisons, caution should exercised in giving weight to this result. Thirty-seven lymphomas were analysed in the French study Research Axed on Tolerance to bIOtherapies (RATIO), of which 27 occurred in people with RA [174]. The OR for exposure to INF or ADA compared to ETA was 6.68 (95% CI 1.90, 23.54). The design of RATIO differs from that of other studies reported here since it was intended only to record adverse events on people taking anti-TNF. Person-years of exposure to anti-TNF were estimated by asking the pharmaceutical companies that manufactured the drugs how many doses had been sold for each of the agents. This may have led to less robust estimates of drug exposure compared to cohort studies. In summary, due to the rarity of lymphomas, further follow up is required to assess drug-specific risks.

Lymphoma subtypes

To date, studies have focussed on lymphoma as a combined outcome, as individual subtypes are rare. In their study published in 2005 Askling *et al.* described twelve lymphomas occurring in ARTIS between 1999 and 2004 [163]. Two of these were HL, three DLBCL, two follicular lymphoma (FL), one mucosa-associated and four NHL not otherwise specified (NOS) in keeping with the distribution of subtypes seen in RA patients not receiving anti-TNF [163]. One pathological specimen of nine tested was positive for EBV [163]. A similar pattern was seen by Geborek with one HL and four NHL

[167]. Wolfe *et al.* included four cases of HL and 42 cases of NHL in their report of cancers at all sites [171]. The OR for exposure to anti-TNF was >1000 (95% CI 0-) for HL and 0.7 (95% CI 0.3, 1.5) for NHL. This finding of an increased risk of HL requires investigating in other cohorts due to the low number of events. In a nested case control study with 6 NHL, the German register found no difference in risk of lymphoma between patients treated with anti-TNF or nbDMARD-only [169].

1.4.5.2 Leukaemia and myeloma

Only one study compared the rate of leukaemia in anti-TNF versus non-anti-TNF treated patients with RA. Wolfe *et al.* included 24 cases of leukaemia in their report of cancers at all sites [171]. The OR for exposure to anti-TNF was 1.2 (95% CI 0.5, 3.1), the wide confidence intervals reflecting the rarity of the outcome. Setoguchi *et al.* grouped lymphoma, leukaemia and myeloma together and found a relative risk of 1.37 (95% CI 0.71-2.65) for anti-TNF treated patients compared to RA controls [170]. The relative risk for NHL, CLL and myeloma was 1.11 (95% CI 0.51, 2.37), indirectly suggesting that the possible elevated risk was due to increased numbers of observed HL or leukaemia. Askling and Geborek found the SIR for leukaemia and myeloma to be similar in anti-TNF and non anti-TNF patients [163, 167].

1.4.6 Subjects with prior cancer

Two European registries specifically explored the influence of anti-TNF therapy upon incidence of cancer in people with a previous history of cancer [169, 175]. One hundred and seventy seven patients starting anti-TNF and 117 biologic-naïve patients with prior malignancy were identified from the BSRBR rheumatoid arthritis study (BSRBR-RA) [175]. The median time from prior cancer to study entry was twelve years for anti-TNF and nine years for nbDMARD. Among them, there were thirteen incident malignancies in eleven patients in the anti-TNF cohort (25 per 1000 pyrs) and nine malignancies in nine patients in the nbDMARD cohort (38 per 1000 pyrs). The age and gender adjusted IRR for anti-TNF was 0.58 (95% CI 0.23, 1.43). Using a propensity score to balance baseline differences in age, sex, disease severity, smoking status and year of entry to the BSRBR-RA, the adjusted IRR was 0.47 (95% CI 0.10, 2.22). Strangfeld *et al.* identified 58 patients treated with anti-TNF and 55 treated with nbDMARD-only with a history of cancer prior to registering with RABBIT [169]. The median time from prior cancer to study entry was four years for anti-TNF and five years for nbDMARD. Nine incident cancers were reported in the anti-TNF cohort (46 per 1000 pyrs) and

five in the nbDMARD cohort (31 per 1000 pyrs). The IRR for anti-TNF versus nbDMARD was 1.4 (95% CI 0.5, 5.5). In this study, all but one cancer were recurrences of the prior malignancy and the mean time between prior cancer and recurrence was 9.5 years. The diverging results, although lacking in statistical precision, may reflect differences in the way that anti-TNF was prescribed in the UK and Germany. British guidelines stated that anti-TNF should be used with caution in patients with a malignancy in the previous ten years [180]. The median time between prior cancer and starting anti-TNF was only four years in RABBIT and so the results are not directly comparable.

1.4.7 Limitations of observational data

In addition to the limitations of specific studies discussed above, all observational studies are also subject to certain pitfalls, in particular the effects of unmeasured confounders. Anti-TNF drugs are expensive and typically reserved for patients with severe disease. For example, in England and Wales, they are subject to NICE guidelines and may only be prescribed to patients with high disease activity, defined as a DAS28 score of >5.1 [17].This issue is particularly pertinent when analysing lymphoma risk which is known to be associated with highly active disease [86], introducing the potential for confounding by indication.

Furthermore, as cases of malignancy have been reported in patients receiving the drugs, bias may arise from physicians screening patients for malignancy prior to starting the drug [180]. If this were the case one would see a reduction of malignancies within the first few months of therapy since any patients in whom a cancer was detected would not go on to receive the drug. Alternatively protopathic bias may result from symptoms of an undiagnosed malignancy being interpreted as active RA leading to anti-TNF therapy. This scenario would result in an increase in malignancies diagnosed in the early stages on treatment. Some studies attempted to account for protopathic bias by excluding the initial months of follow up from the analysis. This in turn may miss a genuine change in risk of cancer occurring early in the course of treatment. One might expect that patients treated with anti-TNF would be followed up more closely for symptoms and signs of cancer (surveillance bias) and that this may lead to earlier diagnosis of cancers in this cohort. A study from the ARTIS registry found no difference in either stage at diagnosis of cancer or post-cancer survival between patients exposed or unexposed to anti-TNF, suggesting that this is not the case [181].

In observational studies patients may switch from one biologic to another. It is not known whether this would alter the risk of malignancy or other adverse events, adding a further layer of complexity to the analysis. To compound matters further, contemporary anti-TNF cohorts cannot be compared to historical nbDMARD cohorts since the background risk of malignancy may not be constant over time. For example, in Europe and elsewhere the incidence of NHL rapidly increased between 1950-1990 and the rate of increase has subsequently slowed, or reversed [182]. Finally, publication bias should also be borne in mind since negative results from non-randomised studies are less likely to be published [183].

Despite these limitations, from the evidence available so far, the overall risk of malignancy does not appear to be increased in patients receiving anti-TNF drugs for RA. When KSC are considered separately, there does seem to be an increase in risk of around 20-50%.

1.5 Summary

It has been shown in European and North American studies that there is an increased risk of certain cancers in people with RA, such as lymphoma, and a reduction of others, such as colorectal cancer. The possible effects of anti-TNF on these risks are difficult to predict since TNF has both tumour-promoting and tumour-inhibiting effects. The influence of anti-TNF drugs on cancer risk has been addressed by meta-analyses of RCTs, the results of which have been conflicting. The first of these found an overall increased risk of malignancy in patients treated with INF or ADA [149], that has not been replicated (Table 1-4). An increased risk for ETA has not been found [150]. Explanations for these conflicting findings may include the use of high dose INF and ADA in trials conferring an increased risk compared to recommended doses, genuine between drug differences or differences in study populations and trial designs. RCTs alone cannot determine whether or not the anti-TNF drugs influence the risk of malignancy in RA due to their short duration and exclusion of those patients who may be at greatest future risk.

Both population and registry based observational studies have attempted to establish the risk in everyday practice. None of these studies found a differential risk of solid organ cancers between anti-TNF treated patients and controls (Table 1-6). However, by pooling cancers at all sites, site-

specific increases or decreases in risk may have obscured. Similarly, by looking at anti-TNF as a class, any between-drug differences caused by different mechanisms of the drugs could not be detected. Furthermore, whilst it is reassuring that no significant increase in cancers has been consistently observed, the previous studies may not have been adequately powered to detect clinically important differences in risk.

There is a suggestion from RCTs and observational studies that anti-TNF is associated with an increased risk of KSC [152, 171, 172], although observational studies were hampered by differing definitions of KSC and incomplete ascertainment of cases. Whilst a number of studies looked at the incidence of lymphoma in anti-TNF versus biologic-naïve cohorts (Table 1-8), these studies included few events in the anti-TNF arms of the study and were inconclusive in their findings. Other than KSC and lymphoma, observational studies have not yet investigated site-specific cancer risks compared to RA biologic-naïve controls.

A number of clinically important questions remain unanswered. First, the influence, if any, of anti-TNF on risk of cancer in patients with RA needs warrants further exploration. In doing so, the background risk in the current UK RA population needs to be considered. Second, drug-specific risks need to be explored due to the different pharmacological properties of the drugs. Site-specific cancer risks are unknown at present and warrant investigation. Of particular interest are; common cancers, such as lung cancer and KSC; melanoma, since TNF has been used in the treatment of this cancer; and lymphoma, since it is recognised that patients with chronically active RA are at increased risk of lymphoma, and these patients are also most likely to receive anti-TNF drugs. This confounding by indication has not been adequately addressed by studies to date. The effect of duration of exposure to anti-TNF therapy remains unknown. Patients are frequently treated with more than one biologic drug, and the effect of this is unclear. There is a theoretical concern that blocking TNF in more than one way may lead to an increase in malignancy. Furthermore, when a patient receiving an anti-TNF drug is diagnosed with a malignancy it is common practice to stop the drug. However, little is known about whether anti-TNF influences the outcome following diagnosis of cancer in anti-TNF-treated patients.

The aim of this thesis is to explore the risk of malignancy in patients with RA, treated with anti-TNF drugs. The BSRBR-RA was established more than ten years ago and at the time of this thesis followed over 20,000 people with RA. This provides the opportunity to tackle the complex questions surrounding the relationship between anti-TNF therapy and cancer risk in RA. In the thesis, challenges of analysing long-term outcomes in observational data will be addressed and methods to overcome these challenges explored.

2. Aims

2 Aim and objectives

2.1 Aim

The broad aim of this PhD is to explore the risk of malignancy in patients with RA treated with anti-TNF therapy. The study population comprises patients registered with the BSRBR-RA, a large national longitudinal observational study.

2.2 Specific study objectives

- To quantify the rates of cancer in a nbDMARD-treated cohort of subjects with RA and compare them to the general population.
- To measure the incidence of malignancies, including lymphoma, solid organ cancers, and skin cancers, in an anti-TNF treated RA cohort.
- To estimate the relative risk of malignancies in an anti-TNF cohort compared to a nbDMARD cohort.
- To explore whether risk of cancer is related to cumulative duration of anti-TNF therapy.
- To describe the outcomes of malignancy in terms of survival.
- To review and compare the histological subtypes of lymphoma reported in anti-TNF and nbDMARD-only treated patients.

3. Methods

This chapter first describes the general methodology of the BSR Biologics Register. Following this, methods specific to the analysis of cancer risk within the study are described. Finally, the statistical methods used in this thesis are presented.

3 Methods

3.1 Methods of the BSR Biologics Register

3.1.1 Background

The BSRBR was established in 2001 with the primary aim to determine the long term safety of biologic therapies in RA. This followed guidelines issues by the British Society for Rheumatology (BSR) that all patients should be enrolled in a national register when commencing biologic therapy [184]. In 2012, the BSRBR launched a new register for people with ankylosing spondylitis. This register is named BSRBR-AS and managed by the University of Aberdeen. At the same time, the existing BSRBR study of patients with RA was renamed 'BSRBR-RA'. The study population in this thesis is drawn solely from the BSRBR-RA. In 2002 The National Institute for Health and Clinical Excellence (NICE) approved the use of anti-TNF therapy in the treatment of chronic, active RA with the recommendation that patients should be registered with the BSRBR-RA [185]. This has bolstered the success of the BSRBR-RA and there are currently more than 17,000 patients with RA registered. The BSRBR-RA is indirectly funded by the pharmaceutical companies that manufacture each of the included biologic drugs. They pay the BSR which in turn oversees the financial management of the study. All analyses are conducted independently of the pharmaceutical companies.

Ethical approval for the BSRBR-RA was granted by the North West Multicentre Research Ethics Committee on 1st December 2000 (reference 00/8/53). All the amendments which have been approved since then, can be viewed on the BSRBR-RA website [186]. Specific to this PhD thesis, an amendment to allow the BSRBR-RA to retrieve lymphomas specimens was approved on 4th September 2009 (Appendix 2). This will be discussed in Chapter 6. The subjects' written consent was obtained according to the Declaration of Helsinki.

3.1.2 Size of the register

A primary aim of the BSRBR-RA was to determine whether biologics are associated with serious adverse events (SAE) including serious infection and malignancy. The size of the study was based on the power required to detect a two-fold increase in the crude incidence rate of lymphoma in patients receiving either ETA, INF or ADA, compared to the background rate of 130 per 100,000 pyrs in RA [42]. Using a 2 sided significance test at the 5% level and 80% power the minimum number of

patients per each treatment group would be 3917 if all patients were followed for 5 years. To allow for losses to follow up, for example control patients starting anti-TNF therapy, a target was set for 4000 patients to be recruited for each of the anti-TNF drugs and to the control cohort.

3.1.3 Recruitment to the register

3.1.3.1 Anti-TNF cohort

Patients were eligible for recruitment to the anti-TNF arm of the study if they fulfilled the following criteria: aged 16 or over; diagnosed with a rheumatic disease by a physician; and starting or have started treatment with ETA, INF or ADA within the previous six months. There were no inclusion or exclusion criteria relating to RA disease severity or co-morbidity. However, national guidelines dictated that people were only eligible to start anti-TNF for RA if they had both highly active disease, with a DAS 28 score of >5.1, and had failed treatment with at least 2 traditional nbDMARDs, one of which should be MTX [17, 180]. Initial recruitment was limited to RA but subsequently the indications for TNF inhibitors have expanded and so patients with any rheumatic disease were eligible for recruitment. These patients were recruited from 251 hospitals across the United Kingdom. Recruitment to the ETA cohort was completed in June 2005, INF in May 2007 and ADA in November 2008.

3.1.3.2 Comparison cohort

The comparison cohort comprised patients recruited by the BSRBR Control Centre Consortium from 28 secondary or tertiary Rheumatology departments around the UK; England 22 centres; Northern Ireland 2; Scotland 2 and Wales 2 (Figure 3-1) (Appendix 3).

Figure 3-1 Map showing members of the BSRBR Control Centre Consortium

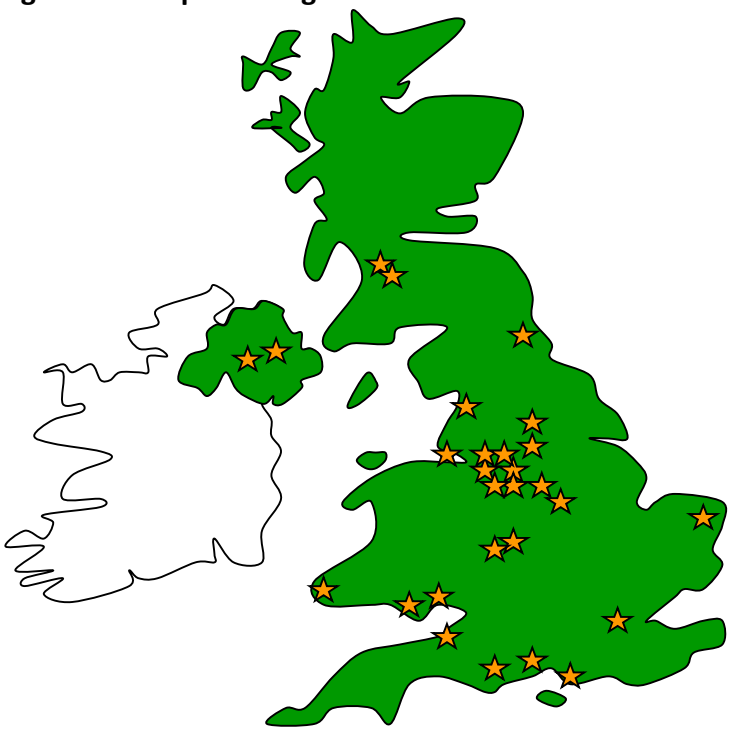


Figure 3-1 demonstrates that whilst all parts of the UK were represented in the control cohort, the centres were clustered around the north west of England, where the BSRBR-RA was hosted. The purpose of the consortium was to recruit a contemporaneous biologic-naïve cohort to whom patients starting biologic treatment could be compared for adverse events. Patients were eligible for recruitment if they fulfilled the following criteria: aged 16 or over; diagnosed with RA by a physician; active RA (guide DAS 28 >4.2); receiving at least one nbDMARD; and biologic naïve. They were not required to be starting a new nbDMARD i.e. prevalent users were included. Recruitment to the control cohort was terminated in 2009 falling short of the target for 4000 patients (3779 patients recruited). This was primarily due to two factors; first, since recruitment was limited to 29 centres, with time the pool of eligible subjects became depleted; and second, there were concerns that ongoing recruitment would limit its comparability to the anti-TNF cohort, to which recruitment had already closed.

3.1.4 Routine data collection

At baseline, data were collected via questionnaire from both the referring Rheumatologist and the patient in an identical manner for the treatment and comparison cohorts.

3.1.4.1 Consultant baseline questionnaire

The consultant baseline questionnaire is available to download from the BSRBR-RA website [187] and can be found in Appendix 4. The form collected data relating to a number of previous and current RA disease characteristics including year of RA diagnosis, systemic features of RA and previous joint surgery. Components of the 1987 revised American Rheumatism Association criteria for classification of RA were included [76]; morning stiffness of more than an hour; arthritis or deformity of three or more joint areas, arthritis or deformity of the hand joints; symmetry; nodules; rheumatoid factor positivity and erosions on radiographs of the hands or feet. Current disease activity was recorded using components of the DAS28 [188]; 28 tender joint count; 28 swollen joint count; ESR and/or CRP and patient global assessment using a visual analogue scale. Consultants were asked to list all current drug treatment for any indication. Doses and start dates of any current nbDMARD and biologic therapies were requested. The form also asked whether patients had ever been exposed to a number of specific nbDMARDs; intramuscular gold; auranofin; penicillamine; sulphasalazine; chloroquine/ hydroxychloroquine; MTX; AZA; CYC; CSA; leflunomide; steroids or other nbDMARD.

Information on co-morbidity was collected on this form. Consultants were asked: 'Has the patient ever had (i.e. required treatment for)' for a list of conditions, one of which was cancer. They were required to tick either 'yes' 'no' or 'don't know'. Other baseline co-morbidities that were included in the list and used in this thesis were hypertension, angina, myocardial infarction, stroke, asthma, bronchitis/emphysema, renal disease, diabetes mellitus, liver disease and depression. Smoking status was also requested with the possible responses current smoker, ex-smoker or never-smoked. The patient was also asked to complete a Health Assessment Questionnaire (HAQ) [189], to be returned with the consultant questionnaire. If this was not received at registration then a copy was posted to the patient, to be returned with their patient baseline questionnaire.

3.1.4.2 Patient baseline questionnaire

Upon receipt of the consultant questionnaire the patient was registered and a questionnaire sent out to them. This collected details including ethnicity and their preferred contact details (Appendix 5). Patients were asked to select the ethnic group to which they belonged from the list; white; black-African; black-Carribean; black-British; black-other; Indian; Pakistani; Bangladeshi; Chinese or other

(please specify). If a patient who was registered in the comparison cohort started biologic therapy then their follow up was censored at that point in time. However, if they switched to a biologic drug for which recruitment was still open then they were invited to switch to the biologic cohort and a supplementary consultant questionnaire was issued to collect additional baseline data.

3.1.4.3 Follow up questionnaires

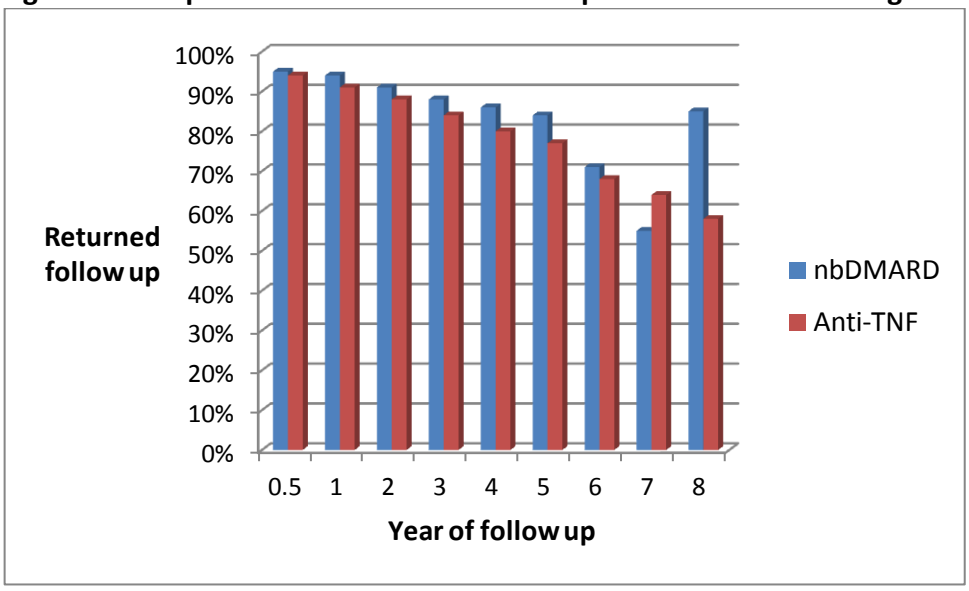
It was initially intended that patients would be followed up by the BSRBR-RA for 5 years. In 2012 approval was given by the North West Regional Ethics Committee for follow up to be extended until at least 30th September 2018 in all patients. This amendment was requested to facilitate analysis of rare and latent adverse events and to allow for recruitment to new cohorts. After registration, consultants were asked to complete and return a questionnaire six monthly for 3 years and then annually thereafter, even if the patient was no longer receiving biologic therapy. These questionnaires collected information regarding disease activity and changes to drug therapy. Consultants were asked to record any adverse event or new illnesses since last follow up, regardless of whether or not they were related to the patient's RA treatment. Patients were asked to return a completed questionnaire and diary every 6 months for 3 years that recorded hospital referrals, admissions and procedures as well as physical function (HAQ).

In addition to the questionnaires detailed above, the BSRBR-RA was directly informed of all deaths for registered patients that occurred in the UK. This was via linkage with the NHS Information Centre (NHS IC) which collates data from the Office for National Statistics (ONS). A copy of the death certificate along with the coded underlying cause of death was received.

3.1.4.4 Response rates to follow up questionnaires

Overall, response rates within the BSRBR-RA were excellent. At the time of this thesis only 0.7% of patients had no consultant follow up returned; Anti-TNF 0.7%, nbDMARD 0.8%. Of the patients that had reached five years follow up as of 31st January 2011, more than 80% had the 3-years consultant follow up form returned and more than three-quarters had the 5-years consultant follow up form returned (Figure 3-2). Response to patient questionnaires was good; 13% of the nbDMARD cohort did not return any patient follow up forms and 12% of the anti-TNF cohort.

Figure 3-2 Proportion of consultant follow up forms returned during the first five years



3.2 Analysis methods specific to this research

3.2.1 Identification and coding of malignancies

The BSRBR-RA was informed about incident cancers in three ways; consultant follow up questionnaires; patient diaries and the UK national cancer agencies.

3.2.1.1 National cancer agencies

When a patient was registered with the BSRBR-RA, consent was obtained to flag them with the national cancer agencies that provided information on all previous and incident cancers. There are eleven separate cancer registries in the UK, each covering populations of between 1.7 and 14 million people [190]. These registries provide complete coverage of the UK for the collection of population-based cancer data. There are eight regional registries in England which all submit a standard dataset to the ONS who collate the data and publish national statistics. The Welsh Cancer Intelligence and Surveillance Unit records all cancers diagnosed in Wales and also reports these to ONS. For patients living in England, Scotland and Wales, information on cancers was provided to the BSRBR-RA by the National Health Service Information Centre (NHS IC), which was informed of all cancers by ONS (England and Wales) and the Scottish Cancer Registry. The Northern Irish Cancer Registry provided cancer details for patients living in Northern Ireland. Data on all previously unreported cancers were posted to the BSRBR-RA approximately every three to six months until mid 2010. Since then, data

have been transmitted electronically on a monthly basis. There was a lag period between cancer diagnosis and the BSRBR-RA being informed, due to the multiple agencies involved in the process of validation and reporting (including the local pathologist, regional cancer register, ONS, NHS IC and the BSRBR-RA). For cancers reported in 2011, the median delay was 442 days.

3.2.1.2 Event of Special Interest Form

Event of special interest forms were developed for adverse events of particular interest, two of which were malignancy and lymphoproliferative malignancy. They are available to download from the BSRBR-RA website [191] and are included in Appendix 6. Upon notification of a cancer from any source an 'event of special interest form' (ESI) was sent via fax to the patient's Rheumatologist requesting further information. These forms were also submitted spontaneously to the BSRBR-RA by health care professionals between consultant follow up forms. The ESIs for malignancy requested diagnosis, location and cell type; date of diagnosis; treatment; and outcome. Consultants were also asked to state if the neoplasm was benign, malignant, CIS and/or whether it was a metastasis or had associated metastases. The ESI for lymphoproliferative malignancy asked for diagnosis and site; histopathological classification; stage; treatment; EBV status; history of Sjögren's disease; family history of cancer and outcome. For all cancers, a copy of the histology report was requested.

3.2.1.3 Coding of malignancies

All adverse events, including malignancy, were assigned a code in the BSRBR-RA using the Medical Dictionary for Regulatory Activities (MedDRA) classification. MedDRA is a clinically validated pan-European terminology that is widely used in pharmacovigilance. The coding of malignancies was done manually, by a dedicated team of two researchers who had both received training in MedDRA coding. The medDRA System Organ Class 'neoplasms benign, malignant and unspecified (incl cycts and polyps)' was used to identify malignancies for the analyses in this thesis. Further verification of the diagnosis was performed for all reported neoplasia.

3.2.2 Verification of incident malignancies

An incident malignancy was defined as a malignancy that was diagnosed after commencing anti-TNF, or for the comparison cohort after registration with the BSRBR-RA. Pre-determined criteria were

then used to categorise each malignancy into one of seven groups: definite; probable; possible; pre-existing; benign; carcinoma-in-situ; or unverified (Table 3-1).

Table 3-1 Verification rules for incident malignancies

Category	Criteria
Definite	Histological confirmation OR Confirmation from a national cancer agency OR Reported as incident malignancy by consultant AND reported on a death certificate AND no previous cancer reported by a cancer agency
Probable	Received treatment for cancer (surgery / radiotherapy / chemotherapy)
Possible	Planned treatment for cancer OR Consultant reported without further verification
Pre-existing	Diagnosed prior to starting anti-TNF therapy (or registration for controls)
Benign	Reported as benign by cancer agency OR If not reported by cancer agency: Consultant reported as benign or histology did not include malignant cells
Carcinoma-in-situ (CIS)	Reported as CIS by cancer agency OR If not reported by cancer agency: Consultant reported as CIS or histology showed CIS only
Unverified	None of the above including patient reported without further verification

Only definite malignancies were included in the primary analyses. This was to try and minimise any reporting bias that may have arisen between the cohorts as one might hypothesise that

Rheumatologists and patients would be more likely to report probable/ possible cancers in patients exposed to anti-TNF.

3.2.3 Identification of subjects with previous malignancy

Subjects with a history of cancer at baseline were defined as those people with cancer diagnosed prior to receiving the first dose of anti-TNF for the anti-TNF cohort, or date of registration for the comparison cohort. The BSRBR-RA was informed about previous malignancies in two ways; through record linkage with the national cancer agencies which reported all prior malignant neoplasia and from the consultant baseline questionnaire question about co-morbidity (see section 3.1.4.1). Consultants were also asked to specify the year of onset and site(s) of cancer. The level of agreement in reporting of prior cancers by the cancer agencies and consultants is discussed later (section 4.6).

3.2.4 Selection of the study population

Patients starting anti-TNF that did not have a physician diagnosis of RA were excluded from the analyses since background risk of cancer, attributable to the underlying condition, may vary between diseases. The nbDMARD cohort comprised solely subjects with physician-diagnosed RA. Participants in the anti-TNF cohort were required to be starting their first biologic drug and were required to register within 6 months of starting anti-TNF to minimise selection bias. This criterion was particularly relevant to the analysis of serious infection risk, since it was found that the risk was highest during the first 6 months of anti-TNF therapy [192]. With respect to the risk of malignancy, it is plausible that Rheumatologists may have selected to register patients retrospectively who were diagnosed with cancer following anti-TNF, if they were not required to register patients prospectively and within the first 6 months. This would have led to a falsely elevated cancer rate for anti-TNF. Subjects were excluded from the primary cancer analyses in this thesis if they had not acquired at least 6 months follow up in the BSRBR-RA at the date at which the data were censored (for example 31st January 2011 for lymphoma). The first six months of follow up (and cancers diagnosed during that time) were excluded to try and minimise bias due to; 1) patients in the anti-TNF cohort being screened for cancer more intensively than those entering the comparison cohort; and 2) prevalent cancers being included in the analysis.

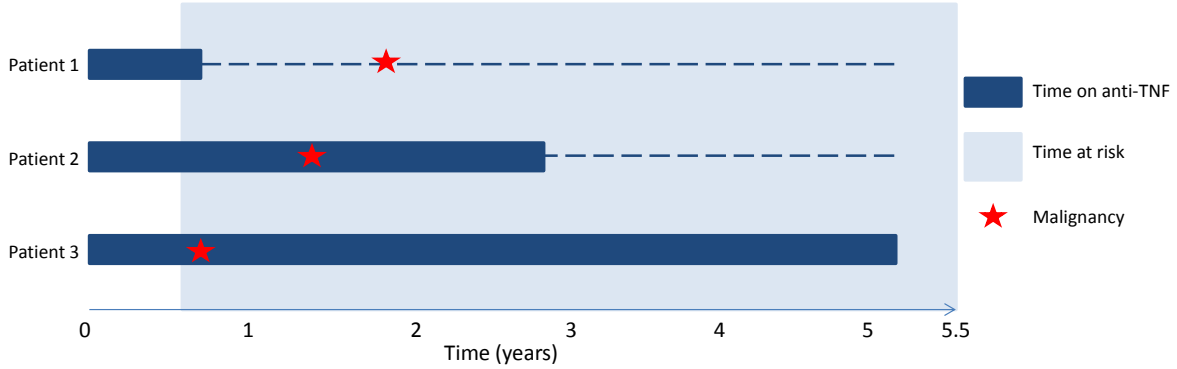
3.2.5 Defining time at risk

3.2.5.1 Attributing risk to drugs

Follow up, and time at risk of cancer, started from six months after the date of registration for the comparison cohort and six months after the date of the first dose of anti-TNF for the anti-TNF cohort. A number of different models for attributing risk to a drug have been described when analysing data from drug registries [193]. In the 'on drug' model the outcome is only attributed to the drug whilst the patient is actively taking it i.e. follow up is censored at the date of discontinuing treatment. For anti-TNF, this was defined in the BSRBR-RA as time up to the first missed dose. This model does not take account of the pharmacokinetics and pharmacodynamics of the drug. For the anti-TNF agents, the dose, mode of administration, dosing frequency and half-life may all affect the duration that a patient could be considered exposed to treatment. A second on drug model includes a lag window after the date of discontinuation, arbitrarily set at 90 days in the BSRBR-RA. As well as allowing for the effect of anti-TNF beyond the date of discontinuation, inclusion of a lag window ensures that adverse events in which drug discontinuation occurs after the onset of symptoms but before a formal diagnosis is made are not censored from the analysis.

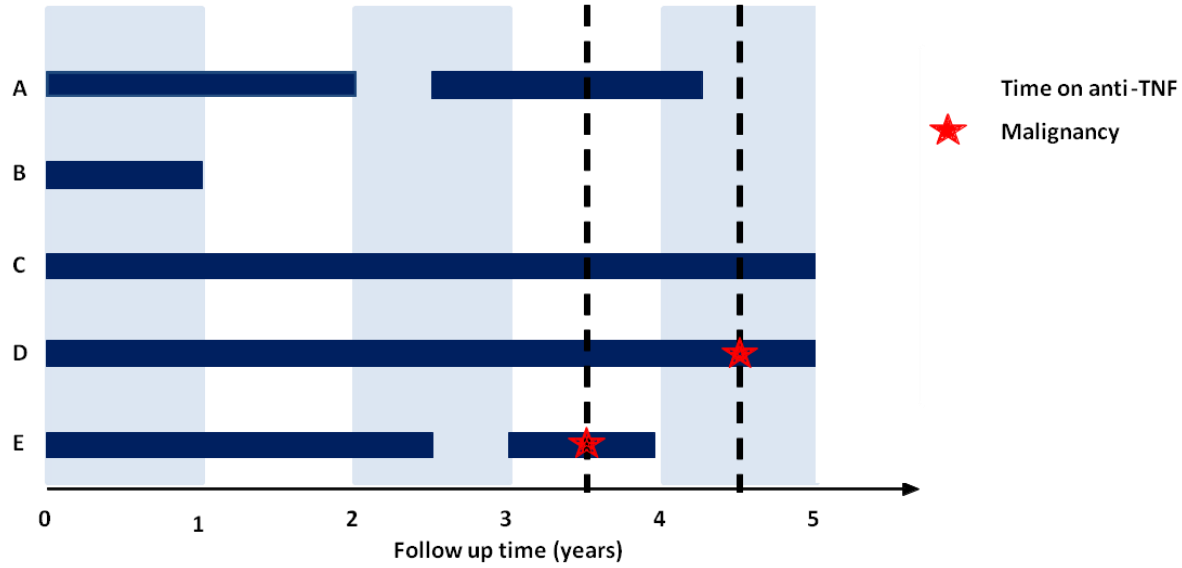
Malignancies typically have a long latent period and the effect of anti-TNF therapy on risk of malignancy may extend beyond the period in which a patient is actively receiving the drug. To account for this a third model was used in this thesis; the 'ever exposed' model. In this model all follow up time after the first dose of anti-TNF is included in the analysis (Figure 3-3). For the three example patients shown, each would be considered at risk for the five-year follow up period and all of the malignancies denoted using a red star would be included.

Figure 3-3 Attributing risk to therapy



An additional model was developed for this thesis, incorporating the effect of cumulative time exposed to anti-TNF. For this analysis, along with on drug analyses, time after last received consultant follow up was dropped since information about current drug exposure status came from these forms. Cumulative time on anti-TNF (plus a 90 day lag window) was calculated for every participant in the anti-TNF cohort for each failure point i.e. cancer (Figure 3-4). For the lymphoma analysis, cumulative exposure was calculated to the nearest day of anti-TNF therapy. However, for the solid cancer analysis, in which there were many more failures (cancers), such an approach led to around 50 million observations being created in the Stata dataset. Adequate computational power to analyse these data was unavailable. Instead, for the solid cancer analysis, each subject's follow up time was split every three months, and cumulative exposure to anti-TNF calculated to the nearest three months. This cumulative exposure time was then categorised into less than 1.5 years, 1.5 to <3 years and more than 3 years for analysis. Each category was compared first to nbDMARD and then to exposure of <1.5 years. A test for trend was conducted (*testparm)* to identify any change in risk with increasing exposure time.

Figure 3-4 Development of the cumulative time on anti-TNF model



The figure shows five patients (A to E). Patients D and E had a cancer during follow up. Patient A contributed 3.75 years of cumulative exposure to anti-TNF at the time of patient D's cancer and 3 years at the time of patient E's cancer. Patient B contributed 1 year at the time of patients D and E's cancers. Patient C contributed 4.5 years to patient D and 3.5 years to patient E. Patient D contributed 4.5 years at the time point of their cancer and 3.5 years for patient E. Patient E contributed 3 years to the analysis of their cancer.

3.2.5.2 Censoring time at risk of cancer

There were a number of reasons that led to patients being censored from the analyses as listed below.

1. All follow up was censored at a defined time point e.g. for the solid cancer and lymphoma analyses on 31st January 2011. This was a year before the dataset was extracted to allow a lag period for cancers to be reported from the cancer agencies and/or Rheumatologists. A year was chosen since Rheumatologists were asked to return follow up forms annually.
2. All patients that died before the data cut off point were censored at the date of their death.
3. All patients were censored at the time of their first incident cancer in each analysis. For the KSC analysis, patients were not censored at this point since it was felt that the overall burden of skin cancer should be considered. This is discussed further in Chapter 8.
4. Participants in the nbDMARD cohort were censored on the date of starting any biologic therapy for RA. At that point all further follow up in the nbDMARD cohort ceased and the patient was invited to join one of the biologic cohorts, if recruitment was open for the drug that they were starting.
5. For the anti-TNF cohort, patients were not censored at the point of starting a second anti-TNF drug or other biologic agent in the primary analysis. Sensitivity analyses in which follow up was limited to time on drug plus lag time or censored at the point of starting a second anti-TNF biologic drug were performed.

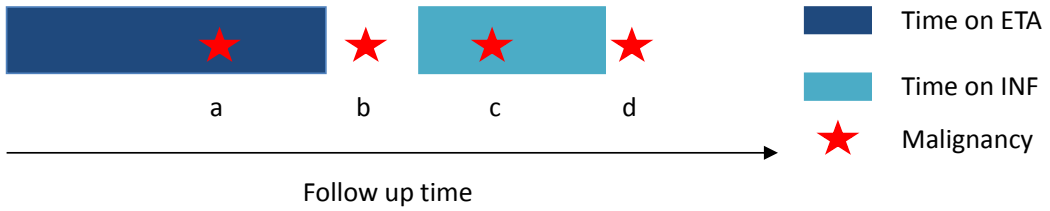
3.2.5.3 Analysis of subjects exposed to two or more anti-TNF drugs

Patients in the anti-TNF cohort remained under follow up if they switched to a second or subsequent TNF inhibitor or other biologic drug. The two main reasons for switching drugs were following an adverse event or inefficacy. Inefficacy was defined by NICE as either failure for the DAS28 to improve by at least 1.2 points or failure to maintain this improvement. In the primary analysis, the anti-TNF agents were treated as a single class and no differentiation was made between switchers and those that continued on their first drug.

When comparing the risk of cancer for each anti-TNF drug separately to the nbDMARD cohort, two approaches were explored. First, from the point of starting a second (or subsequent) anti-TNF, follow up was attributed to the most recently received drug. In this analysis, each cancer was

attributed to a single TNF inhibitor. Using the example in Figure 3-5, a first cancer occurring at time points (a) and (b) would be attributed to ETA and at time points (c) and (d) to INF. In a sensitivity model, patients remained at risk in the analysis of their first anti-TNF for the remainder of follow up, even after switching. In this model, cancers could be attributed to more than one anti-TNF. Using the example in Figure 3-5, a first cancer occurring at all four time points would be attributed to ETA and cancers at times (c) and (d) would also be attributed to INF.

Figure 3-5 Attributing risk to therapy in switchers



If a malignancy was attributed to the most recent anti-TNF then cancers at time points (a) and (b) would be attributed to ETA and (c) and (d) to INF. If an ever had model was used, a first cancer occurring at all time points would be attributed to ETA and cancers at times (c) and (d) to INF.

3.3 Statistical methods

All data were stored in a secure Microsoft access database. From here data were transferred into the statistics program Stata (StataCorp, College Station, TX) for analysis. Stata versions 10.1, 11.2 then 12.1 were used for the analyses.

3.3.1 Comparing baseline characteristics

Baseline characteristics of the anti-TNF and DMARD cohorts and between anti-TNF drugs were compared using the Chi squared test (χ^2) for categorical variables and p-values presented. For continuously distributed items, Wilcoxon rank-sum test was used to compare the anti-TNF to nbDMARD cohorts and Kruskal Wallis one-way analysis of variance was used to compare between anti-TNF drugs and p-values presented. Due to the large size of the BSRBR-RA, small differences in the baseline characteristics between the cohorts, that would not have be considered clinically significant, may have resulted in statistically significant p values. The percentage difference in categorical variables and standardised (mean) difference for continuous variables were also presented. The standardised difference was calculated by dividing the difference in the mean of the variables between groups by its standard deviation.

3.3.2 Missing data

There were missing baseline and follow up data in the datasets used in this thesis. The most frequently missing item at baseline in the BSRBR-RA was the measure of disability, the HAQ score, which was recorded by the patient. Different patterns of missing data can arise in observational studies and these have been classified as; missing completely at random (MCAR); missing at random (MAR) and missing not at random (MNAR) [194].

3.3.2.1 Missing completely at random

This describes the mechanism of missing data in which a subject's probability of having missing data is independent of both their observed and unobserved characteristics. Under these conditions subjects with missing data can be regarded as a random sample of the entire cohort and excluded from the analysis (complete case analysis) without introducing any bias. Complete case analysis does result in loss of precision due to reduced sample size.

3.3.2.2 Missing at random

Data can be considered MAR if the probability of an observation being missing is dependent on the observed variables but not on unmeasured factors. This means that if one takes count of the values of the measured covariates in subjects with and without missing data, the dataset can be analysed without introducing bias.

3.3.2.3 Missing not at random

Data are considered to be MNAR if the reason for missingness is related to an unmeasured characteristic or outcome of the subject. Neither complete case analysis nor use of techniques to replace missing data can be used without introducing bias in this situation.

3.3.3 Handling missing data

Different methods of handling missing data are currently in use in the analysis of observational data. Simple methods, such as complete case analysis, last value carried forward and missing category indicator, nearly always result in biased estimates when data are not MCAR. Valid methods for

accounting for data that are MAR include weighting and multiple imputation (MI). Weighting requires a model for the probability of response to be fitted and subjects with missing data being up-weighted in the analysis. For example, if older men are more likely to have missing data then they would receive a greater weight than young women. Weighting is suited to analyses where there are data missing in one or few covariates and is less effective at managing missingness in large numbers of variables.

Multiple imputation was used to handle missing data in the analyses in this thesis since data were missing for multiple variables. Multiple imputation is a two-step process in which the handling of missing data is performed separately to the analysis addressing the research question. First, missing values for each variable are predicted using known values of the other variables. It is noteworthy that MI is only valid if all the covariates that predict missingness are included in the model used to impute the data. The process of imputing data is performed multiple times, creating multiple unique datasets. Multiple imputation has the advantages of both restoring natural variability in the imputed data and also incorporating uncertainty caused by estimating missing data [195]. Following MI, each imputed dataset is analysed separately using standard methods and then the results of each analysis combined. In this thesis MI was used to replace missing values in the baseline variables DAS28 score, HAQ, RA disease duration, smoking status and ethnicity. Multiple imputation was performed in Stata using the *ICE* command, which imputes using chained equations. The baseline variables used to impute the missing values were the covariates with missing values (listed above), age, sex, components of the DAS 28 score, number of prior nbDMARDs, current or prior exposure to AZA, CSA and CYC, prior cancer, exposure to steroids and NSAID at baseline, year of entry to the BSRBR-RA and number of comorbidities. In addition, the outcome, i.e. the cancer under analysis, was included as a covariate to preserve relationships between the baseline covariates and the outcome. Data were imputed separately for the nbDMARD and anti-TNF cohorts. Twenty cycles of imputation were performed, creating 20 unique imputed datasets. Each dataset was analysed using standard methods for survival analysis (Cox regression) and the results of each analysis combined using the *mim* command in Stata.

3.3.4 Incidence rates of cancer

3.3.4.1 Determining incidence

Crude incidence rates of cancer were calculated for each cohort by dividing the number of observed cancers by the total number of pyrs of follow up. Ninety-five percent CI were constructed assuming a Poisson distribution of cases.

3.3.4.2 Comparing incidence between the cohorts

Cox proportional hazard regression was used to compare incidence rates of cancer between the anti-TNF and nbDMARD cohorts. Whilst both Poisson and Cox regression can be used to model risk over time, Poisson regression, unlike Cox regression, assumes that rates remain constant over time and this assumption was not met in the BSRBR-RA data. Both Poisson and Cox regression assume that that the ratio of the hazard between different exposure groups remains constant over time. For Cox regression this is termed the proportional hazards (PH) assumption. Non-proportionality corresponds to an interaction between the exposure variable, in this case anti-TNF, and time.

In this thesis the PH assumption was first examined graphically by plotting observed survival curves for the anti-TNF-exposed and biologic-naïve cohorts separately alongside corresponding survival curves predicted by the Cox model. If the PH assumption was correct, the observed curves for each exposure group would overlie the predicted curve. Following this, the PH assumption was tested formally, based on Schoenfeld residuals. A residual measures the difference between the observed and expected data under the model assumptions, in the case of Schoenfeld residuals PH. Schoenfeld residuals are calculated at every failure time and under the PH assumption are independent of time. This assumption was tested using the *estat phtest* command in Stata. A statistically significant p value indicated evidence of non-proportionality. If non-proportionality was detected, the analysis period could be divided into smaller time periods and the hazard ratio allowed to vary between time periods. The PH assumption would only need to hold within each time period.

3.4 Confounding

3.4.1 Identifying possible confounders

There are two main ways in which covariates can be selected as possible confounders in analyses. First, data-driven approaches can be used. For example all variables that change the estimated exposure effect by at least 10% can be included in the model, or a stepwise selection process can be applied. This method adds variables one at a time to the model, testing all the other variables to see whether they should be removed. These approaches have the potential advantage of reducing the number of predictors used in a model which may be necessary if a standard multivariate model is used. However, propensity score (PS) methods were used to control for confounding in this thesis and so the need to restrict the number of covariates in the model was removed. Furthermore, PS models that are better discriminators of exposure status do not necessarily result in better estimators of exposure effect. Selecting variables that are strongly associated with exposure status but not with the outcome may introduce bias [196].

An alternative method was selected for the principal analyses in this thesis. Potential confounders were identified *a priori* based on pre-existing knowledge of their relationship with exposure to anti-TNF and cancer. For example, using this approach, age and sex were included in all analyses since both the likelihood of exposure to anti-TNF in the BSRBR-RA and the incidence of cancer were known to differ by age and sex (discussed in section 4.3.1). Other baseline variables considered as possible confounders were smoking, socioeconomic status, ethnicity, co-morbidity, RA disease duration, disease activity (DAS 28), physical function (HAQ) and exposure to nbDMARDs and steroids. There was some variation in the confounders finally included in the models for different analyses, as explained in the relevant chapters. The distribution of confounders in the anti-TNF and nbDMARD cohorts will be discussed in Chapter 4.

3.4.1.1 Ethnicity, socioeconomic status and smoking

Social inequalities in the incidence, and in particular mortality, from cancer are well described [197, 198]. The incidence of cancer is lower, and survival rates higher, in whites than in other ethnic groups but socioeconomic factors such as poverty and low levels of education are more important than genetic differences [198]. Ethnicity was included as a confounder in the analyses. However, more than 95% of the BSRBR-RA were classified as white and so other ethnic groups were combined.

Employment status was also recorded in the BSRBR-RA. However, employment status was deemed to be an unreliable marker of socioeconomic status in this study since patients with RA, especially severe RA, were frequently not able to work due to disability. The patient's home address was recorded, and the possibility of using their postcode to assign them a score from the Index of Multiple Deprivation was explored [199]. Such an approach proved to be problematic since the published scores were calculated differently and at different times for England, Scotland and Wales and were not available for Northern Ireland and so this approach was ultimately not included. Other markers of socioeconomic status such as level of education were not collected. Smoking is an important risk factor for several cancers. In addition, it is a risk factor for RA disease severity [200]. Smoking is also associated with lower socioeconomic status and likelihood of receiving anti-TNF and so was included as a confounder.

3.4.1.2 Co-morbidity

Presence of co-morbidity at baseline was included as a confounder as it is related to both the incidence of cancer and prognosis following diagnosis. A global co-morbidity variable was created from those collected on the BSRBR-RA baseline form as it was felt that adjusting for the overall burden of co-morbidity, rather than each co-morbidity (which may be individually uncommon), would be more meaningful. First, patients were identified as having ischaemic heart disease at baseline if they had angina and/or myocardial infarction recorded on their consultant baseline form. Similarly, asthma and bronchitis/emphysema were combined into a lung co-morbidity variable. A global categorical variable containing the number of co-morbidities present from the list ischaemic heart disease, lung disease, hypertension, stroke, renal disease, diabetes mellitus, liver disease and depression was then made. History of cancer was excluded from this global co-morbidity variable.

3.4.1.3 RA disease severity

Disease severity was considered to be a confounder in this thesis. It was very closely related to the exposure of interest (receiving anti-TNF) and there was evidence from the literature that it was independently associated with the outcome, especially lymphoma (see section 1.3.6.1). The BSRBR-RA collects information about disease severity in several ways; disease duration, DAS28 and HAQ were all considered to be confounders. In addition, year of entry to the BSRBR-RA was put forward as a confounder since there was a temporal trend in the severity of patients being selected for anti-

TNF in the UK, with the patients treated earliest having the most severe disease. Furthermore, by adjusting for the time of entry to the BSRBR-RA it was possible that other unmeasured confounding relating to changes in the way that Rheumatologists managed patients with RA, were accounted for.

3.4.1.4 Non-biologic drug treatment of RA

Exposure to corticosteroids was considered to be a marker of severe RA and included as a potential confounder. Certain nbDMARDs have been associated with specific cancers, namely CYC, AZA and CSA and during the time of this thesis work these nbDMARDs were typically reserved for patients with more severe RA, who had failed MTX, sulphasalazine and/or hydroxychloroquine. The BSRBR-RA also recorded the number of nbDMARDs a patient had taken prior to registration. This acted as a marker of RA disease severity and overall burden of drug therapy. Non-biologic DMARD was included as a confounder in the analyses in this thesis, but the particular variables used was specific to each analysis and will be discussed in the relevant chapters.

Whilst the BSRBR-RA did collect information on NSAIDs at baseline, this was limited to NSAIDs prescribed at the point of registration, with no details about whether the drugs were being used regularly or on an as required basis. Over the counter use of NSAIDs was not captured. These drugs were not included as confounders in the principal analyses due to the poor measure of NSAID exposure in the BSRBR-RA leading to significant risk of misclassification.

3.4.2 Methods of controlling for confounding

Multivariate regression analysis is inappropriate for uncommon outcomes since it is generally accepted that between 10 and 20 events are required for every covariate included in the regression model. An alternative method for analysing rare events requires the calculation of a subject's PS i.e. their probability of receiving treatment (in this case anti-TNF) conditional on all the other factors that may influence whether or not they received treatment. The PS has a single value for each subject that can be substituted into the regression model in place of all of the potentially confounding covariates. Critically, PS methods can only adjust for confounders that have been measured.

Whilst the primary reason for selecting PS methods for the analyses in this thesis was their superior ability to estimate treatment effects when outcomes are uncommon, they have a number of other advantages over standard multivariate regression (reviewed by Glynn *et al.* [201]). First, when using stratification or matching, the PS does not make assumptions about the shape of the relationship between the PS and the outcome. Furthermore, the PS allows detection of different effects of the treatment according to the strength of the indication for its use. One might hypothesise that patients with the greatest indication for treatment are those who are most likely to benefit. Another advantage of PS methods is that areas of non-overlap between the two cohorts can be identified i.e. patients in the untreated cohort that could never receive treatment and vice versa. Since such areas of non-overlap areas dependent on complex interactions of multiple variables, identifying them outside of PS models is difficult.

3.4.2.1 Construction and use of the propensity score model

Variables to include in the PS model were selected *a priori* for each analysis. Use of PS models in epidemiology increased substantially during the course of this PhD. As a result, knowledge about PS model fitting advanced significantly and so the methods used to construct and implement the models evolved during this time. In early work for this thesis, a simple logistic regression model was run and then tested to determine how well confounders were balanced. Interaction terms and powers of variables were then included to improve the fit. Later, this process of selecting powers and interaction terms was semi-automated using propensity software, developed by Mark Lunt at the University of Manchester. This is free to download in Stata. Prior to submission of this thesis, the methods for fitting the PS model advanced further. In the latest analyses the PS model was derived and tested using 'Prop_sel' software in Stata. This was developed by Mark Lunt at the University of Manchester and can be freely downloaded in Stata. Ultimately, earlier analyses were repeated using the Prop_sel methods to ensure that all the analyses in this thesis used the most up to date methodology.

The PS models derived in this thesis were tested to see how well they controlled for confounding bias. The concordance or 'c' statistic (equivalent to the area under the receiver operating characteristic curve) is widely reported as a means of testing this. However, the c statistic measures the discriminatory ability of the PS model at recognising treated and untreated subjects and so

largely reflects how different the two groups were to start with. For example, in an RCT, following randomisation, one would expect the two groups to be very closely matched for confounders. If a PS model was applied to this population then the c statistic would be close to 0.5, since the distribution of PS in the two cohorts would overlap almost completely. This could be interpreted as a poorly performing PS model. Conversely, if untreated patients varied considerably from treated patients with respect to confounders included in the PS, then a high c statistic could be reported, even if the model failed to balance the confounders adequately, as there would be little overlap in the distributions of PS. The c statistic was not used in this thesis. In early analyses the standardised difference (difference in the mean value in exposed/unexposed subjects divided by the standard deviation) for each variable was examined. A standardised difference of less than 0.1 for each variable was accepted as sufficient balance. The disadvantage of using standardised differences was that this method did not take into account the strength of the relationship between the confounder and the outcome and so ignored the fact that precise balancing of the most important confounders was more important than balancing covariates less strongly associated with the outcome. This issue was addressed in the Prop_sel method of constructing the PS model. In Prop_sel a logistic regression analysis was run first to determine the effect of the confounders on the outcome (cancer). A beta matrix with this information was saved and then included in the logistic regression model used to create the PS. The balance of the model was tested by examining the expected bias, which is the likely bias in the treatment estimate due to each confounder. A maximum bias of 2% in either direction was considered acceptable.

Once calculated, there are three main ways that a PS can be used in survival analysis; matching, weighting and stratification. Matching involves comparing the PS in each treated subject to each untreated subject and paring off those with the closest match. As pairs are matched, the pool of remaining subjects diminishes and so the matches become poorer as the process progresses. This can be overcome by pre-specifying the maximum value by which PS can differ in matched pairs. Matching was not used in this thesis due to the three-fold higher number of anti-TNF versus nbDMARD patients in the BSRBR-RA. Weighting using the PS can be done in two main ways; inverse probability of treatment weighting (IPTW) and standardised mortality ratio (SMR) weighting. Inverse probability of treatment weighting up-weights both unexposed patients with the highest PS for treatment and exposed patients with the lowest PS, thus comparing what one would expect to see if the whole cohort was treated versus if nobody was treated. SMR weighting involves up-weighting

unexposed patients with the highest PS whilst not re-weighting the exposed cohort i.e. comparing what happened to the treated cohort to what would have happened to them had they not been treated. These methods yield identical results if the treatment effect is the same in all subjects. Weighting can lead to individual patients being assigned very high weights, for example a weight of 200 would mean that one person would contribute to the analysis 200 times. This is problematic since bias can be introduced by up-weighting subjects at the extreme ends of the distribution of PS to such an extent, especially in the presence of unmeasured confounding. The approach used in this thesis to account for this was to truncate weights at 20 [202].

Stratification is the simplest way of using the PS and involves dividing the subjects into strata according to their PS and looking at the effect of treatment within each strata. It is necessary that each stratum contains both untreated and treated subjects and so use of stratification can be problematic in small datasets. Quintiles of PS are typically used as they remove around 90% of confounding [203, 204]. However, using a larger number of strata results in improved balance of confounders within each stratum and so better control of confounding. The large size of the BSRBR-RA dataset facilitated the use of deciles of PS in this thesis. Both weighting and stratification methods are worked through in the thesis, using the analysis of lymphomas (Chapter 6). Ultimately, stratification of the PS into deciles (DP) was selected as the most appropriate method of balancing confounders in this work and used in subsequent chapters.

4. Characteristics of the nbDMARD and anti-TNF cohorts

This chapter describes the baseline characteristics of the nbDMARD and anti-TNF-treated cohorts. Differences between the cohorts are highlighted and the impact of these differences on the subsequent analyses discussed.

4 Characteristics of the nbDMARD and anti-TNF cohorts

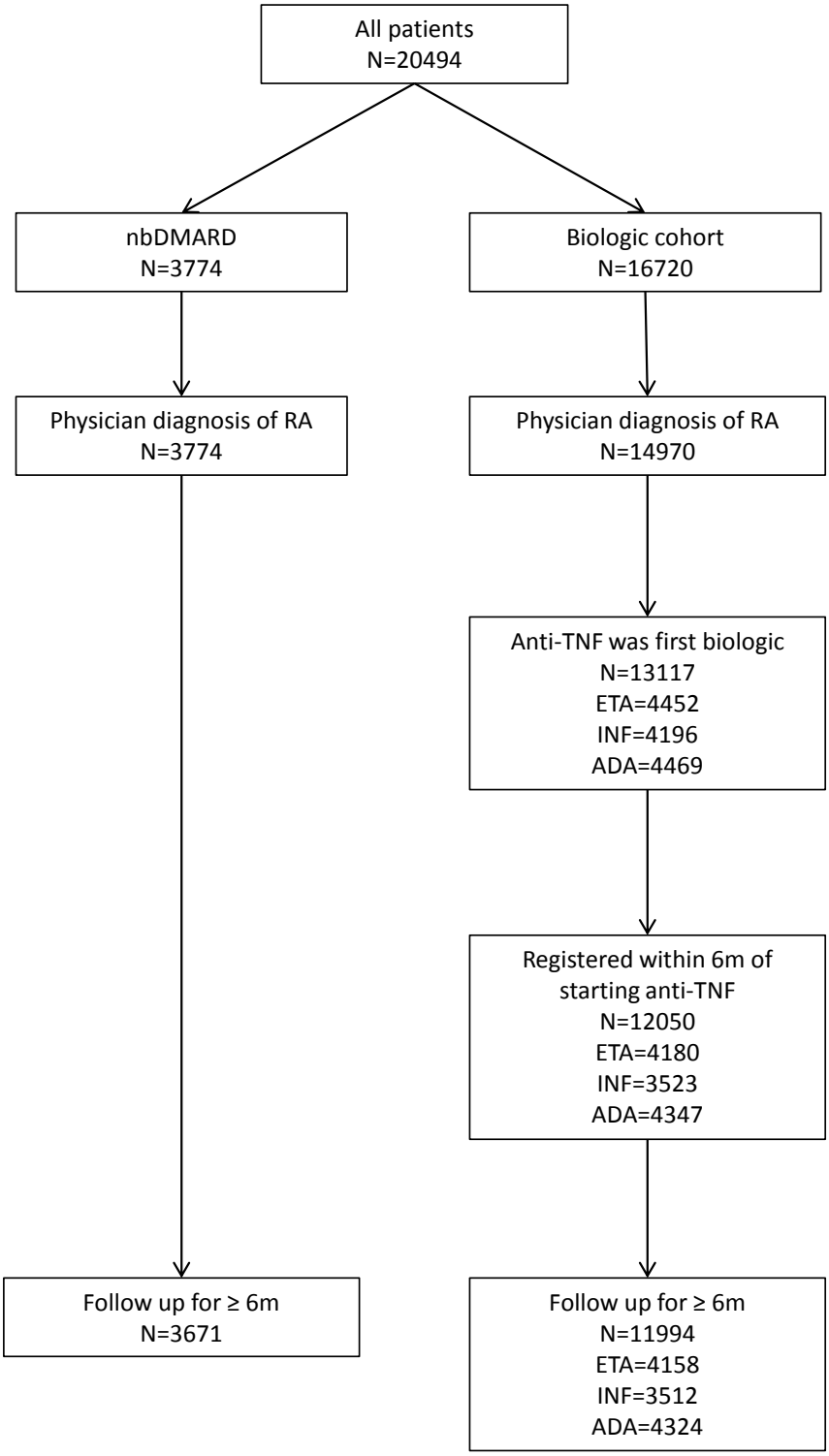
4.1 Aims

The confounding effects of known risk factors for cancer need to be borne in mind when assessing whether or not exposure to anti-TNF influences the risk of cancer. The aims of this chapter are to describe the baseline characteristics of the anti-TNF and biologic-naïve cohorts in the BSRBR-RA and to highlight any differences between them that may influence the observed incidence rate of cancer.

4.2 Selection of the study population

The Stata dataset that was used for the lymphoma and solid cancer analyses in this thesis was created on 31st January 2012. Earlier datasets were used for the nbDMARD-only and KSC analyses. This dataset created in 2012 comprised all follow up time and events occurring up to 31st January 2011, to allow a year for cancers to be reported. At that time 20494 patients had registered with the BSRBR-RA, of whom 3774 were biologic naïve. One hundred and three subjects were excluded because they had either not had time to reach 6 months follow up on 31st January 2011 or had been censored within the first 6 months (Figure 4-1). The biologic cohort comprised 16720 subjects of whom 1750 were starting therapy for an indication other than RA and were excluded. A further 1504 were excluded as they were registering in the rituximab cohort, 167 for certolizumab, 151 for anakinra and 30 for tocilizumab. A further 1067 patients were excluded as they did not register with the BSRBR-RA within 6 months of starting anti-TNF therapy. Fifty-six patients were excluded because they were censored before reaching 6 months follow up.

Figure 4-1 Flowchart showing selection of subjects for analysis



Further details of patient selection are given in each chapter because there were differences in the way in which patients were selected for each separate analysis. For example, patients with previous solid cancer were excluded from the analysis addressing the risk of solid cancer and patients with low RA disease activity were dropped from some analyses. Since each analysis used a cohort of patients that was broadly similar to one another, the baseline characteristics of the parent cohort are described in detail here.

4.3 Baseline characteristics of the nbDMARD versus anti-TNF cohorts

Differences in the baseline characteristics of the nbDMARD and anti-TNF-treated cohorts need to be considered when comparing the incidence rate of cancer between them. There was a higher proportion of men and a higher mean age in the nbDMARD cohort, both of which are risk factors for cancer (Table 4-1). Conversely, the anti-TNF cohort had evidence of more severe disease and greater exposure to immunosuppression (Table 4-3, page 109).

Table 4-1 Baseline characteristics of the nbDMARD and anti-TNF cohorts

	nbDMARD N=3671	Anti-TNF N=11994	p-value	Standardised difference or % difference[#]
Mean age: years (SD)	60 (12)	56 (12)	<0.001	-0.339
Females: %	2659 (72)	9156 (76)	<0.001	4%
Ethnicity: (%)				
- White	2794 (76)	9875 (83)	<0.001	7%
- non-white	71 (2)	410 (3)		1%
- missing	806 (22)	1653 (14)		8%
Country of residence: (%)				
- England	3113 (85)	10139 (85)	<0.001	0%
- Northern Ireland	361 (10)	299 (2)		8%
- Scotland	155 (4)	934 (8)		4%
- Wales	42 (1)	622 (5)		4%
Smoking: (%)				
- Current	868 (24)	2602 (22)	0.001	2%
- Former	1455 (40)	4533 (38)		2%
- Never	1330 (36)	4726 (40)		4%
- Missing	18 (0)	77 (1)		1%
Co-morbidity*: (%)				
- None	1543 (42)	5578 (47)	<0.001	5%
- One	1272 (35)	4110 (34)		1%
- Two	601 (16)	1698 (14)		2%
- Three or more	255 (7)	608 (5)		2%
Prior NHS IC reported cancer (%)	143 (4)	171 (1)	<0.001	3%

[#]Standardised difference presented for continuous variables and percentage difference for categorical variables

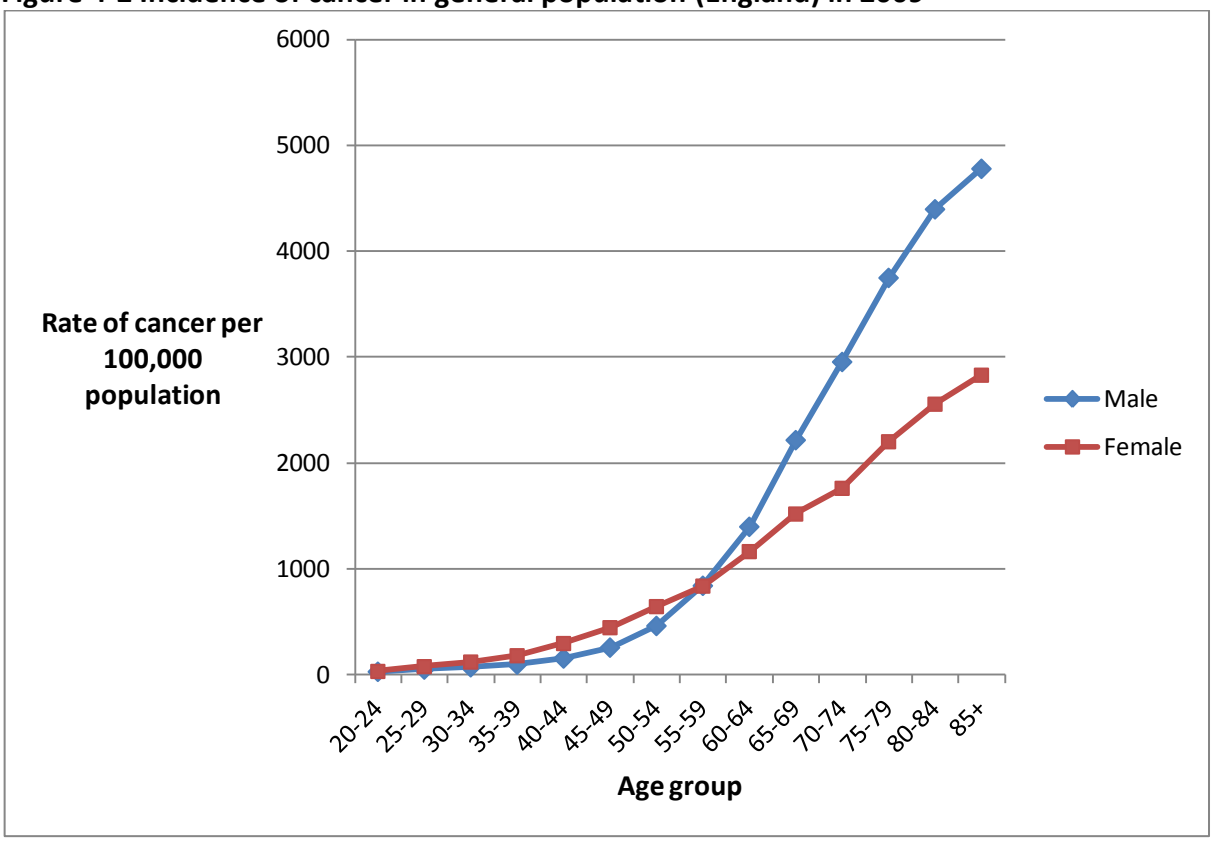
* Hypertension, ischaemic heart disease (myocardial infarction or angina), stroke, chronic obstructive pulmonary disease or asthma, diabetes mellitus, depression, renal disease and liver disease

SD standard deviation

4.3.1 Age and gender

The mean age of the nbDMARD cohort was four years higher than that of the anti-TNF cohort; 60 versus 56 (Table 4-1). In the general population cancer predominantly affects the elderly and the relationship between increasing age and cancer risk is non-linear (Figure 4-2).

Figure 4-2 Incidence of cancer in general population (England) in 2009



The data used to produce this figure were published by ONS, Series MB1 (Number 40) 2011 [57].

Figure 4-2 demonstrates that below the age of 55 the risk of cancer in the general population is low and that it rises sharply above the age of 60. The different age distributions in the nbDMARD and anti-TNF cohorts, although numerically fairly small, could introduce confounding when comparing the cancer risk between the two cohorts. The proportion of males in the nbDMARD cohort was greater than in the anti-TNF cohort (28% versus 24%; Table 4-1). Up to the age of 55 the incidence of cancer is slightly higher in females than males (Figure 4-2). Above this, there is an exponential increase in cancer risk in males. To illustrate these points, the annual incidence of cancer in England for the mean age of the nbDMARD cohort (age category 60-64) was 1400 per 100,000 in men and 1166 in women in 2009 and for the mean age of the anti-TNF cohort (age category 55 to 59) the corresponding rates were 843 and 840 per 100,000 [57]. In summary, the age and sex distributions

of the two cohorts both lead to a higher expected cancer rate in the nbDMARD cohort and both these factors need to be adjusted for in cancer analyses.

4.3.2 Ethnicity and country of residence

Twenty-two percent of participants did not answer the question about their ethnicity in the nbDMARD cohort and 14% in the anti-TNF cohort (Table 4-1). Of the responders, the vast majority were white; nbDMARD 98%; anti-TNF 96%. Both incidence and survival following cancer differ by ethnicity. For example, in the USA, white women have the highest incidence of breast cancer but the mortality rate is highest for black women [205].

Eighty-five percent of both the nbDMARD and anti-TNF cohorts lived in England at the time of registration with the BSRBR-RA (Table 4-1). There were regional differences in the composition of the remaining 15% of the cohorts; subjects from Northern Ireland contributed 10% for nbDMARD and only 2% for anti-TNF. The proportion of Scottish and Welsh patients was greater in the anti-TNF cohorts. Annual cancer rates in the general population vary across the UK (Table 4-2). These rates are directly age-standardised to the European standard population, allowing direct comparisons to be made between countries. In 2009, the rates were lowest in England and highest in Northern Ireland.

Table 4-2 European age-standardised incidence rate of cancer (excluding KSC) per 100,000 population for 2009

Country	European age-standardised incidence rate of cancer per 100,000	
	Males	Females
England [57]	424	367
Northern Ireland [206]	646	503
Scotland [207]	452	407
Wales [208]	454	390

Within England, the incidence of cancer in 2009 was highest in the North West (standardised registration ratio 115 for males and 117 for females) and lowest in London (87 and 80 for the corresponding ratios). These between-country and within-country differences reflect both variation in levels of ascertainment as well as genuine differences in incidence. Any genuine differences may

be due to differences in the prevalence of other risk factors for cancer, such as smoking. Smoking status at baseline was recorded in the BSRBR-RA.

4.3.3 Co-morbidity

More than half of the cohort had at least one co-morbidity at baseline (Table 4-1). A third of each cohort had one co-morbid condition, 16% of the nbDMARD cohort and 14% of the anti-TNF cohort had two recorded co-morbidities and 7% and 5% respectively had three or more. The most frequent co-morbidities were; hypertension, present in 31% of the cohort; depression (19%); chronic obstructive pulmonary disease or asthma (15%); ischaemic heart disease (7%); and diabetes mellitus (6%). The presence of co-morbid disease is a risk factor for poor prognosis in patients diagnosed with cancer [209], but may also be a marker for those people at risk of developing cancer due to shared risk factors. Previous cancers were not included in the combined co-morbidity variable and are discussed in more detail later in this chapter.

4.3.4 Disease severity

The anti-TNF cohort had more severe disease than the nbDMARD cohort with higher disease activity, higher HAQ score (worse physical function) and longer disease duration (Table 4-3).

Table 4-3 Rheumatoid arthritis severity at baseline in the nbDMARD and anti-TNF cohorts

	nbDMARD N=3380	Anti-TNF N=11938	p-value	Standardised difference or % difference[#]
Mean DAS28 (SD)	5.1 (1.3)	6.6 (1.0)	<0.001	1.364
Mean HAQ (SD)	1.5 (0.8)	2.0 (0.6)	<0.001	0.864
Median disease duration: years (IQR)	6 (1, 15)	11 (6, 19)	<0.001	0.366
Number of prior nbDMARD: median (IQR)	2 (1, 3)	4 (3, 5)	<0.001	0.888
4 or more prior DMARD: %	745 (20)	6297 (53)	<0.001	33%
Ever had CYC: %	20 (1)	270 (2)	<0.001	1%
Ever had AZA: %	248 (7)	2508 (21)	<0.001	14%
Ever had CSA: %	144 (4)	1967 (16)	<0.001	12%
Baseline steroid use: %	827 (23)	5303 (44)	<0.001	21%
Baseline NSAID use: %	1960 (53)	7083 (59)	<0.001	6%

There were missing data for DAS28: nbDMARD 53 patients (1%), anti-TNF 110 (1%), HAQ: nbDMARD 742 (20%), anti-TNF 595 (5%) and disease duration: 23 (1%) nbDMARD and 93 (1%) anti-TNF.

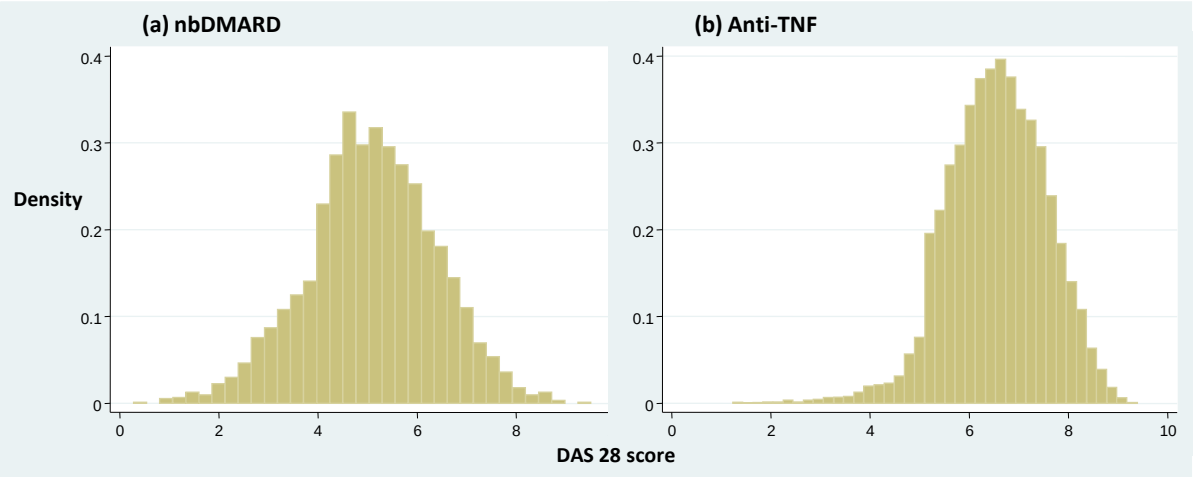
[#]Standardised difference presented for continuous variables and percentage difference for categorical variables

SD standard deviation; IQR inter-quartile range

4.3.4.1 Disease activity

The mean DAS28 score in the nbDMARD cohort was 5.1 compared to 6.6 for anti-TNF. The standard deviation was also higher for the nbDMARD cohort indicating a wider spread of values (Table 4-3; Figure 4-3). Figure 4-3 demonstrates that there was a group of patients in the nbDMARD cohort with low disease activity (DAS28 ≤3.2) whereas there were few patients with low disease activity in the anti-TNF cohort. This is due to national guidelines for prescribing of anti-TNF that mandate that only patients with high disease activity should be treated with anti-TNF [17].

Figure 4-3 Baseline disease activity (DAS28) in the nbDMARD and anti-TNF cohorts



Any possible confounding effect of disease activity is likely to vary between different analyses. Whilst cumulative disease activity is an important risk factor for lymphoma [86], no such relationship has been described for other cancers. However, given the magnitude of difference between the two cohorts, disease activity does need to be considered as a potential confounder in the following analyses.

4.3.4.2 Disability

The HAQ scores represent significantly different levels of disability between the two cohorts, since the minimum important clinically important difference is 0.22 [210, 211]. This, and the high proportion of missing data (20% for nbDMARD versus 5% for anti-TNF), are of importance since poor physical function is a risk factor for worse outcome in people with RA [212]. One might expect that patients who do not return their baseline HAQ form had higher levels of disability. This hypothesis is supported by an earlier publication from the BSRBR-RA in which the mortality rate in patients with complete baseline data in the nbDMARD cohort was 19 per 1000 pyrs compared to 28 per 1000 in those with missing data [213]. For this reason missing data were accounted for in the subsequent analyses using multiple imputation (see section 3.3.3).

4.3.4.3 Disease duration

The median disease duration was nearly twice as long in the anti-TNF compared to nbDMARD cohort (11 versus 6 years; Table 4-3). For both cohorts, the interquartile range was wide and indicated a positive skew in the distribution of values. Twenty-six percent of the nbDMARD cohort had early RA

of less than 2 years duration compared to 3% in the anti-TNF cohort. The low proportion of people with early RA in the anti-TNF cohort may be due to two factors. First, the BSRBR-RA was established at the time the TNF inhibitors were first approved for use in RA and so there was a large group of patients with long-standing disease waiting to start treatment. Second, national guidelines require a patient to have failed two previous nbDMARDs for 6 months each prior to starting anti-TNF. Disease duration will be considered as a confounder in subsequent analyses as it contributes to the overall burden of inflammatory disease which may be a risk factor for some cancers.

4.3.4.4 Exposure to drugs to treat rheumatoid arthritis

The anti-TNF cohort had greater exposure to nbDMARD prior to registration than the nbDMARD cohort, reflective of their more severe disease of longer duration (Table 4-3). An association between the most commonly used nbDMARDs (MTX, sulphasalazine, hydroxychloroquine) and cancer has not been demonstrated (see section 1.3.8.6). However, it is noteworthy that more than half the anti-TNF cohort had been exposed to at least four different nbDMARDs indicative of persistently active disease. Cyclophosphamide, AZA and CSA have all been associated with cancer (see section 1.3.8.6), and a higher proportion of the anti-TNF cohort had previous or current exposure to each of these. Both the number of previous nbDMARDs and these particular drugs were considered to be possible confounders in the analyses.

Twice as many participants in the anti-TNF cohort were taking steroids at baseline (44% versus 23%) in keeping with the higher levels of disease activity in this cohort. Steroid use was considered as another marker of disease severity and considered as a potential confounder in the analyses. The proportion of participants taking NSAIDs at baseline was similar between the cohorts (Table 4-3). This only captures prescribed NSAID and, since ibuprofen is widely available over the counter, the true number of patients taking these drugs is likely to be higher.

4.4 Differences in baseline characteristics within the anti-TNF cohort by drug

The baseline demographics of the three anti-TNF cohorts were very similar to each other (Table 4-4). There were no significant differences in the most important confounders when analysing cancer: age; gender; or smoking history.

Whilst the ETA and INF cohorts were very closely matched for disease severity, patients in the ADA had evidence of less severe RA (Table 4-4). The mean disease activity score was 6.5 in the ADA cohort compared with 6.6 for the other drugs, a difference that was highly statistically significant due to the large size of the cohorts. The ADA cohort had less disability at baseline (HAQ 1.9 versus 2.1), shorter disease duration (10 versus 12 years) and had less exposure to nbDMARDs and steroids. Prior to the availability of the anti-TNFs, patients with severe disease that was resistant to nbDMARD were accumulating and these patients were treated with the first available TNF inhibitors, ETA and INF. As discussed below in section 4.5, the ADA cohort was recruited more recently.

Table 4-4 Baseline characteristics of the three anti-TNF drugs

	ETA N=4158	INF N=3512	ADA N=4324	p-value
Mean age: years (SD)	56 (12)	56 (12)	57 (12)	0.159
Females: %	3215 (77)	2658 (76)	3283 (76)	0.117
Ethnicity: (%)				
- White	3452 (83)	2844 (81)	3618 (84)	0.566
- non-white	142 (3)	127 (4)	144 (3)	
- missing	564 (14)	541 (15)	541 (13)	
Country of residence: (%)				
- England	3577 (86)	3063 (87)	3499 (81)	
- Northern Ireland	45 (1)	56 (2)	198 (5)	<0.001
- Scotland	296 (7)	194 (6)	444 (10)	
- Wales	240 (6)	199 (6)	183 (4)	
Smoking: (%)				
- Current	853 (21)	770 (22)	995 (23)	0.058
- Former	1580 (38)	1327 (38)	1639 (38)	
- Never	1698 (41)	1397 (40)	1658 (38)	
- Missing	27 (1)	18 (1)	32 (1)	
Co-morbidity*: (%)				
- None	1881 (45)	1648 (47)	2049 (47)	0.027
- One	1413 (34)	1234 (35)	1463 (34)	
- Two	629 (15)	478 (14)	591 (14)	
- Three or more	235 (6)	152 (4)	221 (5)	
Prior NHS IC reported cancer (%)	67 (2)	46 (1)	58 (1)	0.456
Mean DAS28 (SD)	6.6 (1.0)	6.6 (1.0)	6.5 (1.0)	<0.001
Mean HAQ (SD)	2.1 (0.6)	2.1 (0.5)	1.9 (0.6)	<0.001
Median disease duration: years (IQR)	12 (6, 19)	12 (6, 19)	10 (5, 18)	<0.001
Number of prior nbDMARD: median (IQR)	4 (3, 5)	4 (3, 5)	3 (3, 5)	<0.001
4 or more prior DMARD: %	2442 (59)	1884 (54)	1971 (46)	<0.001
Ever had CYC: %	105 (3)	93 (3)	72 (2)	0.005
Ever had AZA: %	1073 (26)	730 (21)	705 (16)	<0.001
Ever had CSA: %	800 (19)	711 (20)	456 (11)	<0.001
Baseline steroid use: %	1991 (48)	1623(46)	1689 (39)	<0.001
Baseline NSAID use: %	2482 (60)	2069 (59)	2532 (59)	<0.001

SD standard deviation; IQR inter-quartile range

* Hypertension, ischaemic heart disease (myocardial infarction or angina), stroke, chronic obstructive pulmonary disease or asthma, diabetes mellitus, depression, renal disease and liver disease.

4.5 Year of registration with the BSR Biologics Register

Recruitment of patients to the anti-TNF cohort started before that to the nbDMARD cohort, as discussed above (section 3.1.3). Two-thirds of the anti-TNF cohort had been recruited by the end of 2004 compared to a third of the nbDMARD cohort (Table 4-5).

Table 4-5 Registration with the BSR Biologics Register by calendar year for each cohort

	nbDMARD	Anti-TNF	p-	First anti-TNF drug:			p-
	N=3380	N=11938	value	ETA	INF	ADA	value
				N=4140	N=3503	N=4295	
Entry year: (%)							
- pre-2003	8 (0)	1423 (12)	<0.001	207 (5)	1186 (34)	30 (1)	<0.001
- 2003	303 (8)	3141 (26)		1538 (37)	1122 (32)	481 (11)	
- 2004	884 (24)	3288 (27)		1983 (48)	509 (14)	796 (18)	
- 2005	919 (25)	1640 (14)		427 (10)	349 (10)	864 (20)	
- 2006	771 (21)	1154 (10)		2 (0)	281 (8)	871 (20)	
- 2007	348 (9)	861 (7)		1 (0)	65 (2)	795 (18)	
- 2008-2009	438 (12)	487 (4)		0 (0)	0 (0)	487 (11)	

Etanercept and INF were available for use in the UK prior to ADA and, whilst recruitment to the ETA cohort closed in 2005, only half the ADA cohort had been enrolled at that time. It has previously been described that patients recruited early to the BSRBR-RA had more severe disease at baseline and worse outcomes [214]. Year of entry to the study was converted to a dichotomous variable and included in the following analyses as an additional marker of disease severity. The variable was split at 30th June 2004.

4.6 Reporting of cancers occurring pre-registration

Cancers occurring prior to registration were reported to the BSRBR-RA by both Rheumatologists and flagging with the national cancer agencies (see section 3.2.1). In total, 941 subjects (6%) were

reported to have had one or more neoplasia prior to registration with the BSRBR-RA. When non-malignant neoplasia were excluded, 863 participants had prior cancer reported by the cancer agencies (Table 4-6). The overall agreement between Rheumatologists and the cancer agencies was moderate (kappa=0.53). The sensitivity of the consultant questionnaire was 61% for nbDMARD and 41% for anti-TNF, compared to the gold standard of the cancer registries. The specificities were 97% and 98% respectively.

Table 4-6 Reporting of previous malignant neoplasia by Rheumatologists and cancer agencies at baseline

		National cancer agency reported cancer			
		nbDMARD		Anti-TNF	
		No	Yes	No	Yes
Rheumatologist reported cancer	No	3277	116	11198	330
	Yes	72	182	155	229
	Don't know	24	0	76	6

When CIS and KSC were removed from the neoplasia reported by the cancer agencies, prior cancer was reported in 314 participants. Prior cancer was reported by consultants in 638 study participants. It was not possible to categorise these cancers into invasive cancers, CIS and KSC since these data were not always reported on the baseline form. For example, terms such as 'abnormal smear tests that required treatment' or 'skin cancer', without type, were frequently noted in patients recorded as having cancer at baseline by consultants. The overall agreement between the two data sources remained moderate (kappa=0.53), reflecting the fact that both sources agreed that the majority of study participants had not had a previous cancer. The sensitivity of the consultant questionnaire to report prior cancers improved to 90% for nbDMARD and 78% for anti-TNF (Table 4-7). The lower sensitivity for the anti-TNF cohort may reflect the fact that a high proportion of patients who were known to their Rheumatologist to have a history of cancer were excluded from this cohort, due to national guidelines advising against using anti-TNF therapy in such patients [180].

Table 4-7 Reporting of previous malignant neoplasia by Rheumatologists and cancer agencies at baseline, excluding CIS and KSC reported by cancer agencies

		National cancer agency reported cancer (excluding CIS and KSC)			
		nbDMARD		Anti-TNF	
		No	Yes	No	Yes
Rheumatologist	No	3378	15	11490	38
reported any	Yes	126	128	251	133
cancer	Don't know	24	0	82	0

Due to the differences in reporting of prior cancer between the two data sources, it was decided that only one source would be used to identify subjects with prior cancer in the analyses performed in this thesis. The cancer agencies and not the Rheumatologists were chosen for two reasons. First, the national cancer agencies were considered to be the gold standard for reporting prior cancers due to the high degree of accuracy of these data. Second, the exact date of diagnosis and information about the site of cancer (ICD-10 code and International Classification of Diseases for Oncology code) were reported from the cancer registries.

5. Risk of cancer in the biologic-naïve cohort compared to the general population

In this chapter the risk of cancer in the nbDMARD cohort relative to the general population is explored. This is to set in context the subsequent analyses of cancer incidence in anti-TNF-treated subjects.

5 Risk of cancer in the biologic-naïve cohort compared to the general population

5.1 Introduction

Previous studies of RA populations have reported widely varying estimates for overall and site-specific cancer risks compared to the general population (Table 1-2 and Table 1-3). This may reflect differences in the study cohorts, their treatment or the analysis methods as discussed earlier in Chapter 1. Concurrent with the introduction of TNF inhibitors to the management of RA, there have been significant changes in the overall way that RA is managed with an earlier and more aggressive approach to disease control [215, 216]. Therefore, in order to place the risk of cancers observed in patients exposed to anti-TNF therapy in context it was important to understand further the underlying risk of cancer in patients with RA currently treated with non-biologic therapies in the BSRBR-RA.

5.2 Aims

The aims of this chapter were:

- To quantify the rates of cancer in the nbDMARD cohort of the BSR Biologics Register and compare them to the general population.
- To identify risk factors for cancer among this cohort.

5.3 Methods

Malignancies occurring both prior to and throughout the study were ascertained through flagging with NHS IC and the Northern Irish Cancer Registry. Cancers reported to the BSRBR-RA by the Rheumatologist and/or patient only were not included to facilitate comparison with national cancer rates, published by ONS [217]. For this analysis, patients were not excluded if they had a prior cancer since such people would not be excluded from the general population published rates. Similarly, patients in both the BSRBR-RA and general population were not censored at the time of diagnosis of an incident cancer during follow up i.e. they could contribute multiple cancers to the analysis. Patients were followed until death, initiation of biologic therapy, 31st December 2009 or last returned follow up form, whichever came first. Although the analysis was censored at the end of 2009, data were collected until June 2011 which allowed 18 months for a lag in cancer reporting by

the agencies to BSRBR-RA. All malignancies were included in this analysis except for KSC (ICD-10 code C44) which are considered separately in Chapter 8.

5.3.1 Standardised incidence ratios

The primary outcome measure was incident cancer, defined as ICD-10 C00 – C97 excluding C44 [218]. Standardised incidence ratios were calculated by dividing the number of observed cancers in the nbDMARD cohort by the number of cancers which would have been expected if the rate in the RA cohort was the same as in the general population, allowing for age and sex, and then multiplying by 100. Indirect standardisation was used to obtain the expected number of cancers whereby sex- , 5 year age- and calendar year-specific population rates for England were applied to the corresponding pyrs of follow up in the BSRBR-RA. Population rates for England were derived from tables published annually by ONS [217], and applied to the entire cohort since the BSRBR-RA comprised too few people in Northern Ireland, Scotland and Wales to calculate SIR separately for each country. In a sensitivity analysis, the analysis was restricted to subjects living in England. Confidence intervals around the SIR were calculated assuming a Poisson distribution of cases. As well as overall cancer, a SIR was calculated separately for solid cancers (defined as ICD-10 codes C00-80 excluding C44) and MPM or LPM (ICD-10 C81-96). Site-specific SIR were calculated for sites where there were either at least 5 incident or expected malignancies.

Whilst the anti-TNF cohort comprised an inception cohort of anti-TNF users, the comparison cohort was a heterogeneous cohort of patients starting nbDMARD and prevalent users. A secondary analysis was performed to study the SIR in patients receiving nbDMARDs at different points along the treatment pathway. The SIR for all cancer sites was calculated separately in three subgroups of nbDMARD subjects; 1) patients starting their first nbDMARD within six months of registration with the BSRBR-RA; 2) patients starting a second or subsequent nbDMARD within the preceding 6 months (adding to or switching from a previous nbDMARD); and 3) prevalent users of nbDMARD who had not started a new nbDMARD within the preceding six months.

5.3.2 Factors associated with incident cancer

The following baseline characteristics were identified and assessed as possible predictors of first incident malignancy in addition to age and sex: RA disease duration (<3 years, 3-10 years, >10 years), disease activity (DAS28 <3.2, 3.2-5.1, >5.1), physical function (HAQ <1, 1-2, >2-3), prior or current exposure to CSA, AZA or CYC (analysed together due to low proportion of users for each drug in the nbDMARD cohort), cancer prior to registration with the BSRBR-RA and smoking status. Poisson regression models were used to determine which characteristics were associated with incident malignancy during follow up. Covariates associated with a reduced or elevated risk of cancer in univariate analysis were entered into the multivariate model. Models were adjusted for age and sex by multiplying England population rates of cancer stratified by sex and 5-year age-bands by duration of follow up and including the product as the exposure term. Results are presented as RR per year with 95% CI.

5.4 Results

The cohort comprised 3771 individuals with RA contributing 13315 pyrs of follow up to the analysis; median 3.7 years (inter-quartile range (IQR) 2.1, 4.9). 663 participants (18%) were censored prior to 31st December 2009 due to initiation of biologic therapy. In those switching to biologic therapy, median time to switching was 1.9 years (IQR 1.0, 3.3). 331 subjects (9%) died after a median follow up of 2.6 years (IQR 1.3, 3.8).

5.4.1 Standardised incidence ratios

5.4.1.1 All cancers excluding KSC (ICD 10 C00-C97 x C44)

One hundred and eighty-two cancers were reported in 13315 pyrs equating to a crude incidence rate of 1.37 per 100 pyrs (95% CI 1.18, 1.58; Table 5-1). No participant had more than one incident cancer reported during follow up. Overall the risk of cancer was increased by 28% in the cohort compared to the general population (SIR 1.28, 95% CI 1.10, 1.48). For the analysis restricted to patients living in England the risk was increased by 39%; SIR 1.39 (95% CI 1.19, 1.62).

Table 5-1. Overall and Solid cancer SIRs

Cancer site and ICD 10 code	Observed	Rate per 100 pyrs (95% CI)	Expected	SIR (95% CI)
All sites (ICD 10 C00-C97 x C44)	182	1.37 (1.18, 1.58)	141.80	1.28 (1.10, 1.48)
All sites – England only	168	1.50 (1.28, 1.75)	120.75	1.39 (1.19, 1.62)
Solid cancers C00-C80 xC44	156	1.17 (0.99, 1.37)	131.09	1.19 (1.01, 1.39)
Solid cancers - England only	143	1.28 (1.08, 1.51)	111.50	1.28 (1.08, 1.51)
Oesophagus C15	5	0.04 (0.01, 0.19)	3.39	1.47 (0.48, 3.44)
Stomach C16	6	0.05 (0.02, 0.10)	3.20	1.88 (0.69, 4.09)
Colorectal C18-C20	17	0.13 (0.07, 0.20)	17.69	0.96 (0.56, 1.54)
Lung C34	46	0.35 (0.25, 0.46)	19.24	2.39 (1.75, 3.19)
Melanoma C43	9	0.07 (0.03, 0.13)	4.38	2.05 (0.94, 3.90)

5.4.1.2 Solid cancers

Solid cancer was reported in 156 subjects equating to a crude incidence rate 1.17 per 100 pyrs (95% CI 0.99, 1.37) (Table 5-1). The risk of solid cancer was increased compared to the general population in the whole cohort and England-only; SIR 1.19 (95% CI 1.01, 1.39) and 1.28 (95% CI 1.08, 1.51) respectively. The RR was significantly increased in women but not men; SIR for females 1.38 (95% CI 1.15, 1.64); SIR for males 1.11 (95% CI 0.85, 1.44) (Table 5-2).

Among the solid cancers, there were at least five observed or expected cancers for eight sites; colorectal; stomach; colorectal; lung; melanoma; female breast; prostate; and cancers of the female genital organs (Table 5-1 and Table 5-2). An increased risk of lung cancer (46 cancers; SIR 2.39; 95 CI 1.75, 3.19) and melanoma (9 cancers; SIR 2.05; 95% CI 0.94, 3.90) was observed. There was a trend towards increased RR of oesophageal and stomach cancers, although the absolute numbers were low and 95% CI wide. No differences in RR for colorectal or female breast cancers were seen. A reduced risk of prostate cancer (5 cancers; SIR 0.35, 95% CI 0.11, 0.82) and cancers of the female genital organs (4 cancers; SIR 0.35, 95 % CI 0.10, 0.90) was observed.

Table 5-2 Overall and solid cancer SIRs in men and women

Total follow-up (pyrs)	Male 3732				Female 9584			
Cancer site and ICD 10 code	**Observed**	**Rate per 100 pyrs (95% CI)**	**Expected**	**SIR (95% CI)**	**Observed**	**Rate per 100 pyrs (95% CI)**	**Expected**	**SIR (95% CI)**
All sites (ICD 10 C00-C97 x C44)	58	1.55 (1.18, .01)	51.92	1.11 (0.85, 1.44)	124	1.29 (1.08, 1.54)	89.88	1.38 (1.15, 1.64)
All sites – England only	55	1.70 (1.28, 2.21)	45.76	1.20 (0.91, 1.56)	113	1.42 (1.17, 1.71)	74.99	1.51 (1.24, 1.81)
Solid cancers C00-C80 xC44	49	1.31 (0.97, 1.74)	47.70	1.03 (0.76, 1.36)	107	1.12 (0.91, 1.35)	83.39	1.28 (1.05, 1.55)
Solid cancers - England only	46	1.42 (1.04, 1.89)	42.04	1.09 (0.80, 1.46)	97	1.22 (0.99, 1.49)	69.56	1.39 (1.13, 1.70)
Colorectal C18-C20	7	0.19 (0.07, 0.39)	7.33	0.96 (0.38, 1.97)	10	0.10 (0.05, 0.19)	10.36	0.97 (0.46, 1.78)
Lung C34	16	0.43 (0.25, 0.70)	7.96	2.01 (1.15, 3.26)	30	0.31 (0.21, 0.45)	11.28	2.66 (1.79, 3.80)
Melanoma C43	NR	NR	NR	NR	6	0.06 (0.02, 0.14)	2.93	2.05 (0.75, 4.46)
Breast C50	NR	NR	NR	NR	30	0.31 (0.21, 0.45)	28.16	1.07 (0.72, 1.52)
Prostate C61	5	0.13 (0.04, 0.31)	14.22	0.35 (0.11, 0.82)	NR	NR	NR	NR
Female genital organs C51-C58	NR	NR	NR	NR	4	0.04 (0.01, 0.11)	11.35	0.35 (0.10, 0.90)

NR Not reported (fewer than 5 observed or expected cancers)

5.4.1.3 Myelo-and lymphoproliferative cancer

Twenty-six myelo- or lymphoproliferative cancers were reported. The incidence rate of these cancers was 0.20 per 100 pyrs (95% CI 0.13, 0.29), 2.5-fold increased compared to the general population (SIR 2.43, 95% CI 1.58, 3.55; Table 5-3). There were 16 lymphomas equating to a 3.8-fold increased risk compared to the general population. Whilst there were only 5 HL, the RR was increased nearly 13-fold.

Table 5-3. Myelo- and lymphoproliferative cancers SIRs

Cancer site and ICD 10 code	Observed	Rate per 100 pyrs (95% CI)	Expected	SIR (95% CI)
MPM and LPM C81–C96	26	0.20 (0.13, 0.29)	10.72	2.43 (1.58, 3.55)
MPM and LPM C81–C96 England only	25	0.22 (0.14, 0.33)	9.16	2.73 (1.77, 4.03)
Lymphoma C81-85	21	0.16 (0.10, 0.24)	5.51	3.81 (2.36, 5.82)
Hodgkin lymphoma C81	5	0.04 (0.01, 0.09)	0.39	12.82 (4.16, 29.92)
NHL C82-85	16	0.12 (0.07, 0.20)	5.12	3.12 (1.79, 5.07)

The risk of MPM or LPM was increased more than two-fold in both men and women compared to the general population (Table 5-4). The risks of lymphoma and NHL were increased in both sexes (Table 5-4). There were fewer than five Hodgkin lymphomas in both the male and female cohorts.

Table 5-4 Myelo- and lymphoproliferative cancers SIRs in men and women

	Males				Females			
Total follow-up (pyrs)	**3732**				**9584**			
Cancer site and ICD 10 code	**O**	**Rate per 100 pyrs (95% CI)**	**E**	**SIR (95% CI)**	**O**	**Rate per 100 pyrs (95% CI)**	**E**	**SIR (95% CI)**
MPM and LPM C81–C96	9	0.24 (0.11, 0.46)	4.23	2.13 (0.97, 4.04)	17	0.18 (0.10, 0.28)	6.49	2.61 (1.53, 4.19)
MPM and LPM C81–C96 England only	9	0.28 (0.13, 0.53)	3.73	2.42 (1.10, 4.59)	16	0.20 (0.12, 0.33)	5.43	2.95 (1.68, 4.78)
Lymphoma C81-85	8	0.21 (0.09, 0.42)	2.02	3.95 (1.71, 7.79)	13	0.14 (0.07, 0.23)	3.49	3.73 (1.98, 6.37)
NHL C82-85	5	0.13 (0.4, 0.31)	1.88	2.66 (0.86, 6.21)	11	0.11 (0.06, 0.21)	3.24	3.39 (1.69, 6.07)

O Observed; E Expected

5.4.1.4 Relative risk of cancer according to nbDMARD status at the time of registration

The cohort comprised 720 (19%) patients starting their first nbDMARD, 1596 (42%) switching nbDMARD or adding a new nbDMARD and 1455 (39%) prevalent users of nbDMARD. The incidence of cancer was highest in patients starting their first nbDMARD and prevalent users (Table 5-5). Compared to the general population, the RR of cancer was increased in patients starting their first nbDMARD (SIR 1.45, 95% CI 1.04, 1.96) and prevalent users (1.27, 95% CI 1.07, 1.74) (Table 5-5). Whilst the risk of cancer was numerically also increased in patients switching or adding nbDMARD, this did not reach statistical significance.

Table 5-5 Occurrence of cancer according to nbDMARD status at the time of registration

	First nbDMARD **N=720**	**Subsequent nbDMARD** **N=1596**	**Prevalent users** **N=1455**
Observed cancers	41	72	69
Follow up (pyrs)	2793	5807	4715
Median time to cancer: yrs (IQR)	1.81 (0.56, 3.41)	1.60 (0.59, 3.13)	1.50 (0.69, 2.64)
Cancer also reported by Rheumatologist: N (%)	25 (61)	41 (57)	51 (74)
Rate per 100 pyrs (95% CI)	1.47 (1.05, 1.99)	1.23 (0.97, 1.56)	1.46 (1.14, 1.85)
Expected cancers	28.31	56.82	50.31
SIR (95% CI)	1.45 (1.04, 1.96)	1.23 (0.97, 1.56)	1.27 (1.07, 1.74)

5.4.2 Factors associated with incident cancer

In multivariate analysis both current and prior smoking history were associated with incident cancer (RR 2.53 [95% CI 1.62, 3.95] and 2.09 [95% CI 1.40, 3.12] respectively). RA disease duration of less than 3 years and exposure to one or more of the nbDMARDs AZA, CSA or CYC were significantly associated with incident cancer in this cohort (Table 5-6).

Table 5-6. Factors associated with incident cancer

	RR (95% CI)	Multivariate analysis RR (95% CI)
Smoking (referent never)		
Prior	2.14 (1.43, 3.19)	2.09 (1.40, 3.12)
Current	2.66 (1.71, 4.15)	2.53 (1.62, 3.95)
Prior cancer	1.19 (0.65, 2.19)	
Duration of RA (referent >10 years)		
<3 years	1.59 (1.09, 2.34)	1.65 (1.11, 2.45)
3-10 years	1.31 (0.94, 1.83)	1.30 (0.92, 1.82)
AZA, CSA or CYC	1.46 (0.96, 2.23)	1.63 (1.05, 2.52)
Disease activity; DAS28 (referent >5.1)		
<3.2	0.61 (0.32, 1.14)	
3.2-5.1	0.79 (0.58, 1.07)	
Disability; HAQ (referent <1)		
1-2	1.32 (0.90, 1.93)	
>2	1.02 (0.65, 1.59)	

5.5 Summary of results

The key findings in this chapter were:

- The risk of cancer was increased in the nbDMARD-only-treated cohort of the BSRBR-RA by 28% compared to the general population.
- The risks of lung cancer, NHL and HL were increased compared to the general population.
- The risks of prostate cancer and cancers of the female genital organs were reduced compared to the general population.
- Current or prior smoking, RA disease duration of less than 3 years and prior exposure to AZA, CSA and/or CYC were associated with an increased risk of malignancy.

5.6 Discussion

Overall, the risk of cancer was increased in the nbDMARD-only cohort of the BSRBR-RA by 28% compared to the general population. The risks of lung cancer, NHL and HL were increased compared to the general population. This increased risk should not be interpreted as a causal association. It may be due in part to shared genetic risk factors for RA susceptibility/severity and malignancy. For example, the HLA-DRB1 shared epitope genotype has been shown to be associated with mortality

due to malignancy in RA, particularly *0101 genotypes [103]. Also, the increased RR of lung cancer may be partly explained by the shared risk factor of smoking [69].

The finding of this study of an increased risk of both NHL and HL has been widely reported previously and supported in meta-analysis (see section 1.3.6.1). Chronic inflammation plays an important role in this increased risk [86]. One might hypothesise that due to current practice of early treatment of RA and tighter control of disease activity the risk of lymphoma would be lower now than in historical RA cohorts but this was not borne out in this analysis. However, participants in the nbDMARD cohort were required to have active RA despite treatment with nbDMARD at registration and so they may have represented a cohort with more severe RA than the general RA UK population. Furthermore, almost 40% of the cohort had more than 10 years of RA at baseline, and so may not have benefitted from more aggressive treatment from the outset.

There was a marked reduction in risk of both prostate cancer and female genital cancers in the nbDMARD cohort. A recent population-based study using the Californian discharge register also reported reduced risks of ovarian, uterine, cervical and prostate cancers in subjects with RA [48] but other studies have not [41, 44, 45, 50, 52]. It has been hypothesised that inflammation plays a role in the pathogenesis of prostatic and female genital cancers, and that NSAIDs (in particular aspirin) may be protective against them [118, 219, 220], although not all studies have reported an association [221, 222]. It is hard to attribute the reduced risk of these cancers to NSAID use in this analysis, since neither a reduced risk of colorectal nor of breast cancer, for which a protective role for NSAIDs has been established [73, 223], was observed.

Nineteen percent of the cohort was starting their first nbDMARD at registration. The SIR was increased in this cohort. This finding could be explained by protopathic bias, whereby symptoms of an underlying cancer were being diagnosed as RA and nbDMARD therapy initiated. However, the median time to cancer was longer in this group than the others, although there was no significant difference between the groups (kwallis p=0.718). Also, an increased risk was also observed among prevalent users but not those starting a second or subsequent nbDMARD.

In multivariate analysis, both current and previous smoking were associated with a more than 2-fold relative risk of cancer. It is well established that smoking is a risk factor for cancer in the general population and whether or not smoking conferred any additional risk in this cohort compared to the risk in the general population was not ascertained. Rheumatoid disease duration of <3 years was associated with a 65% increased relative risk. Whilst increasing cancer risk with RA disease duration has been described [52], the pattern of increased risk in early RA and following recruitment to a study has been observed elsewhere [43, 49] and may in part be due to unmasking of prevalent cancers (surveillance bias).

Exposure to AZA, CSA or CYC was associated with a 63% increased RR for cancer but only 10% of the cohort had received one or more of these nbDMARDs. These drugs are known to be associated with increased cancer risk, and the risk appears to be related to dose of immunosuppression [131, 224-227]. In the context of RA, it is noteworthy that they are usually reserved for patients with more severe disease that have failed treatment with other nbDMARDs. The observed association in this cohort may actually reflect underlying disease severity although an association between cancer risk and other markers of disease severity (HAQ, DAS28) was not observed.

There were limitations, specific to this chapter, that need to be considered. Whilst SIR from different studies cannot be compared, it is noteworthy that the relative risk of cancer was higher in this study than has been reported in several others observational studies of RA [41-45, 49, 52]. It is possible that patients who were considered to be unsuitable for anti-TNF (for example those with prior cancer) were preferentially recruited to the nbDMARD-only cohort of the BSRBR-RA, since recruitment took place in parallel with recruitment to the anti-TNF cohort. In addition, patients were not screened for cancer when starting nbDMARD in routine clinical practice and so it is possible that unmasking of certain cancers, such as lymphomas, may have occurred shortly after starting nbDMARD therapy.

Rates of cancer in all participants in the nbDMARD cohort were compared to age- and sex- adjusted population rates for England, as UK-wide rates were not available. Whilst the majority of the cohort lived in England (85%), the SIRs for all cancers, solid cancer and MPM or LPM were around 10%

higher when subjects living in Northern Ireland, Scotland or Wales were excluded. This may reflect both regional differences in cancer risk and differences in promptness and completeness of registration of cancers with the national cancer agencies [228]. Even within England, there were regional differences in the population rates of cancer (see Section 4.3.2). Centres recruiting to the nbDMARD cohort were clustered around the North West of England (Figure 3-1), where population cancer rates were amongst the highest in the country. This clustering occurred because funding was given to the BSRBR-RA to employ research nurses who went out to hospitals to aid recruitment. For convenience and efficiency, these nurses went to centres within commuting distance of Manchester, where the BSRBR-RA was based.

In conclusion, the incidence of cancer was increased by 28% in the nbDMARD cohort compared to the general population. This underlying cancer risk in patients treated with nbDMARD needs to be considered when studying the effects of anti-TNF on cancer risk in people with RA.

6. Relative risk of lymphoma in subjects treated with anti-TNF versus nbDMARD

In this chapter the incidence of lymphoma in the anti-TNF cohort is described and compared to that in the nbDMARD cohort. A brief discussion of the results is also included with further discussion in Chapter 9. This chapter also illustrates how and why the analytical and statistical methods for analysing cancer risk in this thesis were selected. Finally, the chapter includes a small sub-study reviewing and comparing histological subtypes of lymphoma occurring in anti-TNF and nbDMARD-only treated patients.

6 Relative risk of lymphoma in subjects treated with anti-TNF versus nbDMARD

6.1 Introduction

The incidence of lymphoma is increased in people with RA (see section 1.3.6.1). One of the primary aims of the BSRBR-RA was to establish whether exposure to anti-TNF modifies the risk of lymphoma in RA since patients with severe RA are at the highest risk for lymphoma. Few other observational cohorts have investigated this question to date (see section 1.4.5.1), and a definitive answer has not yet been found.

6.2 Aims

- To develop and test methods to analyse the risk of malignancy in subjects with RA exposed to anti-TNF.
- To investigate whether anti-TNF influences the risk of lymphoma in subjects with RA.
- To review and compare the histological subtypes of lymphoma reported in anti-TNF and nbDMARD-only treated patients, using both histological and cancer agency reports as well as tissue-specimen review.

6.3 Methods

The primary outcome measure for this analysis was first lymphoma per subject verified as a definite malignancy. Histology reports and ICD 10 codes reported by the cancer registries were used to classify lymphomas into sub-types. For sub-types with at least ten lymphomas in each cohort, analysis comparing the incidence in the nbDMARD and anti-TNF cohorts was performed. The study population was selected from the patient dataset created on 31st January 2012 which included follow up time until 31st January 2011 (see section 4.2). Patients with a diagnosis of LPM or MPM prior to starting anti-TNF or registration with the BSRBR-RA were excluded (nbDMARD: N=19; anti-TNF: N=7). During development of the PS model an area of non-overlap in PS between the two cohorts was identified. Disease activity was considered to be a confounder in this analysis and there were far fewer anti-TNF-treated patients with DAS28 ≤3.2 (N=56) than nbDMARD (N=290). A PS model to overcome this difference could not be derived i.e. DAS28 could not be balanced between

the two cohorts unless patients with low baseline disease activity were excluded and so all subjects with DAS28 ≤3.2 were excluded from the analysis.

The primary drug exposure model used was the ever exposed model for anti-TNF. Alternative drug exposure models were then applied to test the robustness of the findings, namely on drug, on drug plus 90 days and excluding time after switching to a second or subsequent anti-TNF (or other biologic). A further analysis was performed to investigate whether the risk of lymphoma changed with cumulative exposure to anti-TNF (Figure 3-4). Time after last received consultant questionnaire was excluded from the above sensitivity analyses since information about current drug exposure status came from these questionnaires. When the risk of each TNF inhibitor was compared separately to nbDMARD, follow up and cancers were attributed to the most recent anti-TNF. A model that attributed follow up time and lymphomas to each of the anti-TNF drugs a patient had ever received at the time of event was also used in a sensitivity analysis. Finally, the analysis was restricted to lymphomas reported by the national cancer agencies, in case there was any bias in reporting of lymphomas by patients and Rheumatologists to the BSRBR-RA.

Lymphoma tissue was sought from all reported lymphomas in the nbDMARD and anti-TNF cohorts to allow more detailed classification of the tumour subtype. The methods of this sub-study are included later in this chapter (section 6.5).

6.4 Results

6.4.1 The incidence of lymphoma in the BSRBR-RA

Ninety lymphomas were reported in 90 patients during the entire follow up time in the BSRBR-RA; nbDMARD 23; anti-TNF 67. Six were excluded since they were diagnosed during the first six months of follow up; nbDMARD 3; anti-TNF 3. Twenty lymphomas remained for analysis in the nbDMARD cohort during 13285 pyrs of follow up (151 per 100,000 pyrs) and 64 in 66253 pyrs in the anti-TNF cohort (97 per 100,000 pyrs) (Table 6-1). The unadjusted HR for lymphoma in the anti-TNF cohort was 0.61 (95% CI 0.36, 1.01).

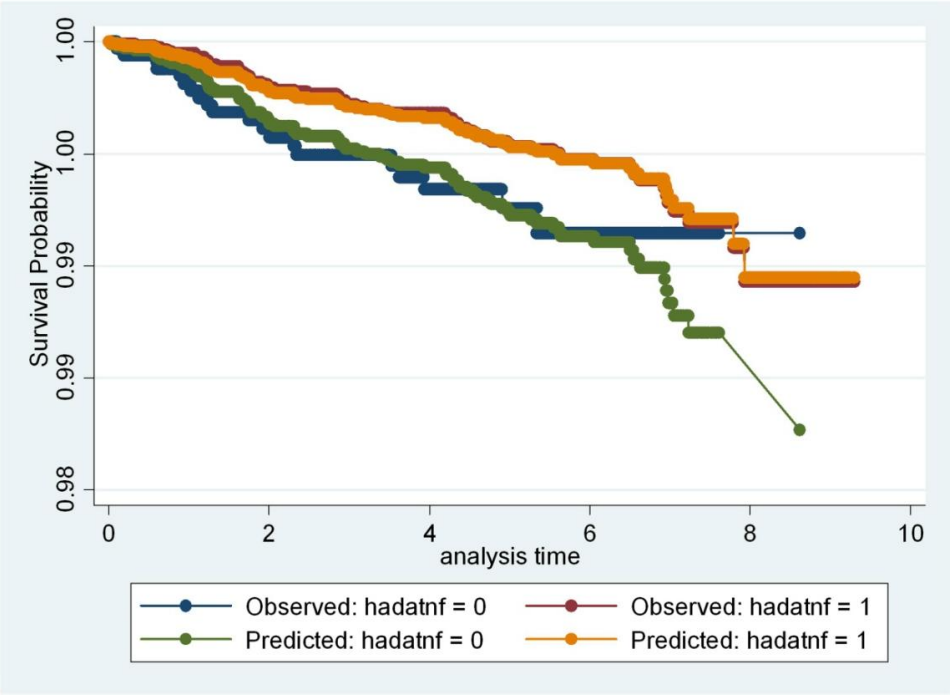
Table 6-1 Incidence of lymphoma in the BSRBR-RA

	nbDMARD N=3368	Anti-TNF N=11931
Follow-up time (pyrs)	13285	66253
Lymphomas	20	64
Incidence rate per 100,000 pyrs (95% CI)	151 (92, 232)	97 (74, 123)
Unadjusted HR (95% CI)	Referent	0.61 (0.36, 1.01)

6.4.1.1 Testing the proportional hazards assumption

The PH assumption was examined graphically by comparing observed and predicted survival (Kaplan-Meier) curves for the anti-TNF and biologic-naïve cohorts (Figure 6-1). For both cohorts, these lines were overlying for the first six years of follow up, indicating that that the PH assumption had not been violated. After six years, the observed curve deviated from the predicted curve for the nbDMARD cohort, indicating possible violation of the PH assumption. The median duration of follow up from the start of analysis in the nbDMARD cohort was 4.1 years (IQR 2.2, 5.4) and few subjects contributed to the analysis beyond 6 years. Therefore, it was decided to limit the analysis period to the first five years i.e. from 6 months after registration/ starting anti-TNF to 5.5 years after that registration.

Figure 6-1 Observed and predicted survival curves



hadatnf=0 denotes the nbDMARD cohort and hadatnf=1 the anti-TNT cohort

Next the PH assumption was tested using a Chi-squared test of Schoenfeld residuals against time, censoring the analysis after 5 years of follow up. This did not indicate evidence of non-proportionality (p=0.255).

6.4.1.2 The incidence of lymphoma after restricting follow up to the first five years

Follow up was limited to the first five years per subject for the remainder of this analysis. During this period, 19 lymphomas were reported in 12132 pyrs in the nbDMARD cohort and 48 in 53214 pyrs in the anti-TNF cohort (Table 6-2). The unadjusted HR for anti TNF was 0.57 (95% CI 0.34, 0.98) indicating a 40% lower hazard in the anti-TNF cohort.

Table 6-2 Incidence of lymphoma, restricted to the first five years follow up per subject

	nbDMARD N=3368	Anti-TNF N=11931
Total follow up time (pyrs)	12132	53214
Follow up per subject; median (IQR)	4.1 (2.2, 5.0)	5.0 (4.4, 5.0)
Lymphomas	19	48
Incidence rate per 100,000 pyrs (95% CI)	157 (94, 24)	90 (67, 120)
Unadjusted HR (95% CI)	Referent	0.57 (0.34, 0.98)

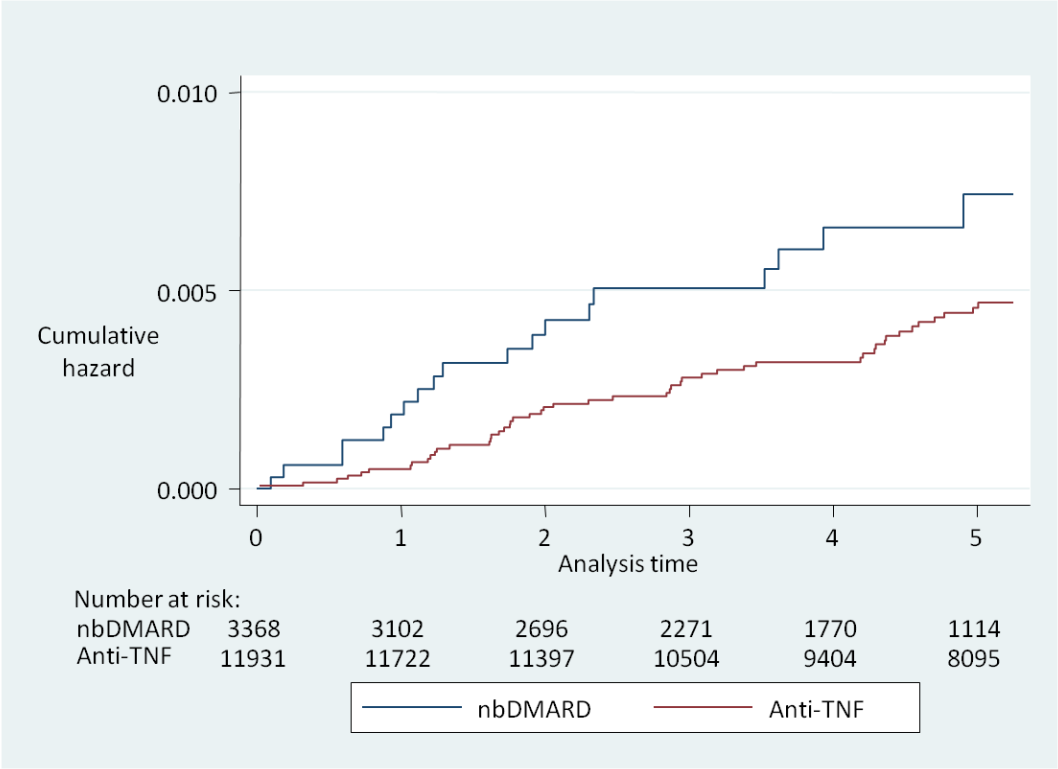
All of the lymphomas in the nbDMARD cohort and 43 (90%) in the anti-TNF cohort were reported by the national cancer registries. In addition, around 85% were reported by the consultant in each cohort (Table 6-3). However, one lymphoma in the nbDMARD cohort and five in the anti-TNF cohort were reported after the last received consultant follow up form. After excluding these, the proportion of consultant-reported cancers was 89% for nbDMARD and 95% for anti-TNF. The proportion of lymphomas reported by the patient was low in both cohorts, although patients were only asked to return information for the first three years.

Table 6-3 Source of reporting of lymphomas

	nbDMARD N=19	Anti-TNF N=48
Cancer registry (%)	19 (100)	43 (90)
Consultant (%)	16 (84)	41 (85)
Patient (%)	3 (16)	11 (22)

Cumulative hazard plots for the nbDMARD and anti-TNF cohorts demonstrate an early separation in the hazard for lymphoma that persisted throughout follow up (Figure 6-2).

Figure 6-2 Nelson-Aalen cumulative hazard estimates for lymphoma



6.4.2 The risk of lymphoma for each anti-TNF drug

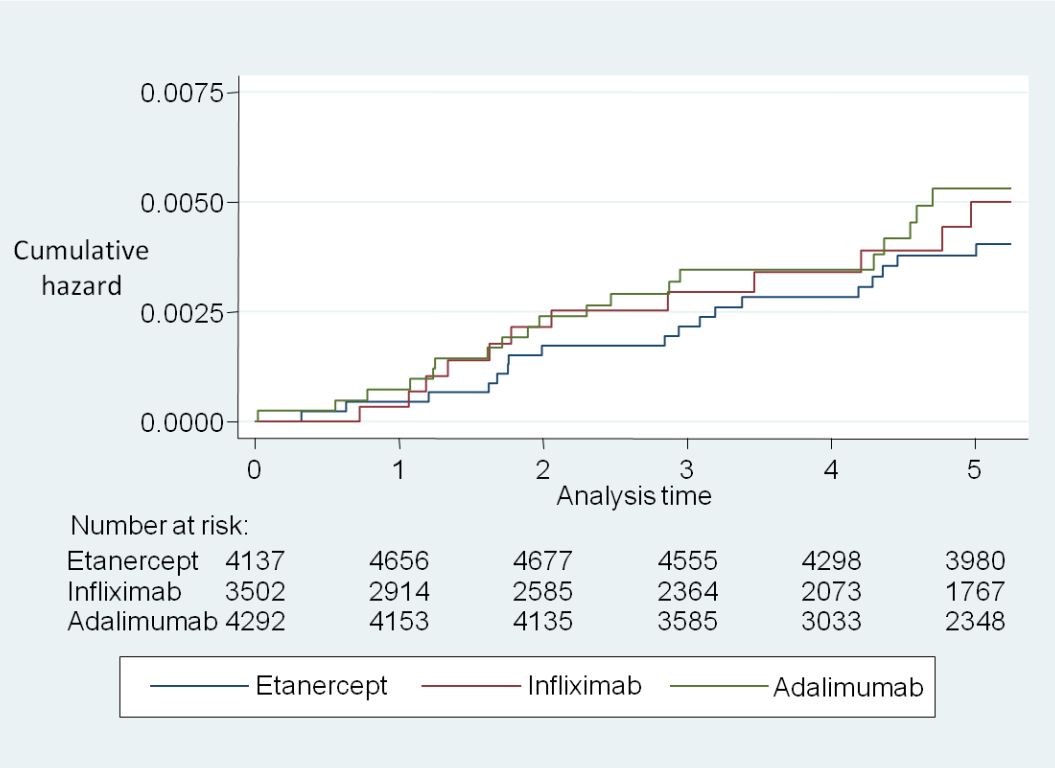
The crude incidence rate of cancer was lowest in the ETA cohort (76 per 100,000 pyrs) and highest for ADA (104 per 100,000 pyrs) (Table 6-4). The HR for ETA was significantly reduced compared to nbDMARD (HR 0.48, 95% CI 0.25, 0.92).

Table 6-4 Drug-specific incidence of lymphoma

	ETA **N=4137**	**INF** **N=3502**	**ADA** **N=4292**
Total follow up time (pyrs)	22403	12542	18270
Follow up per subject; median (IQR)	4.8 (2.5, 5.0)	3.9 (1.3, 5.0)	3.5 (2.0, 4.8)
Lymphomas	17	12	19
Incidence rate per 100,000 pyrs (95% CI)	76 (44, 121)	96 (49, 167)	104 (62, 162)
Unadjusted HR (95% CI); nbDMARD referent	0.48 (0.25, 0.92)	0.61 (0.29, 1.25)	0.66 (0.35, 1.24)

Cumulative hazard plots for the three anti-TNF drugs are shown in Figure 6-3. This figure shows little separation in the lines during the course of the study, indicating a similar hazard for lymphoma for each drug.

Figure 6-3 Nelson-Aalen cumulative hazard estimates by anti-TNF drug



6.4.3 Adjusting for confounders

The data above show that patients treated with anti-TNF had a 40% reduced hazard of lymphoma compared to the biologic naïve cohort. The HR was lower for ETA than INF or ADA compared to nbDMARD. However, the reduced risk of lymphoma cannot necessarily be attributed to receiving anti-TNF. Differences in baseline characteristics between the two cohorts need to be borne in mind when interpreting these results.

6.4.3.1 Association of baseline covariates with lymphoma in the BSRBR-RA

First the associations between candidate confounders and the outcome (lymphoma) were investigated, irrespective of treatment group (Table 6-5). This demonstrated an association between increasing age and lymphoma and male sex and lymphoma, as expected. A negative association

between baseline DAS28 and lymphoma was observed (HR 0.79, 95% CI 0.64, 0.97) in contrast to the known association of high disease activity and lymphoma reported in the literature. However, this HR was independent of treatment allocation and other baseline confounders and so does not indicate a protective effect of high disease activity in the BSRBR-RA cohort. For example, it could be explained if young women had higher baseline DAS28 scores than old men.

Table 6-5 Association between baseline confounders and lymphoma

	Hazard ratio (95% CI)
Age (per year)	1.05 (1.02, 1.07)
Sex (Male referent)	0.53 (0.32, 0.87)
Ethnicity (Non-white referent)	0.79 (0.25, 2.54)
Smoking (Current smoker referent):	
Ex-smoker	1.30 (0.71, 2.40)
Never smoked	0.59 (0.29, 1.20)
Comorbidity (Nil referent):	
1 comorbidity	1.05 (0.61, 1.78)
2 comorbidities	0.92 (0.44, 1.93)
≥3 comorbidities	0.86 (0.26, 2.81)
Entered study before June 2004	0.84 (0.52, 1.37)
Disease duration (per year)	1.01 (0.98. 1.03)
Disease activity (per unit DAS28)	0.79 (0.64, 0.97)
Disability (per unit HAQ)	0.81 (0.56, 1.17)
Baseline corticosteroids	0.95 (0.58, 1.55)
No. prior nbDMARD (≤3 referent):	
≥4	0.86 (0.53, 1.39)

Next, the effect of each baseline covariate on the estimated treatment effect was examined. Age and DAS28 score had the greatest effect on the estimated effect of anti-TNF on risk of lymphoma, indicated by the change in HR for anti-TNF from 0.57 to 0.70 and 0.73 respectively (Table 6-6). None of the other confounders altered the HR by more than 10% in univariate adjustment. None the less, all the *a priori* selected confounders were included in the analysis since interactions and non-linear associations may have existed.

Table 6-6 Effect of each confounder on the treatment effect

	Hazard ratio (95% CI) for covariate	Hazard ratio for anti-TNF (95% CI)
Unadjusted HR for anti-TNF		0.57 (0.34, 0.98)
Age	1.04 (1.02, 1.07)	0.70 (0.41, 1.21)
Sex	0.54 (0.33, 0.88)	0.59 (0.34, 1.00)
Ethnicity	0.76 (0.23, 2.44)	0.57 (0.34, 0.97)
Smoking (Current smoker referent): Ex-smoker Never smoked	 1.31 (0.71, 2.41) 0.60 (0.30, 1.22)	 0.58 (0.34, 0.99)
Comorbidity (Nil referent): 1 comorbidity 2 comorbidities ≥3 comorbidities	 1.04 (0.61, 1.77) 0.90 (0.61, 1.77) 0.81 (0.25, 2.66)	 0.57 (0.33, 0.97)
Entered study before June 2004	0.95 (0.57, 1.57)	0.58 (0.34, 1.02)
Disease duration (per year)	1.01 (0.99, 1.03)	0.56 (0.32, 0.95)
Disease activity (DAS28)	0.83 (0.66, 1.06)	0.73 (0.39, 1.37)
Disability (HAQ)	0.90 (0.61, 1.33)	0.61 (0.34, 1.07)
Baseline corticosteroids	1.04 (0.63, 1.73)	0.57 (0.33, 0.98)
No. prior nbDMARD	0.97 (0.59, 1.62)	0.58 (0.33, 1.01)

6.4.3.2 Controlling for confounding using the propensity score model

The expected bias was used to measure how well the PS model balanced differences in baseline characteristics between the treatment groups. Prior to constructing the PS model, the expected bias was high (Table 6-7). The degree of expected bias, incorporating a matrix of betas of the estimated effect of each variable on the outcome (lymphoma), was -15.3%. This means that the estimated effect of anti-TNF on lymphoma risk could be at least 15.3% lower than the true effect, due to differences in baseline characteristics of the groups and the influence of these variables on risk of lymphoma. This value represents the likely overall bias in the model. It was derived by combining the bias of individual components of the model, some of which resulted in bias in a negative direction and others in a positive direction, thus cancelling each other out (Figure 6-4). In particular, the expected bias for DAS28 was -22% and age -16%, versus 19% for entry period to the study and 12% for HAQ. The expected bias before adjusting was 132.5% using absolute values. The absolute bias is a

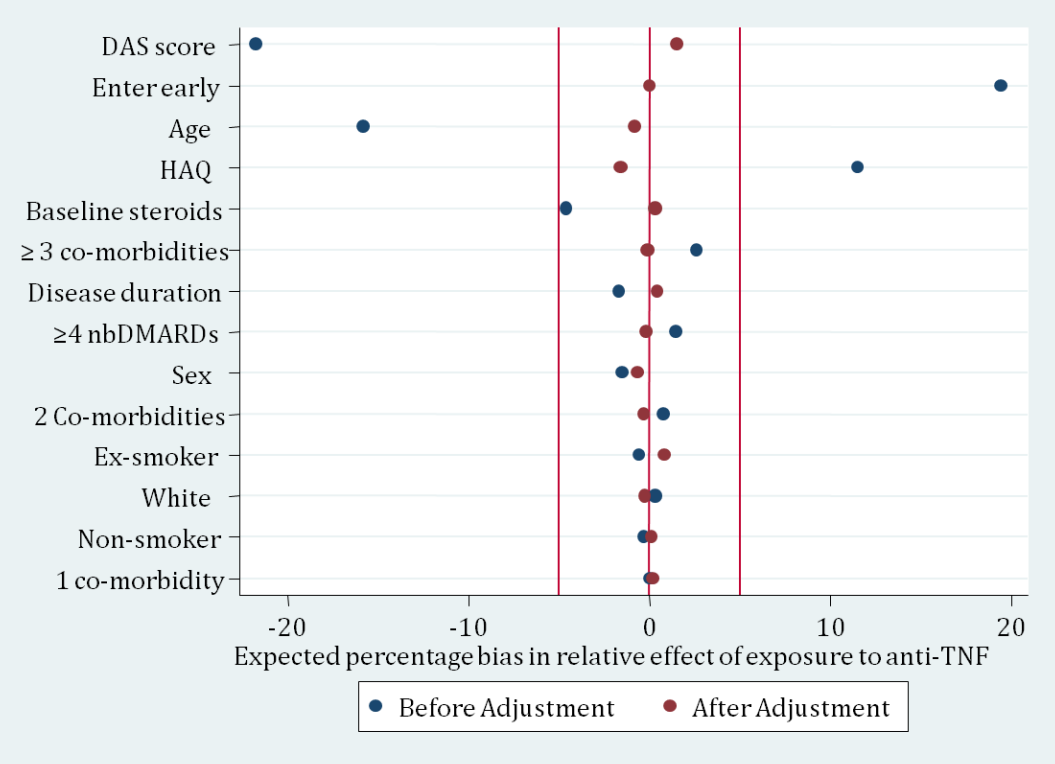
superior measure of the potential for bias in the analysis i.e. how different the two cohorts are from each other.

Table 6-7 Expected bias for different applications of the PS model

	Expected bias (%)	
	Using given betas for confounders*	**Absolute values**
Before creating PS	-15.3	132.5
Overall for PS model	-0.2	7.6
Using PD	-1.6	3.9
IPTW	0.5	7.3
IPTW after trimming	0.1	17.5
SMR	-1.0	10.4
SMR after trimming	1.1	17.3

*Betas were derived from a multivariate logistic regression model of the effect of confounders on developing lymphoma during follow up.

Figure 6-4 Expected bias before and after adjustment using the PS



The variables included in the PS model in addition to those listed in Table 6-5 were the square of DAS28 score, the cube of DAS28 score and an interaction term between age and DAS28 score. After balancing with the PS model, the expected bias was less than 2% for each confounder, indicating good control for the confounders included in the model (Figure 6-4). Even with an expected bias of 0%, there is still scope for residual bias as the estimated effects of each covariate on the outcome may differ from the true effects.

6.4.3.3 Adjusted risk of lymphoma for anti-TNF

Once the older age and higher proportion of males in the nbDMARD cohort were adjusted for the HR for anti-TNF moved closer to unity (0.67, 95% CI 0.39, 1.16) (Table 6-8). After fully adjusting, the HR varied depending on the method of adjustment. Using stratification and adjusting for deciles of propensity score (PD) there was no difference between the two cohorts: HR 1.00 (95% CI 0.49, 2.05). When adjusting the analysis using either IPTW or SMR weights there was a trend towards an increased HR for anti-TNF (Table 6-8). The PD adjusted for each drug compared to nbDMARD suggested a 15% reduced hazard for ETA and a modest increased hazard for both INF and ADA, all with 95% CI that crossed unity. Alternative methods of using the PS resulted in different hazard estimates for each of the drugs (Table 6-8).

Table 6-8 Adjusted HR for lymphoma compared to nbDMARD

HR (95% CI)	Anti-TNF	ETA	INF	ADA
Unadjusted	0.61 (0.36, 1.01)	0.48 (0.25, 0.92)	0.61 (0.29, 1.25)	0.66 (0.35, 1.24)
Age and sex adjusted	0.67 (0.39, 1.16)	0.57 (0.30, 1.12)	0.70 (0.34, 1.46)	0.76 (0.40, 1.44)
PS adjusted:				
PD adjusted	1.00 (0.49, 2.05)	0.85 (0.37, 1.95)	1.08 (0.45, 2.62)	1.07 (0.50, 2.32)
IPTW weighted	1.29 (0.66, 2.52)	1.45 (0.61, 3.46)	0.86 (0.39, 1.88)	1.38 (0.61, 3.10)
SMR weighted	1.23 (0.59, 2.57)	1.04 (0.46, 2.36)	1.28 (0.52, 3.15)	1.41 (0.62, 3.19)

6.4.3.4 Exploring differences between adjusted results

Possible reasons for the different estimated treatment effects using different PS models were explored. It is noteworthy that the basis of weighting was to up-weight subjects in the two cohorts that were most like each other i.e. patients with high PS in the nbDMARD cohort and, in the case of

IPTW, also those with a low PS in the anti-TNF cohort. This resulted in a maximum IPTW of 203 in the nbDMARD cohort and 113 for anti-TNF i.e. individual patients were entered into the analysis 203 and 113 times respectively, prior to truncation. This up-weighting meant that the PS was highly sensitive to bias due to any misspecification in the model. After truncation, the maximum weight allowed was 20, but by truncating the weights the confounders were no longer well balanced between the cohorts. This point is illustrated by comparing the expected bias before and after truncating of the weights (Table 6-7). Before truncation the overall expected bias was 7.3 % for IPTW and 10.4% for SMR weights but after truncation this rose to 17.5% and 17.3% respectively. In comparison, the overall expected bias for PD was 3.9%. Weighted numbers of lymphomas and rates were calculated and compared (Table 6-9).

Table 6-9 Weighted numbers and rates of lymphoma per quintile of PS

	nbDMARD			Anti-TNF		
	Lymphomas	**Pyrs**	**Rate per 100,000 pyrs**	**Lymphomas**	**Pyrs**	**Rate per 100,000 pyrs**
No weighting						
1st quintile	16	8424	190	12	6565	183
2nd quintile	3	2314	130	9	11012	82
3rd quintile	0	848	0	8	11956	67
4th quintile	0	378	0	9	12049	75
5th quintile	0	174	0	10	11690	86
SMR weighted rates						
1st quintile	11.35	5131	221	12	6565	183
2nd quintile	11.41	9201	124	9	11012	82
3rd quintile	0	8633	0	8	11956	67
4th quintile	0	6876	0	9	12049	75
5th quintile	0	3029	0	10	11690	86
IPTW weighted rates						
1st quintile	27.33	13551	202	42.45	16407	259
2nd quintile	14.41	11505	125	11.20	13771	81
3rd quintile	0	9464	0	8.83	13089	67
4th quintile	0	6997	0	9.36	12551	75
5th quintile	0	3029	0	10.14	11865	85

First, the distribution of PS was divided into quintiles and the rates for each quintile calculated. All 19 lymphomas in the nbDMARD cohort occurred in subjects with the lowest two quintiles of PS i.e. those least likely to receive anti-TNF. The effect of no lymphomas occurring in nbDMARD patients with the highest PS was magnified when weighting was applied to the PS. For example, whilst follow up was multiplied 17 times in the highest quintile for nbDMARD, both the number and rate of lymphoma remained at 0 (Table 6-9). When compared to the anti-TNF cohort, this had the effect of increasing the HR for treatment.

Finally, the possibility of effect modification by strength of indication for anti-TNF was investigated as a possible explanation for the different results following stratification and weighting. This did not indicate any trend towards changing hazard of lymphoma by decile of PS (strength of indication for anti-TNF) i.e. no effect modification (p=0.200). Stratification of PS was selected as the principal and preferred way for adjusting subsequent analyses in this thesis, primarily due to the problems of introducing bias following very small misspecifications in the PS model when weighting was applied and the increase in expected bias following truncation of weights.

6.4.4 Sensitivity analyses

Using the primary ever exposed model, the unadjusted HR for lymphoma was 0.61 (95% CI 0.36, 1.01). After adjusting using the PD method the HR was 1.00 (95% CI 0.49, 2.05). Additional sensitivity analyses were performed to test the robustness of these results. After excluding time after the last received consultant follow up form there were 18 lymphomas in 10599 pyrs in the nbDMARD cohort and 43 in 49513 for anti-TNF. The PD-adjusted HR was 0.93 (95% CI 0.44, 1.99). Time after the last received consultant follow up form was excluded for the subsequent sensitivity analyses using alternative drug exposure models.

6.4.4.1 Alternative drug exposure models

The effect of limiting the analysis period to time on anti-TNF was performed. Twenty-one lymphomas were included in the anti-TNF cohort. Both the unadjusted and PD adjusted HR were lower than for the primary analysis (Table 6-10). Conversely, when a 90 day lag window was included (see section 3.2.5.1), the unadjusted and PD adjusted HR were not markedly different from the ever-

exposed model (Table 6-10). Using an ever exposed model, but excluding all follow up time after switching to a second biologic drug (anti-TNF or otherwise) resulted in an adjusted HR of 0.91 (95% CI 0.42, 2.00). The confidence intervals spanned unity for all these analyses.

Table 6-10 Alternative drug exposure models for anti-TNF

	On drug	On drug plus 90 days	Time after switching excluded
Pyrs of follow up	38291	39665	37519
No of lymphomas	21	36	31
Unadjusted HR (95% CI)	0.31 (0.17, 0.59)	0.53 (0.30, 0.94)	0.49 (0.28, 0.88)
Age and sex adjusted HR (95% CI)	0.40 (0.20, 0.73)	0.67 (0.38, 1.20)	0.60 (0.33, 1.09)
PD adjusted HR (95% CI)	0.60 (0.24, 1.46)	1.05 (0.48, 2.29)	0.91 (0.42, 2.00)

The nbDMARD cohort was the referent cohort for all regression analyses

Next, the effect of cumulative exposure to anti-TNF was examined (Table 6-11). This analysis lacked precision, as demonstrated by the wide confidence intervals. The HRs increased with cumulative exposure to anti-TNF but there was no significant difference in the risk of lymphoma according to duration of exposure to anti-TNF.

Table 6-11 Lymphomas in the anti-TNF cohort using the cumulative exposure to anti-TNF model

	Cumulative exposure time on anti-TNF		
	< 1.5 years	1.5 to < 3 years	≥3 years
Pyrs of follow up	16082	16552	16967
No. lymphomas	10	18	15
Unadjusted HR (95% CI):			
nbDMARD referent	0.35 (0.15, 0.81)	0.55 (0.26, 1.13)	0.71 (0.28, 1.79)
<1.5 yrs anti-TNF referent	Referent	1.56 (0.59, 4.13)	2.03 (0.66, 6.31)
PD adjusted HR (95% CI):			
nbDMARD referent	0.66 (0.25, 1.75)	0.97 (0.40, 2.37)	1.31 (0.45, 3.79)
Test for trend	P=0.410		
<1.5 yrs anti-TNF referent	Referent	1.40 (0.46, 4.26)	2.00 (0.52, 7.68)
Test for trend	P=0.595		

The effect of allowing follow up time and lymphomas to be attributed to more than one anti-TNF agent was analysed. This had the effect of reducing the hazard associated with INF and ADA use and increasing the hazard associated with ETA (Table 6-12). The 95% CI around all the estimated treatment effects were wide, reflecting the low numbers of events.

Table 6-12 Attributing lymphomas to multiple anti-TNF drugs

	ETA	INF	ADA
Pyrs of follow up	26739	18289	22624
No. lymphomas	23	17	22
Unadjusted HR (95% CI)	0.55 (0.30, 1.01)	0.58 (0.30, 1.13)	0.63 (0.34, 1.17)
Age and sex adjusted HR (95% CI)	0.70 (0.27, 1.33)	0.72 (0.37, 1.43)	0.77 0.41, 1.45)
PD adjusted HR (95% CI)	1.06 (0.44, 2.57)	0.69 (0.26, 1.87)	0.95 (0.44, 2.05)

The nbDMARD cohort was the referent cohort for all regression analyses

6.4.4.2 Effect of restricting the analysis to cancer registry-reported cancers

The outcome measure was limited to lymphomas that were reported by the national cancer registries, to eliminate bias in reporting of lymphomas by Rheumatologists to the BSRBR-RA (Table 6-13). This resulted in five fewer lymphomas in the anti-TNF cohort. The PD adjusted HR was 0.91 (95% CI 0.44, 1.89).

Table 6-13 Analysis of cancer registry-reported lymphomas only

	nbDMARD	Anti-TNF
Follow up time (pyrs)	12132	53214
Lymphomas	19	43
Unadjusted HR (95% CI)	Referent	0.51 (0.30, 0.88)
Age and sex adjusted HR (95% CI)	Referent	0.63 (0.36, 1.10)
PD adjusted HR (95% CI)	Referent	0.91 (0.44, 1.89)

6.4.5 Subtypes of lymphoma in the BSRBR-RA, as reported by the national cancer agencies and histology reports

There were four (21%) HL in the nbDMARD cohort and 6 (13%) in the anti-TNF cohort (Table 6-14). In total, NHL comprised 85% of the reported lymphomas. The most frequently reported subtype of lymphoma was DLBCL; nbDMARD: 7 (37%); anti-TNF: 18 (38%) (Table 6-14). Follicular lymphomas were reported in 12 (25%) anti-TNF-treated patients and no nbDMARD-treated patients. There was insufficient information to classify eight lymphomas beyond B-cell NHL NOS. Three T cell lymphomas were reported; one immunoblastic T cell lymphoma in each cohort and one mycosis fungoides in the anti-TNF cohort.

Table 6-14 Subtypes of lymphoma reported by the national cancer agencies and histology reports

	nbDMARD N=3368	**Anti-TNF N=11931**	**ETA N=4137**	**INF N=3502**	**ADA N=4292**
Follow-up (pyrs)	12044	53214	22403	12542	18270
Lymphoma: N	19	48	17	12	19
Subtypes: N (%)					
Hodgkin	4 (21)	6 (13)	3 (18)	2 (17)	1 (5)
NHL:					
DLBCL	7 (37)	18 (38)	4 (24)	3 (25)	11 (58)
FL	0 (0)	12 (25)	5 (29)	5 (42)	2 (11)
CLL / small lymphocytic	1 (5)	3 (6)	2 (12)	0 (0)	1 (5)
MALToma	0 (0)	2 (5)	1 (6)	0 (0)	1 (5)
Mantle cell	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Burkitt	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
B-cell NHL NOS	3 (16)	5 (10)	1 (6)	2 (17)	2 (11)
T cell	1 (1)	2 (4)	1 (6)	0 (0)	1 (5)

MALToma mucosal-associated lymphoid tissue lymphoma

Only NHL fulfilled the criteria of at least 10 lymphomas in each sub-group to proceed to comparative analysis between the nbDMARD and anti-TNF cohorts. There were 15 NHL in 12132 pyrs in the nbDMARD cohort (incidence rate 124 per 100,000 pyrs, 95% CI 69, 204) and 42 in 53214 in the anti-TNF cohort (rate 79 per 100,000 pyrs, 95% CI 57, 107). The unadjusted HR was 0.64 (95% CI 0.36, 1.16). The age- and sex-adjusted HR for NHL was 0.76 (95% CI 0.42, 1.38). The PD-adjusted HR was 1.15 (95% CI 0.53, 2.48).

6.5 Review of histological subtypes of lymphoma

6.5.1 Background

Work in biologic-naive subjects with RA has demonstrated that much of the increased risk of lymphoma is due to an increased risk of the DLBCL-subtype [79, 82]. Diffuse large B-cell is a heterogeneous group of lymphomas [78]. Distinct subtypes of DLBCL are identifiable by immunohistochemistry or gene expressing profiling; germinal centre (GC)-like and non-GC-like, in which genes expressed in activated peripheral B-cells are found [77]. Both GC-like and non-GC-like types have been shown to be strongly associated with RA disease activity [86]. In a study of 378 RA subjects with lymphoma more than three quarters of both these subtypes occurred in patients with the highest decile of cumulative disease activity compared to 23% for all other lymphoma subtypes [86]. A predominance of the non-GC subtype of DLBCL has been identified in RA [229]. There is evidence of persistent B-cell activation in RA and it has been proposed that this creates aberrant genetic mutations in peripheral activated B-cells, ultimately leading to non-GC DLBCL [229]. This subtype is associated with worse patient survival in the general population [230] and in RA [229]. The effect of anti-TNF therapy on developing particular subtypes of lymphoma in RA is unknown.

EBV-positive lymphomas have been reported in subjects with RA (see section 1.3.6.1) and may be due to impaired T-cell immune response to EBV in RA [231, 232]. It is not known whether immunosuppression due to anti-TNF increases the risk of EBV-related lymphoma in RA. Unfortunately, EBV status is not routinely tested or reported on standard immunohistological reports and therefore, further examination of specimens would be required to explore this further. The aim of this work was to: 1) reclassify/confirm lymphomas occurring in patients recruited to the BSRBR-RA according to the WHO classification; and 2) determine their EBV status, by re-examining lymphoma tissue obtained at biopsy.

6.5.2 Methods

Prior to this work, ethical approval was required since the original BSRBR-RA ethics approval did not include permission to request biological samples from enrolled patients. Approval was granted by the North-West Regional Ethics Committee to obtain paraffin-embedded lymphoma tissue from subjects treated with anti-TNF in September 2009 (Appendix 2). The first requests for tissue were

made in summer 2010. In spring 2011 ethical approval was granted to obtain tissue from subjects in the nbDMARD cohort and tissue requested shortly afterwards. Newly reported lymphomas were identified, and requests sent out, every 3 months. The final requests were made in February 2012.

The process of requesting tissue was different in patients who were alive at the time of the study to that in patients who were deceased since patient consent was required only from living patients. First, the Rheumatologist caring for each patient (alive or deceased) was contacted and asked to confirm that the subject in question had a diagnosis of lymphoma and provide the histology report with details of the pathologist who reported the diagnosis. A second request was sent out to Rheumatologists who did not respond to the first letter. For subjects that were still living, Rheumatologists were asked to approach their patient by letter to request their participation in the study (Appendix 2). We were not permitted to approach patients directly from the BSRBR but additional action was taken to encourage Rheumatologists to introduce the study to their patients; 1) Upon request, the patient letter was sent electronically to the Rheumatologist so that it could simply be printed onto their Trust's headed paper and posted out; and 2) Rheumatologists and specialist nurses were contacted via telephone to discuss the study and to encourage their involvement. For subjects that consented to the study or who were deceased, the pathology department in which the lymphoma diagnosis was made was contacted by letter and loan of the tissue block requested (Appendix 2). Pathology departments were also contacted by telephone at the time of requesting tissue to confirm that they held the specimen and flag up the request to them. Departments from whom lymphoma tissue was not yet received were later contacted by the pathologist reviewing the specimens (Dr Richard Byers (RB), Senior Lecturer and Consultant at Manchester Royal Infirmary) to try and maximise the number of samples available for study.

Lymphoma tissue was reclassified by the same pathologist (RB), who was blinded to the patients' treatment histories, using the WHO classification [77]. Follicular lymphomas were graded according to the WHO classification, based on the average number of centroblasts (large transformed cells) in ten neoplastic follicles at x40 high powered field (Table 6-15) [77]. In addition, diffuse areas containing >15 centroblasts per high powered field were reported as DLBCL with FL [77]. It was intended that DLBCL would be further classified as GC-type or non-GC type by immunohistochemistry.

Table 6-15 WHO grading of FL (adapted from [77], page 220)

Grading	Definition
Grade 1-2 (low grade)	0-15 centroblasts per hpf
Grade 1	0-5 centroblasts per hpf
Grade 2	6-15 centroblasts per hpf
Grade 3	>15 centroblasts per hpf
Grade 3a	Centrocytes present
Grade 3b	Solid sheets of centroblasts

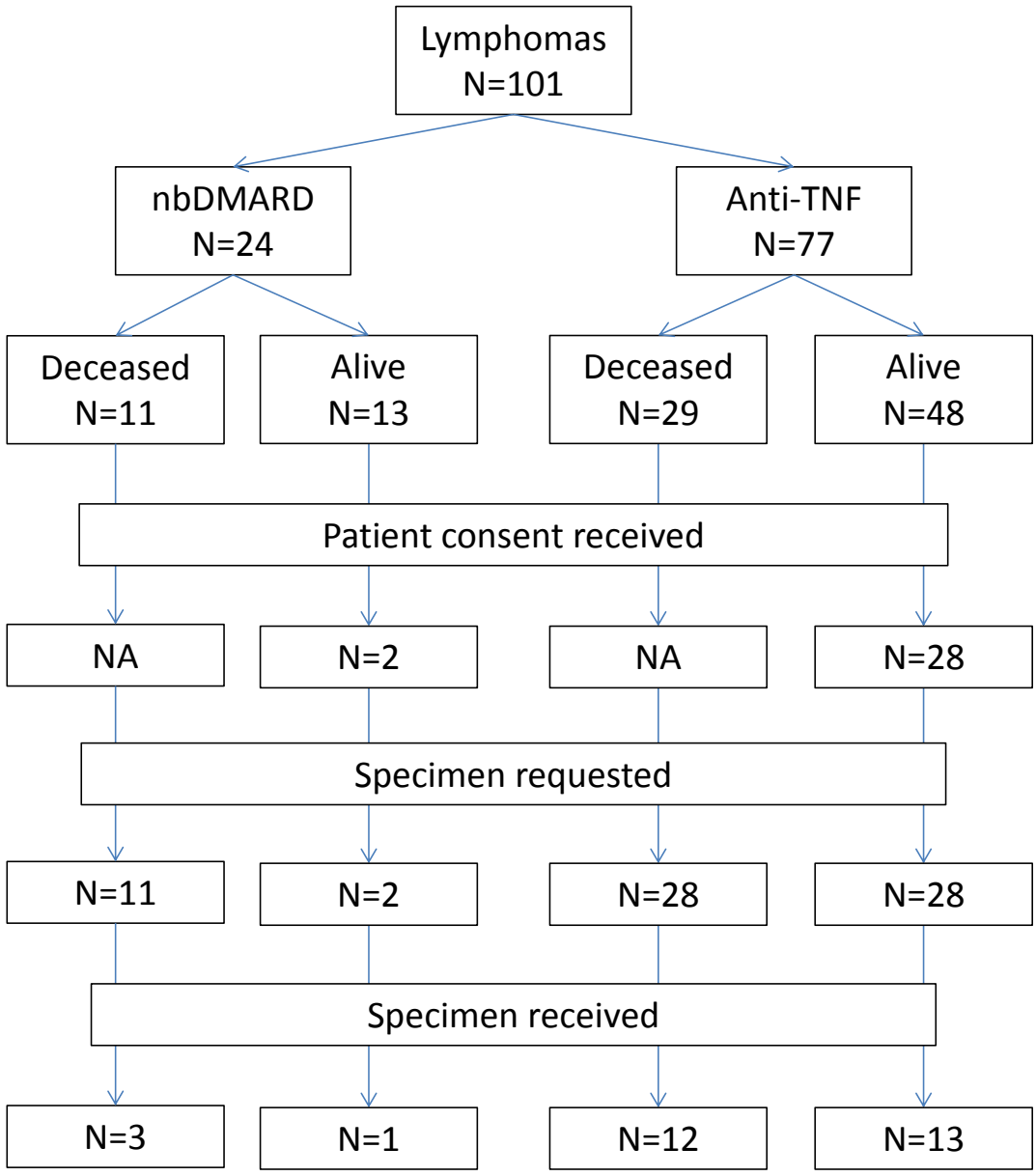
hpf high powered field

Tissue was tested for EBV using EBV-encoded ribonucleic acid in situ hybridization, when sufficient lymphoma tissue was provided. The presence of EBV was reported as positive or negative. The term focal positive was used when only occasional nuclei stained positive for EBV. The significance of focally positive staining is unknown.

6.5.3 Results

One hundred and one lymphomas were identified during the period of this sub-study; nbDMARD-only 24; anti-TNF 77 (Figure 6-5). Of these, 13 (54%) were from patients that were alive at the time of the study in the nbDMARD cohort and 48 (62%) for anti-TNF. Consent was obtained, and so tissue requested, from 2 (15%) nbDMARD and 28 (58%) anti-TNF-treated patients that were alive respectively. In one anti-TNF-treated patient who had died the diagnosis of lymphoma, reported by NHS IC, was refuted by the Rheumatologist. NHS IC were contacted and the diagnosis of lymphoma withdrawn. Of note, this patient was also excluded from the analysis of lymphoma rate and relative risk presented earlier in the chapter, as the case was therefore not validated. Tissue was requested from all other lymphomas in deceased patients. Ultimately, tissue was obtained from 29 lymphomas; nbDMARD 4; anti-TNF 25 (Figure 6-5 and Table 6-16).

Figure 6-5 Flowchart showing patients in whom lymphoma specimens were reclassified



NA not applicable (consent not requested for deceased patients)

For one (25%) nbDMARD and three (12%) anti-TNF-treated patients insufficient lymphoma tissue was received to make a pathological diagnosis of lymphoma (Table 6-16). Excluding these, there were 25 lymphomas; 6 (24%) HL, 6 (24%) DLBCL, 5 (20%) FL, 1 (4%) FL with DLBCL, 2 (8%) B-cell NHL NOS and one (4%) of each of mantle cell lymphoma, MALToma, marginal zone lymphoma, small cell lymphoma and angio-immunoblastic T-cell lymphoma (Table 6-16; Table 6-17). Immunohistochemistry to classify DLBCL into GC-like and non-GC-like lymphomas was not undertaken since the number of DLBCL specimens with sufficient tissue to undertake this work was low (N=5).

Table 6-16 Pathological reclassification of lymphoma tissue

Lymphoma number	Patient Alive	Diagnosis on H&E	Disagreement with histology report	EBV status
nbDMARD cohort				
1	No	DLBCL		Focal positive
2	No	Mantel cell lymphoma		Negative
3	Yes	DLBCL		Negative
4	No	Insufficient material		Insufficient material
Anti-TNF cohort				
5	Yes	FL Grade 1/2		Insufficient material
6	Yes	Classic HL, lymphocyte rich type		Positive
7	Yes	Insufficient material		Insufficient material
8	Yes	DLBCL		Negative
9	Yes	FL Grade 1		Negative
10	No	MALToma		Negative
11	No	DLBCL		Insufficient material
12	No	Classic HL, nodular sclerosing type		Positive
13	No	Marginal zone lymphoma		Positive
14	Yes	B-cell NHL NOS	Report states FL	Positive
15	Yes	Classic HL, mixed cellularity type		Positive
16	Yes	Insufficient material		Insufficient material
17	No	Classic HL, nodular sclerosing type		Positive
18	No	DLBCL		Negative
19	No	Angio-immunoblastic T-cell lymphoma		Negative
20	No	DLBCL		Negative
21	No	FL Grade 3a and DLBCL		Insufficient material
22	Yes	Insufficient material		Insufficient material
23	No	FL Grade 1/2		Focal positive
24	No	FL not graded due to size		Insufficient material
25	Yes	FL Grade 1	Report states FL Grade 3	Negative

26	No	Classic HL, nodular sclerosing type	Negative
27	Yes	Classic HL	Negative
28	Yes	B-cell NHL NOS	Insufficient material
29	Yes	Small cell lymphoma	Focal positive

H&E haematoxylin and eosin; MALToma mucosal-associated lymphoid tissue lymphoma

There was sufficient tissue to stain 20 (69%) lymphomas for EBV, of which 6 (30%) tested positive (Table 6-16; Table 6-17). All EBV-positive lymphomas were in subjects treated with anti-TNF. Four were in HL, one in marginal cell lymphoma and one in B-cell NHL NOS. None of the 5 DLBCL tested for EBV were positive.

Table 6-17 Subtypes of lymphoma and EBV tissue status in patients treated with nbDMARD and anti-TNF

Subtype	All		nbDMARD		Anti-TNF	
	No. (%)	EBV +ve/ tested (% +ve)	No. (%)	EBV +ve/ tested (% +ve)	No. (%)	EBV +ve/ tested (% +ve)
HL	6 (24)	4/6 (67)	0 (0)	NA	6 (27)	4/6 (67)
DLBCL	6 (24)	0/5 (0)	2 (67)	0/2 (0)	4 (18)	0/3 (0)
FL	5 (20)	0/3 (0)	0 (0)	NA	5 (23)	0/3 (0)
FL + DLBCL	1 (4)	0/0 (0)	0 (0)	NA	1 (5)	0/0 (0)
Mantle cell lymphoma	1 (4)	0/1 (0)	1 (33)	0/1 (0)	0 (0)	NA
Marginal zone lymphoma	1 (4)	1/1 (100)	0 (0)	NA	1 (5)	1/1 (100)
MALToma	1 (4)	0/1 (0)	0 (0)	NA	1 (5)	0/1 (0)
Small cell lymphoma	1 (4)	0/1 (0)	0 (0)	NA	1 (5)	0/1 (0)
B-cell NHL NOS	2 (8)	1/1 (100)	0 (0)	NA	2 (9)	1/1 (100)
Angio-immunoblastic T-cell lymphoma	1 (4)	0/1 (0)	0 (0)	NA	1 (5)	0/1 (0)

+ve positive; NA Not applicable; MALToma mucosal-associated lymphoid tissue lymphoma

6.6 Summary of results

The key findings in this chapter were:

- The crude risk of lymphoma was reduced in the anti-TNF compared to nbDMARD cohort.
- There was no difference in the risk lymphoma in patients exposed to anti-TNF compared to patients treated with nbDMARD-only, after adjusting for differences in baseline characteristics.
- The PS and drug exposure models used to investigate the effect of anti-TNF on risk of lymphoma in the BSRBR-RA influenced the estimated treatment effect and should be borne in mind when interpreting the results.
- No difference in lymphoma risk was seen for any of the individual anti-TNF drugs compared to nbDMARD, although the confidence intervals were wide and included clinically important differences in risk.
- The most common subtypes of lymphoma were DLBCL, FL and HL. Two-thirds of HL tested positive for EBV. There were no EBV-positive DLBCL or FL.

6.7 Discussion

This chapter described the development of the methodology used to compare incidence rates of cancer, in this case lymphoma, between the two cohorts that will form the basis of the analyses presented in subsequent chapters. A PS model with stratification into deciles was selected. Stratification is straightforward to perform and creating five strata removes over 90% of bias [204]. For the analyses in this thesis, ten strata were created to further reduce bias since the large size of the BSRBR-RA facilitated this. Stratification also has the advantage over weighting of being less susceptible to bias due to model misspecification. The extent to which the model controlled for confounding was assessed by calculating the expected bias for each confounder and found to be satisfactory with less than 2% expected bias for each covariate.

The BSRBR-RA was powered to detect a doubling in the risk of lymphoma following treatment with any one of the three anti-TNF drugs compared to nbDMARD-only. It was calculated that this would require 20,000 pyrs follow up for each treatment group. In this analysis, with over 50,000 pyrs of exposure for all anti-TNF drugs combined, no difference in the risk of lymphoma was observed after adjusting for differences in baseline characteristics; HR for anti-TNF 1.00 (95% CI 0.49, 2.05).

However, only 12000 pyrs of follow up had accrued in the nbDMARD cohort and the 95% CI for the estimated hazard spanned from a halving to doubling in risk. With the size of the nbDMARD and anti-TNF cohorts and a rate of lymphoma of 157 per 100,000 pyrs in the nbDMARD cohort, the study had 86% power to detect a doubling in the risk of lymphoma following anti-TNF but only 33% power to detect a 50% increase. Nonetheless, the finding of no difference in lymphoma risk is in keeping with results published by Wolfe *et al.* from the NDB, in which an OR for exposure of 1.0 (95% CI 0.6, 1.8) was reported [134]. The advantage of the current work was that only incident users of anti-TNF as their first biologic drug for RA were included. The Swedish biologics register (ARTIS) reported a relative risk of 1.35 (95% CI 0.82, 2.11) in their most recent publication [165]. Despite having more than 350,000 pyrs of follow up in their nbDMARD comparator cohort, they also lacked precision in their estimate of drug effect since they had just 26 lymphomas in 30,000 pyrs in their anti-TNF cohort.

The selection of an 'ever exposed' to anti-TNF drug model reflects the hypothesis that any effect of anti-TNF on cancer risk would be long-lasting and may operate in the latent period of a cancer. Alternative exposure models were constructed, with the analysis limited to time on drug yielding different results. Whilst the confidence intervals spanned unity, the best guess was that the on drug model was associated with a 40% reduced risk of lymphoma. However, when a lag period of 90 days after stopping anti-TNF was included the HR was similar to the ever exposed model (1.05 versus 1.00). These findings highlight the importance of model selection when interpreting the results. The lower HR for the on drug analysis likely reflected patients on anti-TNF stopping the drug when a diagnosis of cancer was suspected but before it was formally confirmed. In subsequent chapters an on drug plus lag period analysis, but not an on drug analysis, will be presented as a sensitivity analysis.

Patients in the anti-TNF cohort were allowed to switch between drugs during the course of follow up and subsequent follow up and lymphomas were attributed to the most recently received anti-TNF drug. A potential pitfall of this method was that adjustment for disease severity at the time of switching drugs could not be made. It was reassuring that a sensitivity analysis in which time after switching was excluded did not alter the results; PD-adjusted HR 0.91 excluding time after switching versus 0.92 for the ever exposed model excluding time after last consultant follow up.

No significant differences in the risk of lymphoma were seen for any of the anti-TNF drugs compared to nbDMARD, although the results were imprecise. The findings were sensitive to changes in the exposure definition chosen. In the primary analysis, lymphomas were only counted once i.e. if occurring after exposure to two or more TNF inhibitors they were attributed to the most recently received drug. The point estimates for each of the drugs all moved in the opposite direction when models allowing exposure time and events to be attributed to all previously received anti-TNF were used. This may reflect limitations in controlling for confounding in disease severity between the drugs since they were available for use at different time periods during the study. In the lymphoma analysis, all results relating to individual TNF inhibitors need to be interpreted cautiously due to the low number of events. In subsequent chapters, where the number of outcomes was greater, both models will be presented.

Similar to this analysis, previous studies looking at individual anti-TNF drugs separately have yielded imprecise estimates [134, 165, 174]. The Swedish registry reported no difference in risk [165]. Analysis from the NDB included multiple analyses of different drug exposures and found that people exposed to both ADA as their first anti-TNF and MTX had an OR of 5.5 (95% CI 1.1, 29.0) compared to the rest of the cohort [134]. However, when all exposure to ADA was included the OR was 1.2 (95% CI 0.3, 5.1). The French study RATIO reported an increased OR for ADA or INF compared to ETA, but the estimates of drug exposure were less robust than for other studies [174]. This current work from the BSRBR-RA represents one of the largest cohorts of its kind worldwide and the findings are reassuring in not finding an increased risk of lymphoma for any of the drugs. Nonetheless further follow up, particularly of the nbDMARD cohort, is required to yield more precise estimates of risk of lymphoma.

The subtype of lymphoma, as reported by the national cancer agencies and histology reports, was determined in 88% of the cohort, with the remaining 12% classified only as B-cell NHL. When the analysis was restricted to NHL, there was no appreciable change in the HR for anti-TNF. Sufficient tissue to reclassify/confirm the subtype of lymphoma was received for 25 lymphomas. The diagnosis of lymphoma was confirmed in all 25 specimens and the level of agreement with the lymphoma subtype reported on the original histology report was high. Only one case was reclassified from FL

to B-cell NHL NOS and another from FL Grade 3 to FL Grade 1. In these cases it is possible that the pathologist who initially diagnosed the lymphomas had access to additional tissue.

The subtypes of lymphoma reported most frequently in this study reflected those seen in biologic-naïve cohorts of people with RA [79, 86], the most common subtype being DLBCL. Epstein Barr Virus was detected most frequently in HL (67%). This is the subtype most frequently associated with EBV positivity in the general population, with the proportion of EBV-positive tumours varying by HL subtype and being highest for mixed cellularity classic HL (75%) [77]. A high proportion of EBV-positive HL has also been reported in RA. Baecklund *et al.* tested 304 lymphomas, occurring in biologic-naïve subjects with RA, for EBV [86]. Nine (47%) of 19 HL were EBV positive. All six cases of mixed cellularity classic HL and three (33%) of the nodular sclerosis type were positive. Two lymphocyte-depleted, one lymphocyte-rich and one nodular lymphocyte-predominant HL were negative. In the current study, 3 of the 6 HL were nodular sclerosing, of which 2 (67%) were EBV positive. There was one mixed cellularity (positive), one lymphocyte-rich (positive) and one classic HL NOS (negative). None of the DBLCL or FL occurring in subjects treated with anti-TNF stained positive for EBV. Previous studies have reported 12-17% of DLBCL to be EBV-positive in RA [86, 135].

A challenge of the lymphoma reclassification was the limited number of samples that were made available to us (25% of all reported lymphomas). This was due to many reasons. First, the number of consent forms received was low. This may be due to lack of willingness of patients to participate but may also be due to the fact that Rheumatologists were required to obtain consent, creating extra work for them. Second, although attempts were made to identify the hospital where the lymphoma specimen was stored (by requesting histology reports, asking Rheumatologists and ringing Pathology departments), lymphoma specimens were frequently sent to tertiary reporting centres and tissue blocks not always returned. Third, tissue blocks may not have been sent due to there being no tissue left.

The proportion of samples received was lower for the nbDMARD cohort (17%) than for anti-TNF (33%) which might be due to the later start date for requesting samples from the nbDMARD cohort. It is also possible that there was greater motivation amongst Rheumatologists to include anti-TNF-

treated patients in the study, due to concerns that the drug may have played a causal role. It is also noteworthy that a lower proportion of tissue blocks was received in patients that were alive (23%) than in those that were deceased (38%), since consent was required from living patients. Thus, lymphoma subtypes that are associated with a poor prognosis might have been over-represented in this sample.

With the low number of responses, it was difficult to draw any firm conclusions about the occurrence of EBV in lymphomas occurring in this population, or to make any comparisons between anti-TNF treated and untreated patients. However, this sub-study did confirm the diagnosis of lymphoma in all 25 patient specimens. It is reassuring that overall agreement between the lymphoma subtype reported to the BSRBR-RA initially by the Rheumatologists /national cancer agencies and reported on reclassification was high, suggesting that the original validation and classification rules used for all reported lymphomas were robust and the results of these analyses valid.

7. Relative risk of solid cancers in subjects treated with anti-TNF versus nbDMARD

This chapter will describe and compare the incidence of solid cancer in the nbDMARD and anti-TNF cohorts of the BSRBR-RA. The distribution of cancer sites will be identified and, where statistically feasible, the incidence of cancers for each site compared between cohorts. Finally the outcome following cancer will be analysed. A brief discussion of the results is also included with further discussion included in Chapter 9.

7 Relative risk of solid cancers in subjects treated with anti-TNF versus nbDMARD

7.1 Introduction

An early meta-analysis of anti-TNF RCT by Bongartz *et al.* raised concerns that the TNF inhibitors may increase the risk of cancer in RA, when it reported an OR for cancer at all sites excluding KSC for INF and ADA versus placebo of 3.7 (95% CI 1.0, 13.2) [149] (Table 1-4). Whilst there were flaws in the methodology of this analysis [154], and subsequent meta-analyses have not replicated the finding (Table 1-4), concerns have persisted. Few long-term observational studies have reported on the risk of solid cancer following anti-TNF and, so far, no association has been found (Table 1-7).

7.2 Aims

- To determine the incidence of solid cancer in people with RA treated with anti-TNF and compare this to biologic-naïve patients treated with nbDMARD.
- To identify the sites of cancer reported in biologic-naïve and anti-TNF treated patients and compare the incidence where appropriate.
- To describe the outcome of patients following cancer in the BSRBR-RA, with respect to mortality, and compare between the nbDMARD and anti-TNF cohorts.

7.3 Methods

The primary outcome measure for this chapter was the first verified solid cancer per subject. Solid cancers comprised all cancers except LPM, MPM and KSC i.e. cutaneous melanomas were included in this chapter. The study population for this analysis was selected from the patient dataset created on 31st January 2012 which included follow up time until 31st January 2011 (see section 4.2). Patients with a diagnosis of solid cancer prior to starting anti-TNF or registration with the BSRBR-RA were excluded (nbDMARD: N=134; anti-TNF: N=165). Patients with low disease activity at baseline (DAS28 score of ≤3.2) were then excluded from this analysis (nbDMARD: N=283; anti-TNF: N=56). Subjects entered the analysis 6 months after registration and were censored after contributing 5 years follow up, if they had not already been censored prior to that.

Histology reports submitted by Rheumatologists and ICD 10 codes reported by the cancer registries were used to determine the site of cancers. For sites with at least ten cancers in each cohort, analysis comparing the incidence in the nbDMARD and anti-TNF cohorts was performed. The PH assumption was met for Cox regression (global PH test p=0.272). A PS model was constructed to control for confounding and the cohort stratified into deciles of PS. The variables selected *a priori* for inclusion were age, sex, ethnicity, smoking status, co-morbidity, RA duration, DAS28, HAQ, steroid exposure, number of prior nbDMARD (≤3 versus 4 or more), prior exposure to AZA and prior exposure to CYC at baseline. In addition, during construction of the PS model, interaction terms between HAQ and CYC; age and DAS28; age and disease duration; prior nbDMARD exposure and smoking; nbDMARD exposure, smoking and disease duration; and nbDMARD exposure, smoking and DAS28 were added.

The proportion of patients in the anti-TNF cohort that continued on their TNF inhibitor 3 and 6 months following diagnosis of cancer was calculated. For this, the cohort was restricted to patients taking anti-TNF, or having stopped within 90 days, at the time of their cancer and that were alive 3 and 6 months after cancer diagnosis respectively. Outcome of the anti-TNF cohort following cancer diagnosis was compared to that in the nbDMARD cohort by comparing all-cause mortality between the two groups. Deaths were determined by record linkage with the national deaths registry. Deaths occurring up to 31st January 2012 were included i.e. one year after the last day of follow up for this analysis. Data on deaths were extracted in August 2012, allowing for at least a six months lag in reporting of deaths to the BSRBR-RA. Kaplan-Meier survival curves for each cohort were constructed. Mortality was compared between the groups by using Cox regression, adjusted for age as a time varying covariate and sex.

7.4 Results

7.4.1 Incidence of solid cancer in the BSRBR-RA

In total 563 cancers were verified; 136 during 11672 pyrs in the nbDMARD cohort and 427 in 52549 pyrs in the anti-TNF cohort (Table 7-1). More than 90% of cancers in both cohorts were reported by the national cancer agencies. The proportion of cancers reported by the patient was low and similar in both cohorts. The proportion of cancers reported by the consultant was higher in the anti-TNF cohort (Table 7-1) and after excluding time after the last received consultant follow up this pattern persisted; 81 of 106 cancers (76%) in the nbDMARD cohort were reported by the consultant and 305 out of 365 (84%) in the anti-TNF cohort. The unadjusted HR indicated a 30% reduced hazard for solid cancer following treatment with anti-TNF (Table 7-1).

Table 7-1 Incidence of cancer in the BSRBR-RA

	nbDMARD N=3249	**Anti-TNF N=11767**
Follow-up time (pyrs)	11672	52549
Follow up per subject: median (IQR)	4.1 (2.3, 5.0)	5.0 (4.4, 5.0)
Solid cancers	136	427
Incidence rate per 10,000 pyrs (95% CI)	117 (98, 138)	81 (74, 89)
Unadjusted HR (95% CI)	Referent	0.70 (0.58, 0.85)
Cancer reported by: N (%)		
National cancer agency	124 (91)	399 (93)
Consultant	83 (61)	322 (75)
Patient	23 (17)	79 (19)

7.4.1.1 Relative risk for anti-TNF versus nbDMARD with univariate adjustment

Increasing age, white ethnicity, co-morbidity, disease severity and exposure to nbDMARD were associated with cancer, after adjusting for anti-TNF (Table 7-2). Never smoking and female sex were associated with a decreased hazard. The variables that had the greatest confounding effect, in univariate adjustment, were age, disease activity and disability (Table 7-2).

Table 7-2 Univariate adjustment of exposure to anti-TNF for each confounder

	Hazard ratio (95% CI) for covariate	Hazard ratio (95% CI) for anti-TNF
Unadjusted		0.70 (0.58, 0.85)
Age (per year)	1.06 (1.05, 1.07)	0.90 (0.74, 1.09)
Sex (Male referent)	0.71 (0.59, 0.85)	0.71 (0.58, 0.86)
Ethnicity (Non-white referent)	2.56 (1.21, 5.41)	0.70 (0.58, 0.85)
Smoking (Current smoker referent)		
Ex-smoker	0.96 (0.79, 1.17)	
Never smoked	0.47 (0.38, 0.59)	0.71 (0.58, 0.86)
Comorbidity: (Nil referent)		
1 comorbidity	1.24 (1.02, 1.50)	
2 comorbidities	1.35 (1.06, 1.72)	0.72 (0.59, 0.87)
≥3 comorbidities	1.91 (1.39, 2.61)	
Entered study before June 2004	0.92 (0.77, 1.09)	0.72 (0.59, 0.88)
Disease duration (per year)	1.01 (1.00, 1.02)	0.67 (0.55, 0.82)
Disease activity (per unit DAS28)	1.11 (1.02, 1.21)	0.61 0.49, 0.76)
Disability (per unit HAQ)	1.19 (1.03, 1.38)	0.64 (0.52, 0.79)
Baseline corticosteroids	1.13 (0.95, 1.34)	0.68 (0.56, 0.83)
No. prior nbDMARD: (≤3 referent)	1.20 (1.01, 1.43)	0.66 (0.54, 0.81)
≥4		
Ever exposed to AZA	1.15 (0.93, 1.42)	0.68 (0.55, 0.83)
Ever exposed to CYC	2.04 (1.30, 3.19)	0.68 (0.56, 0.84)

After adjusting for differences in age and sex the HR for anti-TNF was 0.91 (95% CI 0.75, 1.11) and after fully adjusting there was no significant different in the hazard for first solid cancer between the cohorts (PD adjusted HR 0.83, 95% CI 0.64, 1.07) (Table 7-3). Restricting the analysis to time on anti-TNF did not change the results (Table 7-3). A sensitivity analysis limited to cancers reported by the cancer agencies did not alter the findings (PD adjusted HR 0.88, 95% CI 0.67, 1.16). Similarly, the findings were not influenced by the exclusion of patients who had switched to a second or subsequent biologic (PD adjusted HR 0.86 (95% CI 0.63, 1.16)).

Table 7-3 Adjusted hazard ratio for anti-TNF versus nbDMARD

	nbDMARD N=3249	Anti-TNF N=11767
Follow-up time (pyrs)	11758	52549
Solid cancers	138	427
Unadjusted HR (95% CI)	Referent	0.70 (0.58, 0.85)
Age and sex adjusted HR (95% CI)	Referent	0.91 (0.75, 1.11)
PD-adjusted HR (95% CI)	Referent	0.83 (0.64, 1.07)
Limited to on drug plus 90 days		
Follow-up time (pyrs)	10275	39173
Solid cancers	106	285
Unadjusted HR (95% CI)	Referent	0.69 (0.56, 0.87)
Age and sex adjusted HR (95% CI)	Referent	0.91 (0.72, 1.14)
PD-adjusted HR (95% CI)	Referent	0.81 (0.60, 1.10)

A further sensitivity analysis showed that the HR for anti-TNF did not change with increasing exposure (Table 7-4).

Table 7-4 Cancers in the anti-TNF cohort by cumulative exposure to anti-TNF

	Cumulative exposure time on anti-TNF		
	< 1.5 years	**1.5 to < 3 years**	**≥3 years**
Pyrs of follow up	20264	14729	13969
No. solid cancers	166	99	100
Unadjusted HR:			
nbDMARD referent	0.74 (0.58, 0.93)	0.70 (0.53, 0.93)	0.62 (0.47, 0.82)
<1.5 yrs anti-TNF referent	Referent	0.87 (0.63, 1.20)	0.71 (0.51, 1.00)
PD adjusted HR (95% CI):			
nbDMARD referent	0.87 (0.66, 1.15)	0.85 (0.63, 1.17)	0.77 (0.58, 1.03)
Test for trend	P=385		
<1.5 yrs anti-TNF referent	Referent	0.91 (0.67, 1.24)	0.77 (0.58, 1.02)
Test for trend	P=193		

7.4.2 Incidence of solid cancer for individual anti-TNF drugs compared to nbDMARD

Using the primary drug exposure model, there were 190 solid cancers in the ETA cohort, 98 in the INF cohort and 139 for ADA. The crude incidence rate was highest for ETA at 86 per 10,000 pyrs, but the 95% CI overlapped with those for INF and ADA (Table 7-5). After adjusting for age and sex, and then fully adjusting, there was no difference in the HR for solid cancer for any of the anti-TNF drugs versus nbDMARD (Table 7-5). In a sensitivity analysis, in which follow up time and cancers were attributed to all previously received anti-TNF drugs, there was a 27% reduced hazard for ADA (PD adjusted HR 0.73, 95% CI 0.55, 0.98).

Table 7-5 Incidence of solid cancer for individual TNF inhibitors compared to nbDMARD

	ETA N=4073	**INF N=3457**	**ADA N=4327**
Follow-up time (pyrs)	22146	12379	18027
Follow up per subject: median (IQR)	4.8 (2.5, 5.0)	3.9 (1.3, 5.0)	3.5 (2.0, 4.8)
Solid cancers	190	98	139
Incidence rate per 10,000 pyrs (95% CI)	86 (74, 99)	79 (64, 96)	77 (65, 91)
Unadjusted HR (95% CI)	0.74 (0.59, 0.92)	0.68 (0.53, 0.88)	0.67 (0.53, 0.84)
Age and sex adjusted HR (95% CI)	1.00 (0.80, 1.25)	0.87 (0.67, 1.12)	0.84 (0.66, 1.07)
PD-adjusted HR (95% CI)	0.89 (0.67, 1.19)	0.81 (0.59, 1.11)	0.79 (0.59, 1.05)
Attributing follow up and cancers to each prior or current anti-TNF*			
Follow-up time (pyrs)	26401	18072	22334
Solid cancers	227	153	165
Unadjusted HR (95% CI)	0.73 (0.59, 0.91)	0.73 (0.58, 0.92)	0.65 (0.52, 0.81)
Age and sex adjusted HR (95% CI)	0.99 (0.79, 1.230	0.93 (0.74, 1.18)	0.84 (0.67, 1.06)
PD-adjusted HR (95% CI)	0.94 (0.68, 1.28)	0.89 (0.64, 1.26)	0.73 (0.55, 0.98)

nbDMARD was referent for regression analyses

*In this model, follow up time and cancers could be attributed to more than one anti-TNF agent

7.4.3 Site specific incidence of solid cancers

The most frequently reported cancers in the cohort were lung cancer, breast cancer and colorectal cancer. The proportion of cancers occurring at these subtypes was similar in the two cohorts (Table 7-6). The next most common cancer sites were gastro-oesophageal comprising 9% of cancers in the nbDMARD cohort and 5% for anti-TNF, and female reproductive cancers; 3% and 10% respectively.

Table 7-6 Subtypes of verified solid cancers in the BSRBR-RA

Cancer site: N(%)	nbDMARD N=136	Anti-TNF N=427
Lung	40 (29)	103 (24)
Female breast	22 (16)	73 (17)
Colorectal	19 (14)	43 (10)
Female reproductive cancers	4 (3)	42 (10)
Gastro-oesophageal	12 (9)	20 (5)
Urinary/renal tract	7 (5)	29 (7)
Male reproductive cancers	4 (3)	23 (5)
Lip to larynx	3 (2)	16 (4)
Melanoma	7 (5)	7 (2)
Pancreas	2 (1)	12 (3)
Nervous system	3 (2)	11 (3)
Hepatobiliary	3 (2)	5 (1)
Endocrine	0 (0)	5 (1)
Mesothelioma	1 (1)	2 (0)
Small bowel	0 (0)	4 (1)
Peritoneal	1 (1)	2 (0)
Sinus	0 (0)	3 (1)
Anal	0 (0)	2 (0)
Metastasis, no primary site	2 (1)	6 (1)
No site	6 (4)	19 (4)

All values are number (%)

The rates of lung cancer, breast cancer, colorectal cancer and gastro-oesophageal cancers in the anti-TNF cohort were compared to those in the nbDMARD cohort (Table 7-7). There was no significant difference in relative risk observed for any of these cancers, although there was a suggestion that the RR of both breast and colorectal cancers were reduced for the anti-TNF cohort: HR 0.58 (95% CI 0.32, 1.06) for breast cancer and HR 0.51 (95% CI 0.24, 1.06) for colorectal cancer.

Table 7-7 Site-specific cancer risks for anti-TNF compared to nbDMARD

	nbDMARD N=3249	Anti-TNF N=11767	ETA N=4073	INF N=3457	ADA N=4327
Lung cancer					
Number	40	103	49	25	29
Incidence rate per 10,000 pyrs (95% CI)	34 (24, 47)	20 (16, 24)	22 (16, 29)	20 (13, 30)	16 (11, 23)
Unadjusted HR (95% CI)	Referent	0.57 (0.40, 0.82)	0.64 (0.42, 0.98)	0.59 (0.36, 0.97)	0.49 (0.29, 0.76)
Age and sex adjusted HR (95% CI)	Referent	0.81 (0.56, 1.17)	0.95 (0.62, 1.46)	0.81 (0.49, 1.35)	0.64 (0.40, 1.04)
PD-adjusted HR (95% CI)	Referent	0.85 (0.52, 1.39)	1.02 (0.58, 1.76)	0.92 (0.50, 1.71)	0.69 (0.39, 1.23)
Female breast cancer					
Number	22	73	30	18	25
Incidence rate per 10,000 pyrs (95% CI)	34 (20, 48)	18 (14, 22)	17 (11, 23)	19 (10, 28)	17 (10, 23)
Unadjusted HR (95% CI)	Referent	0.72 (0.45, 1.17)	0.70 (0.40, 1.22)	0.76 (0.41, 1.42)	0.74 (0.42, 1.31)
Age adjusted HR (95% CI)	Referent	0.83 (0.51, 1.35)	0.83 (0.47, 1.45)	0.86 (0.46, 1.61)	0.83 (0.47, 1.48)
PD-adjusted HR (95% CI)	Referent	0.58 (0.32, 1.06)	0.56 (0.28, 1.10)	0.59 (0.28, 1.24)	0.59 (0.31, 1.15)

	nbDMARD N=3249	Anti-TNF N=11767	ETA N=4073	INF N=3457	ADA N=4327
Colorectal cancer					
Number	19	43	16	10	17
Incidence rate per 10,000 pyrs (95% CI)	16 (9, 25)	8 (6, 11)	7 (4, 12)	8 (4, 15)	9 (5, 15)
Unadjusted HR (95% CI)	Referent	0.52 (0.30, 0.89)	0.46 (0.24, 0.90)	0.50 (0.23, 1.07)	0.59 (0.31, 1.14)
Age and sex adjusted HR (95% CI)	Referent	0.71 (0.41, 1.23)	0.66 (0.33, 1.29)	0.67 (0.31, 1.44)	0.79 (0.41, 1.52)
PD-adjusted HR (95% CI)	Referent	0.51 (0.24, 1.06)	0.45 (0.19, 1.05)	0.47 (0.19, 1.20)	0.57 (0.26, 1.27)
Gastro-oesophageal cancer					
Number	12	20	8	5	7
Incidence rate per 10,000 pyrs (95% CI)	10 (5, 18)	4 (2, 6)	4 (2, 7)	4 (1, 9)	4 (2, 8)
Unadjusted HR (95% CI)	Referent	0.35 (0.17, 0.73)	NR	NR	NR
Age and sex adjusted HR (95% CI)	Referent	0.51 (0.24, 1.05)	NR	NR	NR
PD-adjusted HR (95% CI)	Referent	0.59 (0.23, 1.52)	NR	NR	NR

NR Not reported (Indicates fewer than ten events in each cohort so comparative analyses were not performed.)

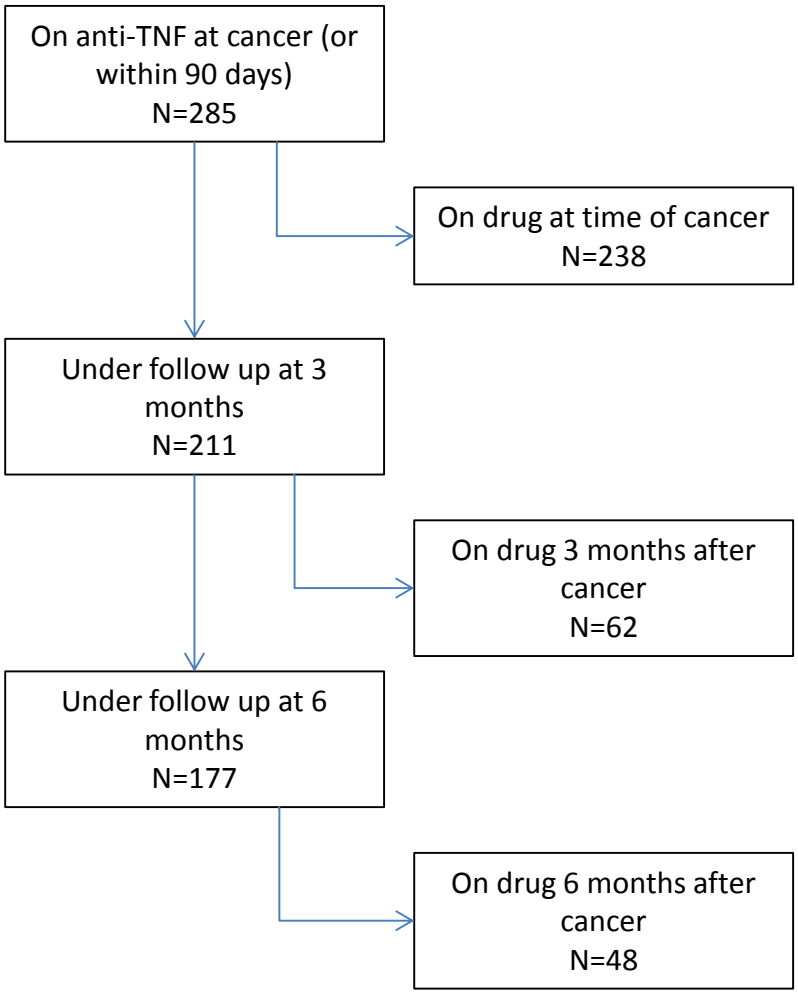
7.4.4 Outcome following solid cancer

7.4.4.1 Exposure to anti-TNF following solid cancer

Excluding time after last received consultant follow up, there were 365 cancers in the anti-TNF cohort, of which 285 (78%) were diagnosed whilst the patient was taking the drug (or within 90 days of stopping). Of these, 47 patients (16%) stopped the drug within the 90 days prior to formal diagnosis of their cancer (Figure 7-1). Of the 211 patients that were alive and under follow up three

months later, 62 (29%) were still on anti-TNF. At 6 months 177 patients remained, of whom 48 (27%) were still on their drug.

Figure 7-1 Continued exposure to anti-TNF following the diagnosis of solid cancer

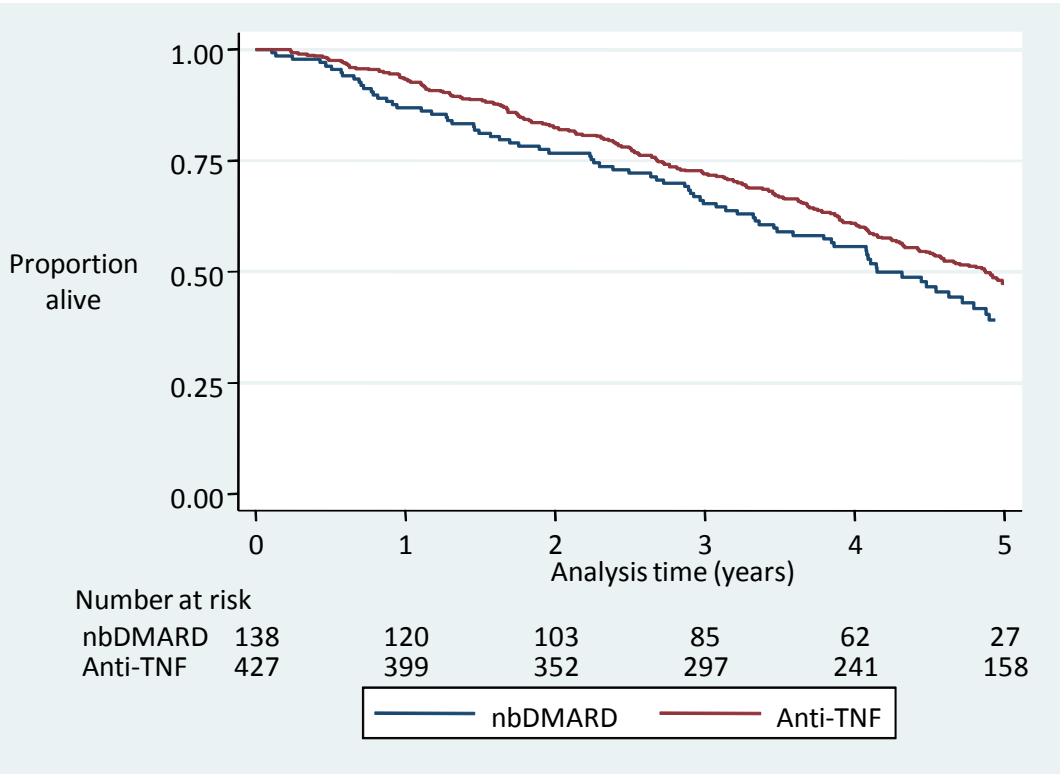


There was no difference in the distribution of cancer sites in patients who continued on their anti-TNF drug immediately following diagnosis or 3 or 6 months later compared to that in the overall cohort. However, it is noteworthy that in the 47 patients who stopped the drug within the 90 days prior to diagnosis 45 (96%) were consultant reported compared to 202 of 238 (85%) subjects who didn't stop in the 90 days prior to diagnosis. Of those who had stopped their anti-TNF at 3 months, 138 of 149 (93%) were consultant reported compared to 38 of 62 (61%) in patients that remained on anti-TNF.

7.4.4.2 Mortality

Among the 563 patients with solid cancer, 309 patients died during subsequent follow up; nbDMARD 77 (57%); anti-TNF 232 (54%). Kaplan Meier survival curves show that mortality was similar between the two cohorts and approximately linear, following cancer diagnosis (Figure 7-2). Among patients that died following their diagnosis of cancer the median time to death from date of cancer diagnosis was 118 days (IQR 6, 342).

Figure 7-2 Kaplan Meier survival curves for death following diagnosis with solid cancer in the BSRBR-RA



The unadjusted HR for death was 0.86 (95% CI 0.67, 1.12) and after adjusting for age and sex there was no difference between the cohorts; HR 0.90 (95% CI 0.70, 1.17).

7.5 Summary of results

- There was no difference in the overall risk of solid cancer in patients with RA treated with anti-TNF, or for any of the individual TNF inhibitors, compared to nbDMARD.
- There was no evidence of change in risk of solid cancer with increasing exposure to anti-TNF.
- The commonest cancers were lung cancer, breast cancer, colorectal cancer and gastro-oesophageal cancer.
- There was no difference in the risk of either lung cancer or gastro-oesophageal cancer between the cohorts.
- There was a signal that the risks of both female breast and colorectal cancers were reduced in the anti-TNF-treated cohort.
- Less than a third of patients exposed to anti-TNF at the time of cancer diagnosis remained on treatment three or six months later.
- There was no difference in mortality following cancer between the two cohorts.

7.6 Discussion

There was no difference in the overall risk of solid cancer in patients with RA treated with anti-TNF compared to nbDMARD-only, after adjusting for confounders (HR 0.83, 95% CI 0.64, 1.07). This finding is in keeping with the results of analyses from the Swedish and German biologics registers [164, 169], and from observational studies in North America [170, 171], all of which failed to find a change in risk following treatment with anti-TNF. The robustness of the estimate was tested in this thesis by using an on drug plus 90 days model and this did not alter the results. Reassuringly, there was no evidence of change in risk of solid cancer with increasing exposure to anti-TNF. Key strengths of this analysis were the size of the cohort and completeness of capture of the outcome in both cohorts, by using data from the national cancer registries as well as from death certificates, Rheumatologists and patients. Several markers of RA disease severity were recorded at baseline and found to be associated with cancer after univariate adjustment for exposure to anti-TNF (Table 7-2). Differences between these covariates were accounted for in the analysis using a PS model. The large size of the BSRBR-RA meant that this analysis had sufficient power to investigate the relative risk of cancer for individual TNF inhibitors compared to nbDMARD. Based on the rate of cancer on the nbDMARD cohort, the study had 100% power to detect a halving in risk of cancer for each individual anti-TNF drug, using the primary drug exposure model. The power to detect a 50% increased risk was 99% for ETA, 96% for INF and 98% for ADA. No difference in risk was found, and the 95% CI for

each drug did not include a relative increased risk of more than 20% (Table 7-5). The Swedish biologics register have previously reported no increased risk of cancer for individual TNF inhibitors, but their analysis was not sufficiently powered to rule out clinically important differences, for example the RR for ADA: 1.32 (95% CI 0.87, 1.98) [164].

The most frequently reported cancers were lung cancer, female breast cancer, colorectal cancer, female reproductive cancers and gastro-oesophageal cancer. The proportion of cancers for which no site was determined was low in both cohorts (4%). There was no difference in the risk of either lung cancer or gastro-oesophageal cancer between the cohorts.

Although no significant difference in risk of breast cancer was observed between the cohorts, the best estimate was that the risk of breast cancer was reduced by 42% in the anti-TNF versus nbDMARD cohort (HR 0.58, 95% CI 0.32, 1.06). Both the Swedish and German biologics registers have reported a reduced risk of breast cancer in subjects with RA, treated with anti-TNF, compared to the general population [43, 169]. Wolfe and Michaud identified 102 cases of breast cancer in the NDB amongst 10541 participants, half of whom were users of biologics, and calculated an OR of 0.9 (95% CI 0.5, 1.3) for biologic exposure [171]. The signal for a reduced RR of breast cancer observed in the current analysis (although not statistically significant) could reflect either unmeasured differences in subjects selected for anti-TNF or nbDMARD in the BSRBR-RA or a true effect of the drug. Tumour necrosis factor within the microenvironment of breast cancer has been shown to be associated with increased tumour invasiveness and poor prognosis [233], and so it is plausible that blocking the effects of TNF may slow or prevent the progression of breast cancer. However, the effects of TNF on tumourigenesis are pleotropic and it also acts in ways that might inhibit breast cancer cell adhesion and proliferation [234]. Administering a TNF inhibitor has been proposed as an approach to treating breast cancer and ETA has been trialled in a phase II RCT [235]. That study only involved patients with advanced metastatic cancer and no objective disease responses were seen.

There was no significant difference in the risk of colorectal cancer, although the point estimate was in the direction of a reduced risk in patients treated with anti-TNF (HR 0.51, 95% CI 0.24, 1.06). In an analysis using the NDB in North America, no difference in the rate of colorectal cancer was observed

following biologic therapy, although the confidence intervals were wide; OR 0.8 (95% CI 0.3, 1.7) [171]. It is noteworthy that the rates of both breast and colorectal cancers in the nbDMARD cohort were the same as in the general population (SIRs 1.07 (95% CI 0.72, 1.52) and 0.96 (95% CI 0.56, 1.54) respectively; Table 5-2 and Table 5-1), in contrast to other biologic-naïve cohorts in which reduced risks have been reported [41, 43, 45, 48]. Thus, the HRs may reflect higher than expected rates in the nbDMARD cohort, rather than lower than expected rates following anti-TNF. An alternative reason for observing a reduced risk of breast cancer following anti-TNF might be screening prior to starting therapy, thus excluding cancers that would otherwise have been diagnosed during follow up. Whilst it is not routine practice to perform an additional breast examination or mammogram prior to starting anti-TNF, it is plausible that women were self-examining and/or more likely to have attended routine mammography prior to treatment. Likewise, patients may have been more likely to participate in screening for colorectal cancer and/or report any rectal bleeding, than those entering the nbDMARD cohort. If that were the case, one might have expected patients to continue these practices during treatment with anti-TNF, leading to earlier diagnosis of cancers and improved survival during follow up. Neither or these outcomes were addressed specifically for breast or colorectal cancers in this analysis, but results from the Swedish register showed no difference in either outcome in their anti-TNF versus biologic-naïve cohorts [181].

The incidence of female reproductive cancers was not compared between the two cohorts due to the low number of events in the nbDMARD cohort (N=4). This was below the number that one would have expected to see in the nbDMARD cohort, if the rate was the same as in the general population (expected number 11; SIR 0.35 (95% CI 0.10, 0.90); Table 5-1).

For cancers occurring whilst the patient was actively taking anti-TNF, it was usual practice for the drug to be stopped with only 29% of patients under follow up at 3 moths still exposed to the drug and 27% at six months. Analysis to compare outcome, such as overall mortality, between those stopping and continuing anti-TNF was not performed due to both low numbers of people and lack of detailed information about other factors affecting survival at the time of the event that may have influenced the decision to continue or stop anti-TNF. It is noteworthy that in patients on anti-TNF three months after cancer diagnosis the proportion of cancers that were reported by the

Rheumatologist was lower (61%) than for those who stopped the drug (93%). It is possible that many of the patients that continued on their anti-TNF did so because their Rheumatologist was not aware of their cancer diagnosis and anti-TNF drugs are prescribed by Rheumatologists rather than General Practitioners. Even for Rheumatologist-reported cancers, it is possible that the Rheumatologist was not aware of the cancer at the time of the event since a proportion of these cancers were reported on the next routine consultant follow up form, rather than reported immediately using an event of special interest fax.

Overall survival following cancer diagnosis was compared between the cohorts and no difference observed. One hypothesis was that cancers occurring in anti-TNF-treated subjects would be diagnosed earlier, leading to improved survival following cancer. Alternatively, anti-TNF might accelerate carcinogenesis leading to more rapidly progressing cancers and higher mortality. Since these factors may differ for cancers at different sites, site-specific comparison of survival warrants analysis. Such analyses were not performed in the BSRBR-RA, due to low numbers of events and pyrs follow up for each cancer site.

8. Relative risk of keratinocyte skin cancer in subjects treated with anti-TNF compared to the general population and to nbDMARD

This chapter will describe the incidence of KSC in the nbDMARD and anti-TNF cohorts of the BSRBR-RA. The incidence rates in each cohort will be compared first to rates in the general population and then to each other. A discussion of the results is also included with further discussion in Chapter 9.

8 Relative risk of keratinocyte skin cancer in subjects treated with anti-TNF compared to the general population and to nbDMARD

8.1 Introduction

Data are conflicting regarding whether or not the risk of KSC is increased in people with RA (see section 1.3.2.1). Both meta-analyses of RCTs of anti-TNF and observational studies have reported an increased risk of KSC following treatment with anti-TNF (see section 1.4.4.1). Whilst KSCs are rarely fatal, this is of importance since if anti-TNF drugs were to have an effect on the incidence of malignancy one might hypothesise than an increased risk would be seen first for KSC as 1) they are the most common cancers and 2) the risk is increased soon after initiation of other forms of immunosuppression e.g. following organ transplantation.

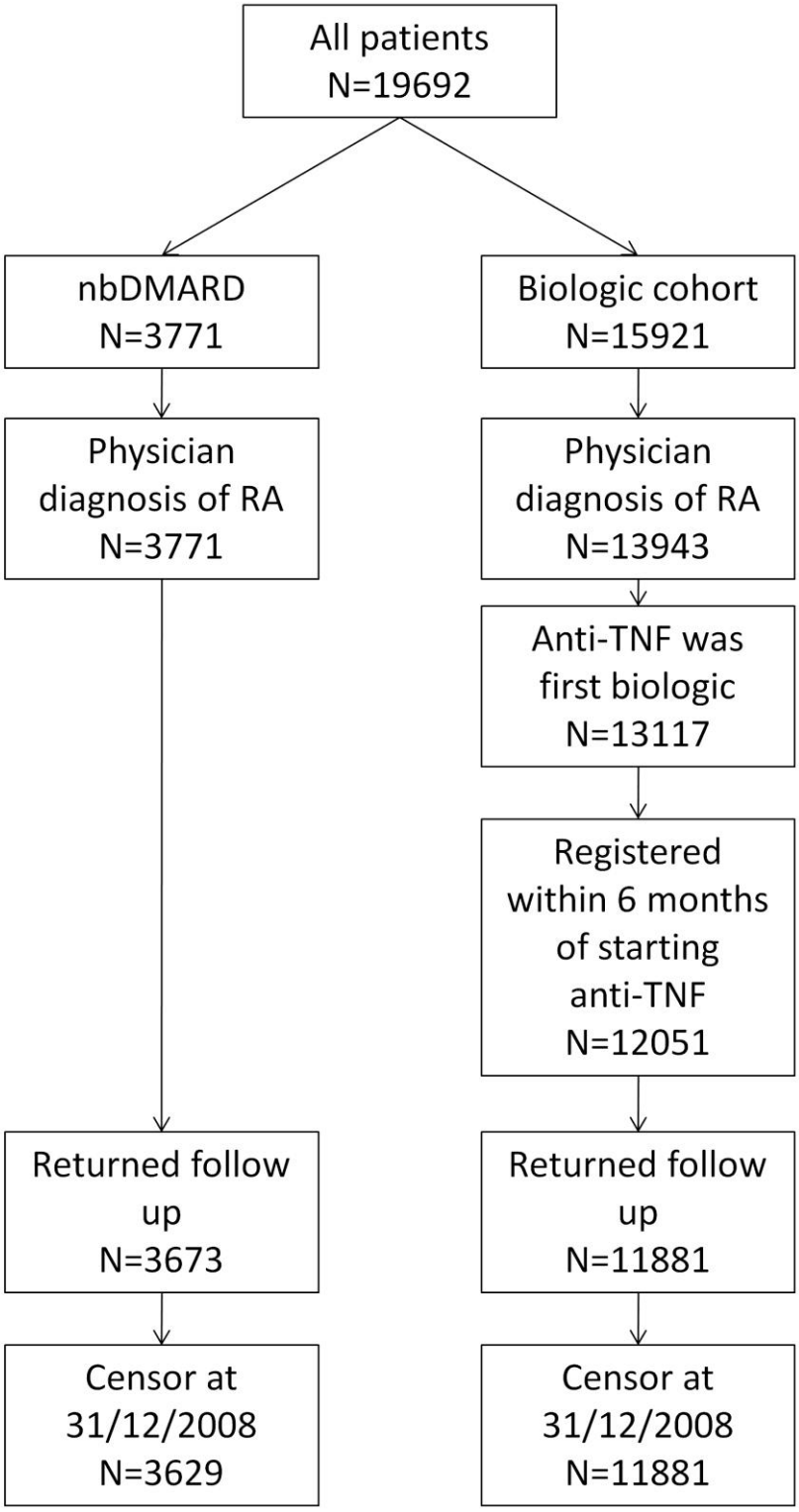
8.2 Aims

- To compare the incidence of KSC and then BCC and SCC separately in patients with RA treated with anti-TNF or nbDMARD-only to rates in the general population.
- To investigate the influence of addition of anti-TNF to nbDMARD therapy in RA on the risk of BCC and SCC.

8.3 Methods

The datasets used in this chapter were created earlier than those in the preceding chapters. However, the data were re-analysed using the most up to date methods in line with previous chapters. The datasets were created on 30th September 2010 and follow up censored on 31st December 2008 (or death or last received follow up form if before that date) (Figure 8-1).

Figure 8-1 Flowchart showing selection of patients for the KSC analysis



8.3.1 Standardised incidence ratios

First, the incidence rates of KSC in the nbDMARD and anti-TNF cohorts of the BSRBR-RA were compared separately to those in the general population. The primary outcome measure for this analysis was incident KSC i.e. BCC, SCC or other skin cancer, excluding melanoma, as a combined end point since England population rates for BCC and SCC individually were not available. Cancers were indentified in the BSRBR-RA as those reported by the national cancer registries with the ICD-10 code C44, after the date of starting anti-TNF or registration. Rates of KSC in the BSRBR-RA were compared to age- and sex- matched rates in England, using the methods described in the nbDMARD SIR chapter (see section 5.3).

In a second analysis, the nbDMARD and anti-TNF cohorts were compared to rates from the Scottish general population. The main reason for this was to attempt to capture the range of background risk across the UK population. Whilst the majority of participants in the BSRBR-RA cohort were living in England, there were two advantages of using the Scottish population data. First, the most recently published population rates for England were from 2000 where as for Scotland five year summary rates from 2003-2007, coinciding with the time period of the BSRBR-RA, were available. Second, Scotland publish rates for BCC and SCC separately, as well as for KSC as a combined outcome, and so analyses for each type of KSC were performed.

8.3.2 Anti-TNF versus nbDMARD

Next, the incidence of KSC in the anti-TNF cohort was compared to that in the nbDMARD cohort. The primary outcome measures for this analysis were incident BCC and SCC of the skin, analysed separately. Morphology codes from the International Classification of Diseases for Oncology, reported by the cancer agencies, and histology reports were used to distinguish BCC and SCC. Subjects with prior skin cancer reported by the national cancer agencies were analysed separately from those with no previously reported skin cancer. In keeping with previous chapters, patients with baseline DAS28 scores of ≤3.1 were excluded from this analysis (nbDMARD: N=284; anti-TNF: N=55). There were differences in the selection of the study population and verification process of the outcome measures for this analysis compared to previous chapters as follows:

- Subjects were not censored at the time of diagnosis of their first KSC, i.e. patients were allowed to contribute more than one incident KSC during follow up. The reasons for this

were; it was felt that the burden of skin cancer was more important than the first KSC; and that, unlike for other cancers, patients did not routinely stop their anti-TNF drug following diagnosis.

- Time after the last received consultant follow up form was excluded, since the national cancer registries acknowledged that recording of KSC was incomplete during the period of the study and so there was greater reliance on reporting of cancers from patients and Rheumatologists than for other cancers [57].
- The first six months of follow up was not excluded from the analysis since it was hypothesised that any change in the risk of KSC might occur early after exposure to anti-TNF. Instead, a separate analysis of the risk KSC in the first 6 months was performed.
- Patients in the anti-TNF cohort were censored from further follow up if they switched to a non-anti-TNF biologic to avoid further confounding. It was felt that any KSC occurring after starting other non-anti-TNF biologic therapy may be better attributed to the most recently received drug.
- Skin cancers were independently verified by two clinicians (James Galloway and Louise Mercer) and any disagreement resolved through discussion. Double verification was performed as there was greater reliance on Rheumatologist-reported KSC and the histology reports used to verify cancers frequently referred to multiple skin lesions.
- Patients were not censored after contributing five years of follow up.

A PS model was constructed to control for confounding and the cohort stratified into deciles of PS. The variables selected *a priori* for inclusion were age, sex, ethnicity, smoking status, co-morbidity, RA duration, DAS28, HAQ, steroid exposure, number of prior nbDMARD (≤3 versus 4 or more), prior exposure to AZA and prior exposure to CSA at baseline. During construction of the PS model ethnicity was excluded since all KSC occurred in white subjects. No interaction terms or powers of variables were required to reduce the expected bias to below 2% in the PS model.

8.3.2.1 Patients without prior skin cancer

For the primary analyses, patients with prior skin cancer were excluded (nbDMARD: N=98; anti-TNF: N=177). The rates of BCC and SCC in subjects treated with anti-TNF were compared separately to the nbDMARD cohort using Cox regression. The PH assumption was met (for example p=0.362 for the

global PH test for the primary analysis for BCC). No further analyses were performed for SCC due to the low numbers of events. For BCC, additional analyses were performed: an on drug plus 90 days exposure model was used; each drug was compared separately to nbDMARD; the effect of cumulative exposure to anti-TNF was analysed; and an analysis restricted to the first six months of follow up per person was performed. The effect of clustering of KSC within individual patients was accounted for in the Cox regression models. A sensitivity analysis in which patients ceased to contribute to the study after diagnosis of first BCC was performed.

8.3.2.2 Patients with skin cancer prior to registration

For BCC, an analysis restricted to subjects with a history of skin cancer prior to starting anti-TNF or registration, as reported by the national cancer agencies, was performed. The rate of new or recurrent BCC in the anti-TNF cohort was compared to that in the nbDMARD cohort.

8.4 Results

8.4.1 Standardised incidence ratios

For this analysis, 3629 patients contributed 9620 pyrs in the nbDMARD cohort and 11881 anti-TNF-treated patients contributed 44425 pyrs. The SIR for overall skin cancer was similar and increased by 90% in both treatment cohorts, when compared to the England population data (Table 8-1). When compared to the Scotland data, the magnitude of increased risk was reduced and no longer remained significant for the nbDMARD cohort. When stratified by type of skin cancer, the risk for BCC remained around 30% elevated (Table 8-1). However, an increased risk of SCC was not observed in any cohort.

Table 8-1 SIR of cancer agency-reported KSC in the BSRBR-RA compared with the English and Scottish populations

	KSC			BCC		SCC	
	N	SIR (95% CI) England	SIR (95% CI) Scotland	N	SIR (95% CI) Scotland	N	SIR (95% CI) Scotland
nbDMARD							
All	40	1.93 (1.38, 2.63)	1.24 (0.88, 1.68)	34	1.34 (0.93, 1.88)	5	0.70 (0.23, 1.64)
Male	15	1.78 (1.00, 2.93)	1.12 (0.63, 1.84)	10	1.03 (0.50, 1.90)	4	1.03 (0.28, 2.63)
Female	25	2.03 (1.31, 3.00)	1.32 (0.86, 1.95)	24	1.54 (0.98, 2.29)	1	0.31 (0.01, 1.72)
Anti-TNF							
All	134	1.89 (1.58, 2.24)	1.23 (1.03, 1.81)	114	1.28 (1.05, 1.54)	18	0.92 (0.54, 1.45)
Male	50	2.16 (1.61, 2.85)	1.37 (1.02, 1.81)	41	1.47 (1.06, 2.00)	9	1.03 (0.47, 1.96)
Female	84	1.76 (1.40, 2.18)	1.16 (0.93, 1.44)	73	1.19 (0.93, 1.50)	9	0.83 (0.38, 1.57)

This table includes subjects with previous skin cancer

8.4.2 Anti-TNF versus nbDMARD (subjects without prior skin cancer)

Two hundred and sixteen KSC were reported in subjects without a previous history of skin cancer (nbDMARD 40, anti-TNF 176). For anti-TNF, 19% of patients with incident KSC had multiple or recurrent lesions during follow up compared to 9% of the nbDMARD cohort (Table 8-2). The proportion of first KSC reported by the national cancer agencies was similar in the two cohorts (Table 8-2). The proportion of cancers reported by the Rheumatologist and/or patient was lower than for the analyses of lymphoma and solid cancer, and lower in the nbDMARD cohort than anti-TNF (49% versus 61%).

Table 8-2 KSC reported in patients without prior history of skin cancer

	nbDMARD N=3247	Anti-TNF N=11649	ETA N=4047	INF N=3423	ADA N=4179
Follow-up time (pyrs)	8384	43612	19028	11674	12911
Follow up per subject: median (IQR)	2.5 (1.3, 3.7)	4.0 (2.5, 5.0)	3.7 (1.7, 4.6)	2.7 (1.3, 4.7)	2.1 (1.0, 3.3)
Subjects with KSC	35	139	54	49	36
KSC	40	176	67	67	42
Subjects with multiple KSC (%)	3 (9)	27 (19)	10 (19)	13 (27)	4 (11)
Subtypes of KSC					
BCC (%)	36	150	57	59	34
SCC (%)	3	23	9	8	6
Basosquamous cell carcinoma (%)	0	1	0	0	1
Dermatofibrosarcoma protuberans	0	1	1	0	0
Unclassified skin cancer (%)	1	1	0	0	1
First KSC reported by (%):					
National cancer agency	32 (91)	121 (87)	49 (91)	38 (78)	34 (94)
Physician and/or patient	17 (49)	85 (61)	35 (65)	33 (67)	17 (47)

8.4.2.1 Basal cell carcinoma

Thirty six BCC were reported in the nbDMARD cohort and 150 for anti-TNF; unadjusted HR 0.79 (95% CI 0.55, 1.14) (Table 8-3).

Table 8-3 Incidence of BCC in the BSRBR-RA

	nbDMARD N=3247	**Anti-TNF N=11649**
Follow-up time (pyrs)	8384	43612
BCC	36	150
Incidence rate per 10,000 pyrs (95% CI)	43 (29, 40)	34 (29, 40)
Unadjusted HR (95% CI)	Referent	0.79 (0.55, 1.14)

Age, male sex, prior smoking or never smoking, comorbidity, RA duration and prior exposure to AZA or CSA were associated with BCC after adjusting for exposure to anti-TNF (Table 8-4). After fully adjusting for confounders, using PD, there was no difference in the risk of BCC following anti-TNF compared to nbDMARD only (HR 1.06, 95% CI 0.64, 1.75). The results did not materially alter when an on drug model was used (Table 8-5). The HR was numerically highest during the first six months of follow up, but there was no significant change in HR over time. When the analysis was restricted to the first incident BCC per subject, there was no difference in risk between the cohorts (PD-adjusted HR 0.97, 95 % CI 0.57, 1.65).

Table 8-4 Univariate adjusted HR for BCC following anti-TNF

	Hazard ratio (95% CI) for covariate	Hazard ratio (95% CI) for anti-TNF (nbDMARD referent)
Unadjusted	-	0.79 (0.55, 1.14)
Age (per year)	1.08 (1.06, 1.09)	1.13 (0.78, 1.64)
Sex (Male referent)	0.68 (0.50, 0.93)	0.80 (0.56, 1.16)
Smoking: (Current smoker referent)		
Ex-smoker	2.28 (1.43, 3.64)	0.79 (0.55, 1.14)
Never smoked	1.89 (1.18, 3.04)	
Comorbidity: (Nil referent)		
1 comorbidity	1.92 (1.39, 2.66)	0.80 (0.56, 1.16)
2 comorbidities	1.33 (0.84, 2.11)	
≥3 comorbidities	1.44 (0.74, 2.81)	
Entered study before June 2004	1.15 (0.83, 1.58)	0.76 (0.52, 1.11)
Disease duration (per year)	1.03 (1.01, 1.04)	0.73 (0.50, 1.05)
Disease activity (per unit DAS28)	0.96 (0.83, 1.11)	0.83 (0.55, 1.26)
Disability (per unit HAQ)	1.16 (0.90, 1.49)	0.74 (0.50, 1.09)
Baseline corticosteroids	1.28 (0.95, 1.71)	0.75 (0.51, 1.09)
No. prior nbDMARD: (≤3 referent)		
≥4	1.09 (0.81, 1.48)	0.77 (0.52, 1.13)
Ever exposed to AZA	1.60 (1.15, 2.22)	0.73 (0.50, 1.06)
Ever exposed to CSA	1.65 (1.16, 2.24)	0.73 (0.50, 1.05)

Table 8-5 Adjusted HR for BCC following anti-TNF

	nbDMARD N=3247	Anti-TNF N=11649
Age and sex adjusted HR (95% CI)	Referent	1.15 (0.79, 1.67)
Overall PD-adjusted HR (95% CI)	Referent	1.06 (0.64, 1.75)
Limited to time on anti-TNF plus 90 days		
Follow-up time (pyrs)	8384	37432
BCC	36	121
Unadjusted HR (95% CI)	Referent	0.75 (0.52, 1.09)
Age and sex adjusted HR (95% CI)	Referent	1.11 (0.76, 1.63)
PD-adjusted HR (95% CI)	Referent	0.97 (0.57, 1.65)
Analysis by year of follow up: PD-adjusted HR (95% CI)		
First six months	Referent	1.88 (0.42, 8.48)
1st year	Referent	0.91 (0.40, 2.10)
2nd year	Referent	1.31 (0.60, 2.82)
3rd year	Referent	0.87 (0.38, 1.97)
4th year	Referent	1.33 (0.49, 3.61)
5TH year	Referent	0.92 (0.11, 7.38)
Limited to first BCC per person		
BCC	32	121
Unadjusted HR (95% CI)	Referent	0.74 (0.50, 1.10)
Age and sex adjusted HR (95% CI)	Referent	1.08 (0.73, 1.62)
PD-adjusted HR (95% CI)	Referent	0.91 (0.53, 1.55)

The crude incidence rate of BCC was higher for INF than for ETA or ADA (Table 8-6). There was no difference in the hazard for ETA or ADA when compared to nbDMARD, although the confidence intervals were wide (Table 8-6). There was a trend towards increased hazard for INF that did not reach statistical significance; PD-adjusted HR 1.64 (95% CI 0.94, 2.85). The results did not significantly alter when follow up and cancers were attributed to each anti-TNF drug ever received, but the point estimate for ADA did change from a reduced to increased hazard Table 8-6. Twenty-seven percent of the INF cohort had multiple or recurrent BCC reported during follow up and when the analysis was limited to the first BCC per subject the HR was attenuated to 1.31 (95% CI 0.72, 2.39).

Table 8-6 Incidence of BCC for individual anti-TNF drugs

	ETA N=4047	INF N=3423	ADA N=4179
Follow-up time (pyrs)	19028	11674	12911
BCC	57	59	34
Incidence rate per 10,000 pyrs (95% CI)	30 (23, 39)	51 (38, 65)	26 (18, 37)
Unadjusted HR (95% CI)	0.67 (0.44, 1.03)	1.18 (0.78, 1.79)	0.61 (0.38, 0.98)
Age and sex adjusted HR (95% CI)	1.02 (0.67, 1.57)	1.65 (1.08, 2.52)	0.85 (0.53, 1.37)
PD-adjusted HR (95% CI)	0.92 (0.53, 1.61)	1.64 (0.94, 2.85)	0.83 (0.47, 1.47)
Attributing follow up and cancers to each prior or current anti-TNF			
BCC	70	77	43
PD-adjusted HR (95% CI)	0.91 (0.48, 1.73)	1.44 (0.75, 2.78)	1.10 (0.60, 2.01)
Limited to first BCC per subject			
BCC	47	44	30
PD-adjusted HR (95% CI)	0.79 (0.43, 1.43)	1.31 (0.72, 2.39)	0.77 (0.42, 1.41)

Referent cohort was nbDMARD for regression analyses

8.4.2.2 Squamous cell carcinoma

The incidence rate of SCC was low in both cohorts (Table 8-7), yielding imprecise estimates when the incidence was compared between groups. After adjusting using PD, the HR for anti-TNF was 1.62 (95% CI 0.44, 5.90).

Table 8-7 Incidence of SCC in the anti-TNF and nbDMARD cohorts

	nbDMARD N=3247	Anti-TNF N=11649
Follow-up time (pyrs)	8384	43612
SCC	3	23
Incidence rate per 10,000 pyrs (95% CI)	3.6 (0.7, 10.5)	5.3 (3.3, 7.9)
Unadjusted HR (95% CI)	Referent	1.11 (0.33, 3.78)
Age and sex adjusted HR (95% CI)	Referent	2.11 (0.61, 7.32)
PD-adjusted HR (95% CI)	Referent	1.62 (0.44, 5.90)

8.4.3 Risk of BCC in patients with known previous skin cancer

Two hundred and seventy-five subjects had a known history of skin cancer prior to entering the study (nbDMARD 98, anti-TNF 177). In these subjects the crude incidence rate of BCC was more than ten-fold higher than in those without prior cancer, and higher in the nbDMARD cohort compared with anti-TNF (892 versus 470 per 10,000 pyrs) (Table 8-8). The PD-adjusted HR was 0.60 (95% 0.24, 1.49).

Table 8-8 Incidence of BCC in subjects with prior skin cancer (anti-TNF versus nbDMARD)

	nbDMARD N=98	**Anti-TNF N=177**
Follow-up time (pyrs)	247	617
BCC	22	29
Incidence rate per 10,000 pyrs (95% CI)	892 (559, 1350)	470 (315, 675)
Unadjusted HR (95% CI)	Referent	0.50 (0.29, 0.88)
Age and sex adjusted HR (95% CI)	Referent	0.66 (0.37, 1.17)
PD-adjusted HR (95% CI)	Referent	0.60 (0.24, 1.49)

8.5 Summary of results

- The risk for KSC was similar and increased by 90% in both treatment cohorts compared to the England general population.
- When compared to Scotland, there was a 30% increased risk of BCC in patients with RA in the BSRBR-RA but no difference in RR of SCC.
- In patients without prior skin cancer, there was no difference in the risk of BCC following treatment with anti-TNF compared with nbDMARD only (PD-adjusted HR 1.06, 95% CI 0.64, 1.75).
- The HR for BCC did not change with duration of follow up.
- There was no significant difference in risk of BCC for any of the TNF inhibitors when compared individually to nbDMARD.
- There was no difference in the incidence of SCC between treatment groups, although few SCC were reported during follow up: nbDMARD 3, anti-TNF 23.
- The rate of BCC was more than tenfold higher in patients with previous skin cancer. In this cohort there was no significant difference in the risk of incident BCC between treatment groups (HR 0.60, 95% CI 0.24, 1.49).

8.6 Discussion

The results of this analysis show that the risk of KSC was increased in patients with RA, regardless of treatment history, when compared to the general English population. When the BSRBR-RA cohorts were compared to Scottish data, the risk of BCC but not SCC was elevated. Several other studies have investigated the risk of KSC in RA compared to the general population (Table 1-2). A Danish population-based study found a 40% increased risk for SCC and 30% for BCC [45]. However, this finding has not been consistent and studies from Finland, Sweden and Scotland have not reported an increased risk [40-42]. An explanation for the increased incidence of KSC in the current analysis may be that it included individuals that with long standing active RA, all of whom have been exposed to nbDMARD and so were relatively immunosuppressed compared to the general population. For this analysis, there was difficulty in determining valid population rates of KSC. The differences in relative risk compared to the English and Scottish population data may reflect a higher prevalence of KSC in the Scottish than English population due to possible differences in skin type, although one might expect the higher latitude in Scotland to result in a lower population rate of KSC there. An alternative explanation is differences in the completeness of capture of KSC by the national cancer agencies. The UK Association of Cancer Registries suggests that the first BCC and SCC per subject should be recorded, but not necessarily further KSC, but practice does vary between regional cancer registries [59]. The ONS exclude KSC from their annual publication on cancer incidence (series MB1), due to incomplete registration [57]. The problem of notification of KSC is compounded further by the fact that BCC can be treated by cryotherapy, destroying the tumour and preventing tissue being sent to histology. None the less, the potential for bias was limited when calculating SIRs by only including cancers reported by the cancer registries in the numerator, meaning any under-reporting would occur in both the numerator and denominator.

In patients without prior skin cancer, the addition of anti-TNF did not exacerbate their risk of BCC when compared to nbDMARD alone. This is in keeping with results from a meta-analysis of RCT of anti-TNF in RA, published in 2009, that reported a RR for KSC of 1.01 (95% CI 0.42, 2.44) [151]. Conversely, another meta-analysis of anti-TNF RCT across all indications, using patient level data, reported a two-fold increased risk for anti-TNF [152]. Results from observational studies comparing anti-TNF to nbDMARD are limited to North American databases [171-173]. Each of these studies reported an increased risk for anti-TNF. However, there was greater potential for bias due to differential reporting of KSC in these studies compared to the current analysis since they did not

benefit from linkage to an independent cancer registry. There was some evidence of such differential reporting in the BSRBR-RA, with 49% of first KSC being reported by the Rheumatologist and/or patient in the nbDMARD cohort compared to 61% for anti-TNF. Reporting of KSC by the cancer registries, a source that was blind to treatment, was more similar between the cohorts (91% versus 87%). In order to minimise bias, this analysis allowed for a lag of at least 21 months in reporting of cancers to the BSRBR-RA via the national registries to maximise ascertainment of cases from this source.

There was no significant difference in risk of BCC for any of the TNF inhibitors when compared individually to nbDMARD. There was a suggestion that the incidence of BCC was higher for INF compared to nbDMARD than for ETA or ADA, although this finding did not reach statistical significance. A study from the US NDB study reported an increased risk of skin cancer for INF (OR 1.7, 95% CI 1.3, 2.2) but not for ETA (1.2, 95% CI 1.0, 1.5) or ADA (0.9, 95% CI 0.5, 1.8) [171]. That study was unable to distinguish between BCC and SCC, which makes interpretation difficult given their different pathobiologies. In the current analysis the higher rate for INF may be partly explained by a higher proportion of INF-treated patients being diagnosed with multiple BCC compared with other cohorts. The HR for INF was attenuated when the analysis was limited to first KSC. Surveillance bias may also have contributed to this finding as INF treated patients were clinically assessed every 8 weeks prior to each INF infusion.

There was no difference in the incidence of SCC in patients treated with anti-TNF compared to nbDMARD-only. However, few SCC were reported during follow up and the analysis lacked sufficient power to detect even a doubling in risk following anti-TNF. The analysis had only 10% power to detect a doubling in risk of SCC following anti-TNF from the nbDMARD background rate of 4 per 10,000 pyrs. Likewise, the analysis of BCC risk in patients with prior known skin cancer lacked sufficient power to determine the effect of anti-TNF on recurrent cancer with precision. In contrast, given the rate of BCC of 4.3 per 1000 pyrs in the nbDMARD cohort, the study had 99% power to detect a doubling in the risk of BCC in patients without prior skin cancer. For ETA, INF and ADA the powers were 97%, 93% and 94% respectively.

In addition to the difficulties in determining population rates of KSC there are limitations specific to the analysis of KSC that warrant discussion. Skin type, sun bed use and history of sun exposure, especially sunburn during childhood, are risk factors for KSC in the general population [236]. Data on these confounders were not available and so no adjustments could be made for them. A reduced risk of KSC has been associated with exposure to NSAIDs, especially with sporadic or infrequent use [237]. However, in a more recent analysis, when both time-varying and time-fixed survival analyses were performed no association was found using time-varying models [238]. A negative association was seen with fixed-time models and the use of simulated data demonstrated the potential for strong bias in such models. People with RA routinely take NSAIDs during the course of their disease to treat pain and inflammation. Insufficient information about exposure to NSAIDs was captured in the BSRBR-RA to allow for careful adjustment. Prescribed NSAIDs were recorded at baseline, but not duration of exposure of these drugs, prior exposure or any data on over the counter use. Therefore, it was decided not to adjust for exposure to NSAIDs in this analysis.

In summary, both subjects treated with nbDMARD-only and anti-TNF had an increased risk of KSC compared to the general population. There was no difference in relative risk of BCC between the two RA treatment groups.

9. DISCUSSION

This chapter will summarise the key findings of the analyses and discuss their contribution to the current literature. The strengths and limitations of the work will be discussed and the clinical implications of the research will be highlighted.

9 Discussion

The overarching purpose of this PhD thesis has been to explore the risks of a number of malignancies, including lymphoma, solid organ tumours and KSC in patients with RA receiving anti-TNF therapies compared to those receiving traditional nbDMARD therapy. The first of the results chapters identified that patients with RA treated with nbDMARD are already at increased risk of cancer compared with the general population (discussed in full in Chapter 5). Subsequent chapters explored whether the addition of anti-TNF to nbDMARD influenced this risk (Chapters 6, 7 and 8). The aim of this final chapter is to review the results of those subsequent chapters and discuss their contribution to current medical knowledge. The strengths and limitations of the work will be discussed. Finally, the clinical implications of the research will be highlighted and proposals for future work made.

9.1 Relative risk of lymphoma

The question of whether or not anti-TNF influences the risk of lymphoma is of particular concern to Rheumatologists due to the known association between severity of RA and lymphoma [86]. The analysis in this thesis, with 65,000 pyrs of exposure to anti-TNF or nbDMARD-only did not identify a difference in lymphoma risk following the addition of anti-TNF; HR for anti-TNF 1.00 (95% CI 0.49, 2.05). No difference in risk was found for any of the TNF inhibitors when compared separately to nbDMARD, adding to results from the Swedish biologics register and the US NDB [134, 165].

The analysis in this thesis was then stratified by cumulative exposure to anti-TNF. The hypothesis was that due to both the latent period in the development of lymphoma and the association between chronic inflammation and lymphoma, any change in risk attributable to the drug itself might not be evident until several months or years of treatment had accrued. Thus any reduced risk of lymphoma seen very early on in treatment could be due to screening for cancer prior to anti-TNF and an increased risk could be attributable to protopathic bias. In this analysis, no significant association was seen between cumulative exposure to anti-TNF and risk of lymphoma. However, the analysis was limited due to the low number of events in each category (10 lymphomas for <1.5 years exposure, 18 for 1.5 to 3 years and 15 for ≥3 years). There was a non-significant trend towards increasing HR with increasing exposure to anti-TNF that warrants further attention. An earlier analysis from the Swedish register reported no trend towards increasing HR with cumulative

exposure to anti-TNF, although the number of events in their analysis was very low (for example: 1 to 2 years of treatment; 5 lymphomas; 2-3 years; 1 lymphoma) [165].

This work forms an important contribution to the current medical literature since the large size of the BSRBR-RA meant that a clinically meaningful increased risk of lymphoma associated with anti-TNF was excluded: a relative increased risk of more than two-fold of that observed in the nbDMARD cohort (157 per 100,000 pyrs) was excluded. The analysis was carefully conducted to account for potential biases. For example, the first six months of follow up were excluded, unlike some previous studies [134, 167, 174], to reduce the probability of prevalent lymphomas being included. In addition, prevalent users of anti-TNF at baseline were excluded. The analysis adjusted for a wider range of confounders than for previous studies due to the detailed and extensive data collection in the BSRBR-RA. Adjustments for multiple confounders were made in the regression models, despite lymphoma being a relatively uncommon outcome, by using PS methods to minimise bias due to differences in the baseline characteristics of patients treated with nbDMARD-only and anti-TNF. Stratifying the PS into deciles was shown to reduce the expected bias in the analysis to less than 5%.

Paraffin embedded lymphoma tissue was requested for all lymphomas reported in nbDMARD and anti-TNF treated subjects to enable reclassification using the WHO method and to determine EBV status of the tumours. The proportion of EBV-positive lymphomas was not increased in the samples received, although an increased risk of EBV-related lymphoma following anti-TNF cannot be excluded due to the low proportion of lymphomas tested. The reclassification verified that lymphomas were being reported with a high degree of accuracy to the BSRBR-RA.

The possibility that treatment with anti-TNF is associated with an increased risk of lymphoma has been a leading concern for Rheumatologists and their patients and so the results of this study will provide reassurance.

9.2 Relative risk of solid cancer and site-specific risks

In the third results chapter the overall risk of solid cancer in patients treated with anti-TNF was compared to that in the nbDMARD-only cohort and then site-specific risks were compared. Overall, 563 cancers were included in the analysis and no difference in risk was seen following treatment with anti-TNF (HR 0.83, 95% CI 0.64, 1.07). This finding adds to the results published by the Swedish and German biologics registers and the NDB which also showed no difference in risk [164, 169, 171]. However, this work included greater exposure time (and more cancers) in the anti-TNF-treated cohort than the previous European studies [164, 169], and more rigorous data collection methods than the American study [171].

The Swedish biologics register reported a reduced risk of first cancer for ETA in the first year of treatment based on 10 malignancies and an increased risk for ADA based on 15 malignancies; RR 0.43 (95% CI 0.22, 0.84) and 1.91 (1.11, 3.31) respectively [164]. However, no overall differences in risk were noted for each TNF inhibitor compared to biologic-naïve patients over the entire period of follow up. In their discussion the authors noted that any differences early on in treatment might be due to existing preclinical tumours becoming manifest and differences in the types of patients prescribed each drug, rather than true biologic differences in the risk of new cancers attributable to the drugs. The analysis in this thesis had sufficient power to detect a clinically important 50% increased risk of solid cancer for each individual anti-TNF drug versus nbDMARD; no difference in risk was observed for any drug. The risk of solid cancer by cumulative exposure to anti-TNF was explored in this thesis. The analysis included 166 cancers occurring with <1.5 years of cumulative exposure to anti-TNF, 99 with 1.5 to 3 years and 100 with ≥3 years. No trend for changing risk with cumulative exposure was seen.

The most frequently reported cancers were lung cancer, female breast cancer and colorectal cancer. Little was known about the influence of anti-TNF on specific cancer sites at the time of this thesis. Whilst SIRs have been presented from other European biologics register, the NDB and a pool of North American administrative databases [43, 169-171], analysis comparing the risk to a RA comparator cohort, adjusted for differences in baseline characteristics, has only been performed in the NDB [171]. The analysis in this thesis confirmed the findings of the NDB study of no difference in the risk of lung, female breast or colorectal cancers following treatment with anti-TNF, although the

HR for breast cancer was 0.58 (95% CI 0.32, 1.06) and for colorectal cancer was 0.52 (95% CI 0.25, 1.07). The key advantages of the current work compared to the NDB study were: the separation of subjects exposed to anti-TNF from users of other biologic drugs; the exclusion of prevalent users of anti-TNF, patients exposed to other previous biologic therapies and those with prior solid cancer identified by the national cancer agencies; and the careful verification of the outcome based on reports by the national cancer agencies and histology reports.

The data in this thesis demonstrate that it is usual clinical practice to stop anti-TNF at the time of diagnosis of a solid cancer in the UK. The effects of continuing anti-TNF on prognosis following cancer could not be addressed due to low numbers of people continuing therapy and lack of detail about other prognostic factors, such as cancer stage at diagnosis. Overall survival did not differ between the nbDMARD and anti-TNF cohorts following cancer diagnosis (HR 0.90, 95% CI 0.70, 1.17). Little is known from previous studies about whether or not cancers occurring in patients treated with anti-TNF differ in their prognosis from those in biologic-naïve patients, with just one previous study from the Swedish biologics register (ARTIS) addressing this question [181]. Whilst they included nearly 5000 RA patients with incident cancer, only 314 of these had been exposed to anti-TNF. They compared 302 patients treated with anti-TNF to 586 biologic-naïve matched controls. There were 256 deaths during follow up in the biologic-naive matched cohort and 113 in patients exposed to anti-TNF. There was no difference in the relative risk of dying between the groups (HR for anti-TNF 1.1, 95% CI 0.8, 1.6). The Swedish study also looked at tumour stage at presentation and found this to be largely similar between the groups, although the proportion of late presentations was higher in the control cohort (29% versus 20% stage IV). They also explored the stage at presentation by cancer site for the most common cancers and found a marked discrepancy for lung cancer: 60% stage IV in the biologic-naïve cohort versus 26% for anti-TNF supporting the hypothesis of surveillance bias with earlier investigation in anti-TNF-treated patients. Whilst this Swedish study was well conducted and reassuringly didn't demonstrate that cancer was more aggressive in patients treated with anti-TNF, it was limited by lack of statistical power. The confidence intervals around the survival analysis included clinically important differences in hazard.

9.3 Relative risk of KSC

The first key finding of this chapter was an increased risk of KSC, specifically BCC, in subjects with RA compared to the general population, irrespective of treatment with anti-TNF. The degree of increased risk was lower when the nbDMARD-only and anti-TNF cohorts were compared to Scottish population data than when compared to English data. This difference highlights the key limitation of analysis of KSC risk in an observational study; the difficulty in determining true incidence rates. None the less, the finding of an increased risk supports the regular monitoring of patients with RA for new or changing skin lesions, regardless of whether or not they are treated with anti-TNF. Recommendations for skin cancer prevention in the general population, such as sun avoidance, also apply.

In patients without known prior skin cancer, there was no change in risk of BCC with the addition of anti-TNF to nbDMARD alone. The analysis had insufficient power to determine the effect of anti-TNF on risk of SCC or recurrent KSC. Other observational studies of KSC risk associated with anti-TNF in RA have used KSC as a combined end point and reported an increased risk [171-173]. Possible reasons for the discordance between these findings and those in this thesis are as follows: 1) In this thesis the comparator cohort had well established RA and were already at increase risk of KSC compared to the general population. Thus, it might be that anti-TNF does not increase the risk above that associated with other forms of DMARD used in for RA or the effects of the disease itself. 2) Bias due to differential reporting of KSC in other studies. Two of the previous studies relied on patient reporting of KSC, without the need for further validation [171, 173]. The other study used administrative codes for KSC but in a validation exercise at the principal investigator's institution only 43 of 71 reported KSC were confirmed following review of the case notes [172]. Only 38 KSC were confirmed histologically. 3) There were differences in the outcome measures. There was no increased risk of BCC in this thesis but the risk of SCC could not be determined accurately. Previous studies that reported an increased risk of KSC in patients treated with anti-TNF might have been observing an increased risk of SCC that the BSRBR-RA was not powered to detect.

9.4 Strengths and weakness of the analyses

9.4.1 Design of the BSR Biologics Register

The BSRBR-RA was established with the primary aim of determining the long term safety of biologic therapy in RA, making it an excellent setting to study the safety of TNF inhibitors with respect to cancer. The register was in fact powered to detect a doubling in risk of lymphoma for each individual anti-TNF drug. It is the largest register of its kind worldwide, and at the time of this thesis contained more than 50,000 pyrs of exposure to anti-TNF in around 12000 patients. A key strength of this study was the detailed and prospective collection of drug exposure and adverse events in both cohorts. Data on cancers were collected by flagging all participants with the UK cancer agencies which has near complete capture of cases, thus minimising potential for bias in reporting between cohorts. In addition, cancers were reported by the patient, Rheumatologists and the national deaths registry. Further information was requested, including histology reports, for all reported cancers using an ESI proforma ensuring that a standard dataset was received for each cancer.

The careful and detailed prospective collection of data relating to both drug exposure and outcomes (incident cancers) means that a clinically important increase in relative incidence of lymphoma and solid cancer in patients treated with anti-TNF for up to five years has been excluded, in the context of the BSRBR-RA. At the time of recruitment to the BSRBR-RA anti-TNF cohort, it was mandated by NICE that patients starting anti-TNF should be included in the register, ensuring the high level of capture of incident users which is necessary when applying the study findings to routine clinical practice. The broad inclusion criteria of the register mean that the results are more generalisable than those for RCTs. However, the study findings reflect the way in which British Rheumatologists selected patients for treatment with anti-TNF at the time of the study. There was, at this time, concern amongst Rheumatologists about the safety of anti-TNF drugs, particularly with respect to infection and cancer. Patients with cancer within the previous 5 to 10 years were excluded from the RCT of anti-TNF and UK national guidelines listed this as a contra-indication [180].

Even 11 years after the start of the register, the nbDMARD cohort, in particular, lacks sufficient pyrs of follow up to allow for estimates for less common cancers, including subtypes of lymphoma. This is in part because recruitment to this cohort was not completed until early 2009 and it was originally intended that all subjects should be followed for at least 5 years. In addition, the target of 4000

patients was not reached (3774 patients recruited). As well as losses to follow up through death, patients have been censored from the nbDMARD cohort due to starting biologic therapy. In a way, the fact that the cohort is being depleted in this way is reassuring; it suggests that they are comparable in RA-related and other characteristics to those taking anti-TNF. However, it has contributed to the fact that the comparator cohort has not yet reached the target of 20,000 pyrs that was intended (currently approximately 13000 pyrs).

9.4.2 Choice of comparator cohort

Any analysis of the influence of anti-TNF on cancer risk requires a comparator cohort. Since RA itself is associated with a change in risk of certain cancers, the comparator comprised other patients with RA, recruited in parallel to recruitment to the anti-TNF cohort. Patients registering with the nbDMARD cohort were required to have active RA and be treated with nbDMARD, in common with patients starting anti-TNF. This means that when applying the results of this thesis to routine clinical practice, Rheumatologists could compare what happened to patients treated with anti-TNF to what happened to a similar cohort that was not treated.

Subjects were recruited from 28 Rheumatology departments, representing all parts of the UK and both secondary and tertiary treatment centres. There was a cluster of centres in the North West of England, close to where the BSRBR-RA was run from the University of Manchester. Population rates of cancer were higher in this part of England than for other regions and so patients selected for the BSRBR-RA from this region may have also carried this increased background risk. Subjects in the nbDMARD cohort were followed up in an identical manner to the anti-TNF cohort.

9.4.3 Controlling for confounding

Despite the measures taken to ensure comparability of the nbDMARD to the anti-TNF cohort, there were differences in the baseline characteristics of the cohorts that needed to be accounted for. The nbDMARD cohort was older and comprised more men than the anti-TNF cohort; both risk factors for cancer. Acting in the opposite direction, the anti-TNF cohort had more severe RA. Propensity score models were constructed to balance these and other known confounders. This technique was successful, as demonstrated by the low level of expected bias following stratification of the PS into

deciles. Ethnicity was included in the PS models, dichotomised as white or non-white since the proportion of non-whites was less than 5%. As a result, the findings of these analyses may not be extendable to patients from individual minority ethnic groups. Missing data can adversely affect all studies, particularly observational studies. Overall, the proportion of missing baseline data was low in the BSRBR-RA. To minimise bias introduced by missing baseline data, multiple imputation was used. Response rates to follow up questionnaires were excellent; less than 1% of patients in each cohort had no returned consultant follow up.

No adjustments were made for time-dependent confounding although follow up data were collected for some confounders, for example RA disease activity (DAS28). However, adjusting for DAS28 using conventional methods may have introduced bias into the risk estimates because changes in DAS28 score were closely linked to changes to anti-TNF therapy and so controlling for DAS28 could have diminished the observed treatment effect. Marginal structural modelling, in which subjects are weighted at each time point using IPTW, has been used as an approach to eliminate the problem that confounders could also be intermediate on the treatment pathway [239]. Future work should consider these approaches to include the entire patient history while keeping the introduction of bias to a minimum.

A problem with any observational study, including this one, is the potential for unmeasured confounding. Subjects were not randomised to receive anti-TNF or not and so adjustment using PS or other techniques could not control for unmeasured confounding. Patients considered to be at high risk for developing cancer may have been preferentially recruited to the nbDMARD-only cohort if it was felt that they were unsuitable for anti-TNF. For example, the prevalence of prior cancer at baseline was higher in the nbDMARD cohort. Whilst patients with a prior history of the cancer of interest were excluded from each analysis to ensure that recurrent cancers weren't being included, more subtle risk factors for cancer may have influenced the Rheumatologist's decision when deciding whether or not to prescribe anti-TNF. Similarly, the Rheumatologist's beliefs about individual anti-TNF drugs and cancer risk may have influenced which of the TNF inhibitors they chose in higher risk patients. In addition, the anti-TNF drugs became available at different time points during recruitment with ETA and INF coming to the market before ADA. There was also a shortage of available ETA following its launch and so INF was predominantly used in the earliest years of the

BSRBR-RA. Changes in RA severity in people starting anti-TNF over the period of recruitment were accounted for by adjusting for disease severity in the PS models. In addition, time of entry was included as an additional confounder to try and capture some of the unmeasured changes in the way in which Rheumatologists managed RA, and prescribed anti-TNF, during that period.

A potential confounder that was not accounted for in the analyses in this thesis was socioeconomic status. Employment status was recorded and this has been used as a marker of socioeconomic status in the general population. It was deemed to be unsuitable in the context of severe RA because of the high prevalence of work disability among such patients. Forty-nine percent of patients of working age (<62), starting anti-TNF in the UK self-reported that they were work disabled in an analysis from the BSRBR-RA in 2010 [240]. Deprivation indices such as the Index of Multiple Deprivation were available [199], but these are calculated differently for different parts of the UK and data for Northern Ireland were not available, which would have limited the available sample size further. Methods are being developed to compare deprivation scores from across the UK that could be used in future work from the BSRBR-RA, although this work has focused on the employment and income domains so far [241].

9.4.4 Modelling drug exposure

An 'ever-exposed' to anti-TNF model was selected as the primary exposure definition for anti-TNF. This was because it was hypothesised that any effect of anti-TNF on cancer risk would be long-lasting and may operate in the latent period of a cancer. These assumptions need to be considered when interpreting the results. In the ever-exposed model, all patients exposed to anti-TNF were considered collectively i.e. 5 years into the study, a patient who had received a single dose of anti-TNF was not differentiated from a patient who had been on continuous therapy for the previous 5 years or one that had received intermittent treatment. To test the robustness of the findings alternative drug exposure models were applied; an on drug plus 90 days model and a model in which subjects in the anti-TNF cohort were stratified by cumulative exposure to anti-TNF. When an on drug model without a 90 day lag period was applied to the lymphoma analysis, the HR for anti-TNF reduced markedly, although the 95% CI were wide. This likely reflected patients on anti-TNF stopping the drug when a diagnosis of cancer was suspected but before it was formally diagnosed and highlights the importance of model selection when performing analyses and interpreting their

findings. Patients in the anti-TNF cohort were permitted to switch between drugs between follow up and/or start of non-anti-TNF biologics. A potential pitfall of this method was that adjustment for disease severity at the time of switching drugs could not be made. In contrast, data collection in the nbDMARD cohort ceased when they started a biologic drug. At that point they may have started follow up in the biologic cohort, if recruitment was still ongoing.

Further complexities in the possible relationship between anti-TNF therapy and cancer risk exist that could not be fully accounted for in this analysis. Although the BSRBR-RA has been following some patients for more than ten years, the median follow up at the time of this thesis was four to five years meaning that any long-term effects of anti-TNF could not yet be fully explored, particularly for rarer cancers such as lymphoma. It is also possible that the overall finding of no difference in the relative incidence of solid cancer between the two cohorts was the result of risks acting in opposite directions for different cancer sites at different stages in the latent phase. A signal for reduced risk of breast cancer was observed but with further follow up an increased risk of one or several less common cancers may become apparent.

When each anti-TNF drug was compared separately to the nbDMARD cohort, follow up time and cancers were attributed to the most recently received drug. A potential pitfall of this approach might be protopathic bias: An undiagnosed cancer that developed whilst exposed to a first TNF inhibitor might have resulted in an increase in DAS28 score (through elevated ESR and/or patient global score as well as 28 joint counts) leading to the patient being switched onto a second TNF inhibitor. An alternative model in which follow up was attributed to multiple drugs did not alter the findings, except for lymphoma where all between drug analyses yielded imprecise estimates due to low power.

For the lymphoma and solid cancer chapters, the first six months of follow up were excluded from the analysis time. This was because it was felt that any cancers occurring in the first six months were likely to have been prevalent cancers. Also, due to concerns about a possible association between anti-TNF and cancer and infection at the time of this work, Rheumatologists may have carefully examined patients and performed other tests such as chest radiograph prior to treatment. Patients

enrolling in the nbDMARD cohort did not undergo such examinations. In contrast to the lymphoma and solid cancer analyses, patients were considered at risk from time of registration in the KSC work. This was due to both the fact that an increased risk of KSC can occur early after other forms of immunosuppression and the fact that, at the time of recruitment to the BSRBR-RA, Rheumatologists did not routinely screen for skin lesions when starting anti-TNF. In fact, the initial national guidelines on the prescribing of anti-TNF in RA, from the British Society for Rheumatology, stated that prior malignancy or pre-malignant condition in the previous 10 years was a contra-indication to anti-TNF but BCC were explicitly excluded from this [242].

9.5 Implications for clinical practice

The following recommendations are suggested:

- Patients with active RA treated with non-biologic DMARD in the UK are at increased risk of cancer, in particular lung cancer, lymphoma and KSC. Clinicians should be vigilant for cancer.
- Clinicians should be reassured that the addition of anti-TNF to nbDMARD therapy does not exacerbate the risk of cancer in patients selected for anti-TNF in the UK. However, the analysis was performed in the context of national guidelines that listed prior cancer within 10 years as a contraindication. The finding should not be extrapolated to include patients at high risk of cancer, such as those with prior cancer.
- There was no difference in the relative risk of cancer for any of the individual anti-TNF drugs and so clinicians can base their decision on which drug to prescribe on other factors, including patient preference. The newer anti-TNF drugs, golimumab and certolizumab pegol, were not included in this analysis and so no conclusions about their safety with respect to cancer can be drawn.
- Clinicians should be reassured that following a diagnosis of solid cancer, there was no difference in mortality in patients treated with anti-TNF. However, the majority of patients stopped their TNF inhibitor at the time of the cancer and so it cannot be advised that it is safe for patients to continue therapy.
- An increased risk of KSC compared to the general population was observed in patients treated with anti-TNF that was similar in magnitude to that in biologic-naive patients. Clinicians should consider screening patients with RA treated with nbDMARD or anti-TNF for KSC at annual review appointments, because KSC are common.

9.6 Recommendations for future work

9.6.1 Within the BSRBR-RA

The BSRBR-RA offers an excellent opportunity to continue to study the safety of anti-TNF therapy with respect to malignancy in the longer term, since follow up via Rheumatologists and flagging with the national cancer and death agencies is ongoing. Further follow up will facilitate more accurate assessment of relative risk for rarer cancers and enable any changes in risk related to long-term exposure to be identified.

Recently, other biologic drugs have been introduced to the management of severe RA; rituximab, abatacept and tocilizumab. It is of interest to clinicians to understand the safety of anti-TNF with respect to cancer relative to that for these newer agents. In the real-world when faced with a patient with severe RA, a clinician will want to know the relative risk of cancer, and other adverse events, of starting the patient on anti-TNF versus other biologics rather than versus leaving them on nbDMARD, which has failed to control their RA. The BSRBR-RA is currently recruiting inception cohorts for tocilizumab and certolizumab as well as a new inception cohort for ETA, INF or ADA to act as a contemporaneous comparator. Recruitment to a rituximab cohort has recently completed and so in the future comparisons of cancer incidence can be made between patients treated with each of these therapies. There is a belief amongst Rheumatologists that rituximab may be a safe treatment for patients at high risk of cancer, such as those with prior cancer, due to its role in treating B-cell lymphomas. In this context rituximab is typically given as a single course, every three weeks, for six cycles. However, there is still reason for caution since the long term effect of repeatedly administering rituximab, as is the case in RA, remains unknown and data from longitudinal observational studies in RA are lacking. There have been suggestions that immunoglobulins may be depleted with repeated courses [243]. Common variable immunodeficiency, which causes predominantly immunoglobulin deficiency, is associated with an increased risk of NHL and stomach cancer [244]. However, these patients also have altered T cell and natural killer cell function that may contribute to the risk of malignancy.

9.6.2 Beyond the BSRBR-RA

The newer biologic cohorts within the BSRBR-RA have not been powered to detect an increased risk of cancer. For rituximab, the primary safety concern related to infection and therefore the study was designed to have adequate power to detect a 50% or greater increased risk of serious infection. For tocilizumab, the initial study was powered to detect a 50% increased risk in myocardial infarction. For this reason, analyses restricted to BSRBR-RA-only data may be insufficient to study the relative safety of these drugs with respect to cancer. Even within the original anti-TNF and nbDMARD cohorts, there is insufficient power to answer clinically important questions. Examples of these are as follows:

- Melanoma. It is biologically plausible that anti-TNF will increase the risk of melanoma. An increased risk has been reported, in abstract form, from the Swedish biologics register [245]. In addition, there was a signal from the BSRBR-RA that treatment with anti-TNF exacerbated the risk of recurrent melanoma in patients with a history of melanoma prior to starting treatment [175]. So far, there have been too few melanomas reported in the BSRBR-RA to give robust estimates about the relative risk of melanoma in patients treated with anti-TNF compared to nbDMARD.
- Prior cancer. The effect of anti-TNF in people with prior cancer is currently unknown. Results from the BSRBR-RA and German register suggested risks in opposite directions, although both studies lacked power. Current UK guidelines recommend avoiding anti-TNF within ten years of a prior cancer. Whilst this is sensible given the lack of data, it may be that patients are being needlessly prevented from receiving a drug form which they would derive great benefit. Collaborative analyses with other biologic registries may allow the safety of anti-TNF therapy in such patients to be determined.
- Lymphoma. Due to the heterogeneous nature of lymphomas, to further understand the influence of anti-TNF on lymphoma risk this should be investigated for different subtypes separately.
- Effect of continuing anti-TNF following diagnosis with cancer. Whilst determining the influence of continued therapy on outcome following cancer would be very challenging, it is a question of interest to Rheumatologists. It is a question that is frequently posed to the BSRBR-RA via email or following presentations at national and international conferences.

To answer the above questions, collaboration with other drug registries may be preferable to waiting for further follow up to accrue in the BSRBR-RA for two reasons: first, so that patients and clinicians do not have to wait several more years for the results; and second, since the longer the time since registration with the BSRBR-RA, the greater the potential for losses to follow up, multiple changes to drug therapy and changes in other confounders such as smoking and co-morbidity. Within the European League Against Rheumatism (EULAR) a standing committee on European drug registries has been established. One of the remits of this committee is to devise and implement ways of analysing data across several registries simultaneously. Exploratory work is underway to first understand the differences in baseline characteristics of the different European registries. Safety analyses are currently being planned.

9.7 Final conclusions

In conclusion, this thesis has demonstrated that people with RA, treated with non-biologic DMARD are at increased risk of cancer compared to the general population. In particular, lung cancer, lymphoma and KSC are increased. This thesis found no difference in the risk of lymphoma, cancer of the solid organs or skin cancer in patients treated with the TNF inhibitors ETA, INF or ADA compared to that in patients treated with nbDMARD-only.

References

1 Wolfe F, Cathey MA. The assessment and prediction of functional disability in rheumatoid arthritis.[erratum appears in J Rheumatol 1991 Nov;18(11):1774]. *Journal of Rheumatology* 1991;**18**:1298-306.

2 Yelin E, Henke C, Epstein W. The work dynamics of the person with rheumatoid arthritis. *Arthritis & Rheumatism* 1987;**30**:507-12.

3 Allaire S, Wolfe F, Niu J et al. Contemporary prevalence and incidence of work disability associated with rheumatoid arthritis in the US. *Arthritis & Rheumatism* 2008;**59**:474-80.

4 Symmons DP, Jones MA, Scott DL et al. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. *Journal of Rheumatology* 1998;**25**:1072-77.

5 Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. *The Journal of Rheumatology* 2001;**28**:1431-52.

6 Deighton C, O'Mahony R, Tosh J et al. Management of rheumatoid arthritis: summary of NICE guidance. *BMJ* 2009;**338**:b702.

7 Maini R, St Clair EW, Breedveld F et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;**354**:1932-39.

8 Weinblatt ME, Keystone EC, Furst DE et al. 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.[see comment][erratum appears in Arthritis Rheum. 2003 Mar;48(3):855]. *Arthritis & Rheumatism* 2003;**48**:35-45.

9 Klareskog L, van der Heijde D, de Jager JP et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *The Lancet* 2004;**363**:675-81.

10 Feldmann M, Brennan FM, Williams RO et al. The transfer of a laboratory based hypothesis to a clinically useful therapy: the development of anti-TNF therapy of rheumatoid arthritis. [Review] [68 refs]. *Best Practice & Research in Clinical Rheumatology* 2004;**18**:59-80.

11 Beutler BA. The role of tumor necrosis factor in health and disease. [Review] [13 refs]. *Journal of Rheumatology - Supplement* 1999;**57**:16-21.

12 Torres D, Janot L, Quesniaux VF et al. Membrane tumor necrosis factor confers partial protection to Listeria infection. *American Journal of Pathology* 2005;**167**:1677-87.

13 US Food and Drug Administration. Etanercept Product Approval Information. http://www.fda.gov/Cder/biologics/products/etanimm110298.htm. 2 Nov 1998. (Accessed:Jan 2009).

14 US Food and Drug Administration. Infliximab Product Approval Information. http://www.fda.gov/cder/foi/appletter/1999/inflcen111099L.htm. 10 Nov 1999. (Accessed:Jan 2009).

15 Weinblatt ME, Kremer JM, Bankhurst AD et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.[see comment]. *New England Journal of Medicine* 1999;**340**:253-59.

16 Maini RN, Breedveld FC, Kalden JR et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis.[see comment]. *Arthritis & Rheumatism* 1998;**41**:1552-63.

17 National Institute for Health and Clinical Excellence. Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. http://guidance.nice.org.uk/TA36. 1 Mar 2002. (Accessed:Oct 2008).

18 Gresser I. A. Chekhov, M.D., and Coley's toxins. *New England Journal of Medicine* 1987;**317**:457.

19 Carswell EA, Old LJ, Kassel RL et al. An endotoxin-induced serum factor that causes necrosis of tumors. *Proceedings of the National Academy of Sciences of the United States of America* 1975;**72**:3666-70.

20 Lienard D, Eggermont AM, Schraffordt KH et al. Isolated perfusion of the limb with high-dose tumour necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma) and melphalan for melanoma stage III. Results of a multi-centre pilot study. *Melanoma Research* 1994;**4**:Suppl-6.

21 Eggermont AM, Schraffordt KH, Klausner JM et al. Isolation limb perfusion with tumor necrosis factor alpha and chemotherapy for advanced extremity soft tissue sarcomas. *Seminars in Oncology* 1997;**24**:547-55.

22 Eggermont AM, Schraffordt KH, Klausner JM et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. *Annals of Surgery* 1996;**224**:756-64.

23 Balkwill F. TNF-alpha in promotion and progression of cancer. [Review] [71 refs]. *Cancer & Metastasis Reviews* 2006;**25**:409-16.

24 Moore RJ, Owens DM, Stamp G et al. Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis.[erratum appears in Nat Med 1999 Sep;5(9):1087]. *Nature Medicine* 1999;**5**:828-31.

25 Knight B, Yeoh GC, Husk KL et al. Impaired preneoplastic changes and liver tumor formation in tumor necrosis factor receptor type 1 knockout mice. *Journal of Experimental Medicine* 2000;**192**:1809-18.

26 Egberts JH, Cloosters V, Noack A et al. Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis. *Cancer Research* 2008;**68**:1443-50.

27 Jaiswal M, LaRusso NF, Burgart LJ et al. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Research* 2000;**60**:184-90.

28 Szlosarek PW, Grimshaw MJ, Kulbe H et al. Expression and regulation of tumor necrosis factor alpha in normal and malignant ovarian epithelium. *Molecular Cancer Therapeutics* 2006;**5**:382-90.

29 Leibovich SJ, Polverini PJ, Shepard HM et al. Macrophage-induced angiogenesis is mediated by tumour necrosis factor-alpha. *Nature* 1987;**329**:630-632.

30 Rosen EM, Goldberg ID, Liu D et al. Tumor necrosis factor stimulates epithelial tumor cell motility. *Cancer Research* 1991;**51**:5315-21.

31 Maeda M, Watanabe N, Okamoto T et al. Endogenous tumor necrosis factor functions as a resistant factor against adriamycin. *Int J Cancer* 1994;**58**:376-79.

32 Harrison ML, Obermueller E, Maisey NR et al. Tumor necrosis factor alpha as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard and high dose. *Journal of Clinical Oncology* 2007;**25**:4542-49.

33 Brown ER, Charles KA, Hoare SA et al. A clinical study assessing the tolerability and biological effects of infliximab, a TNF-alpha inhibitor, in patients with advanced cancer. *Annals of Oncology* 2008;**19**:1340-1346.

34 Tsimberidou AM, Thomas D, O'Brien S et al. Recombinant human soluble tumor necrosis factor (TNF) receptor (p75) fusion protein Enbrel in patients with refractory hematologic malignancies. *Cancer Chemotherapy & Pharmacology* 2002;**50**:237-42.

35 Woyach JA, Lin TS, Lucas MS et al. A phase I/II study of rituximab and etanercept in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma. *Leukemia* 2009;**23**:912-18.

36 Mueller H. Tumor necrosis factor as an antineoplastic agent: pitfalls and promises. [Review] [117 refs]. *Cellular & Molecular Life Sciences* 1998;**54**:1291-98.

37 Khan I, Rahman L, McKenna DB. Primary cutaneous melanoma: a complication of infliximab treatment? *Clinical & Experimental Dermatology* 2009;**34**:524-26.

38 Fulchiero GJ, Jr., Salvaggio H, Drabick JJ et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *Journal of the American Academy of Dermatology* 2007;**56**:Suppl-7.

39 Qin Z, van Tits LJ, Buurman WA et al. Human lymphotoxin has at least equal antitumor activity in comparison to human tumor necrosis factor but is less toxic in mice. *Blood* 1995;**85**:2779-85.

40 Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *Journal of Chronic Diseases* 1978;**31**:691-96.

41 Gridley G, McLaughlin JK, Ekbom A et al. Incidence of cancer among patients with rheumatoid arthritis.[see comment]. *Journal of the National Cancer Institute* 1993;**85**:307-11.

42 Thomas E, Brewster DH, Black RJ et al. Risk of malignancy among patients with rheumatic conditions. *Int J Cancer* 2000;**88**:497-502.

43 Askling J, Fored CM, Brandt L et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis* 2005;**64**:1421-26.

44 Cibere J, Sibley J, Haga M. Rheumatoid arthritis and the risk of malignancy. *Arthritis & Rheumatism* 1997;**40**:1580-1586.

45 Mellemkjaer L, Linet MS, Gridley G et al. Rheumatoid arthritis and cancer risk. *European Journal of Cancer* 1996;**32A**:1753-57.

46 Prior P. Cancer and rheumatoid arthritis: Epidemiologic considerations. *The American Journal of Medicine* 1985;**78**:15-21.

47 Hemminki K, Li X, Sundquist K et al. Cancer risk in hospitalized rheumatoid arthritis patients. *Rheumatology* 2008;**47**:698-701.

48 Parikh-Patel A, White RH. Risk of cancer among rheumatoid arthritis patients in California. *Cancer Causes & Control* 2009;**20**:1001-10.

49 Chen YJ, Chang YT, Wang CB et al. The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. *Arthritis & Rheumatism* 2011;**63**:352-58.

50 Yamada T, Nakajima A, Inoue E et al. Incidence of malignancy in Japanese patients with rheumatoid arthritis. *Rheumatology International* 2011;**31**:1487-92.

51 Katusic S, Beard CM, Kurland LT et al. Occurrence of malignant neoplasms in the rochester, minnesota, rheumatoid arthritis cohort. *The American Journal of Medicine* 1985;**78**:50-55.

52 Abasolo L, Judez E, Descalzo MA et al. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. *Seminars in Arthritis & Rheumatism* 2008;**37**:388-97.

53 Franklin J, Lunt M, Bunn D et al. Influence of inflammatory polyarthritis on cancer incidence and survival: Results from a community-based prospective study. *Arthritis & Rheumatism* 2007;**56**:790-798.

54 Kim YJ, Shim JS, Choi CB et al. Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. *Journal of Rheumatology* 2012;**39**:226-32.

55 Smitten AL, Simon TA, Hochberg MC et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis.[see comment]. *Arthritis Research & Therapy* 2008;**10**:R45.

56 Macfarlane GJ, Black RJ. Rheumatoid arthritis and lymphatic cancer. *European Journal of Cancer* 1996;**32A**:1630-1632.

57 Office for National Statisitcs. Cancer Statistics Registrations, England (Series MB1), No. 40, 2009. http://ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--40--2009/index.html. 7 Sep 2011. (Accessed:Feb 2012).

58 McGuire JF, Ge NN, Dyson S. Nonmelanoma skin cancer of the head and neck I: histopathology and clinical behavior. *American Journal of Otolaryngology* 2003;**30**:121-33.

59 Goodwin RG, Holme SA, Roberts DL. Variations in registration of skin cancer in the United Kingdom. *Clinical & Experimental Dermatology* 2004;**29**:328-30.

60 Oberyszyn TM. Non-melanoma skin cancer: importance of gender, immunosuppressive status and vitamin D. [Review] [122 refs]. *Cancer Letters* 2008;**261**:127-36.

61 De Hertog SA, Wensveen CA, Bastiaens MT et al. Relation between smoking and skin cancer. *Journal of Clinical Oncology* 2001;**19**:231-38.

62 Webb MC, Compton F, Andrews PA et al. Skin tumours posttransplantation: a retrospective analysis of 28 years' experience at a single centre. *Transplantation Proceedings* 1997;**29**:828-30.

63 Hartevelt MM, Bavinck JN, Kootte AM et al. Incidence of skin cancer after renal transplantation in The Netherlands. *Transplantation* 1990;**49**:506-9.

64 Jensen P, Hansen S, Moller B et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens.[see comment]. *Journal of the American Academy of Dermatology* 1999;**40**:t-86.

65 Bouwes Bavinck JN, Hardie DR, Green A et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. *Transplantation* 1996;**61**:715-21.

66 London NJ, Farmery SM, Will EJ et al. Risk of neoplasia in renal transplant patients.[Erratum appears in Lancet 1995 Sep 9;346(8976):714]. *Lancet* 1995;**346**:403-6.

67 Buchbinder R, Barber M, Heuzenroeder L et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. *Arthritis & Rheumatism* 2008;**59**:794-99.

68 Khurana R, Wolf R, Berney S et al. Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans.[see comment]. *Journal of Rheumatology* 2008;**35**:1704-8.

69 Symmons D, Harrison B. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. I. Risk factors for the development of inflammatory polyarthritis and rheumatoid arthritis. *Rheumatology* 2000;**39**:835-43.

70 Mori S, Cho I, Koga Y et al. Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. *Journal of Rheumatology* 2008;**35**:1513-21.

71 Hubbard R, Venn A, Lewis S et al. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study.[see comment]. *American Journal of Respiratory & Critical Care Medicine* 2000;**161**:5-8.

72 Siemes C, Visser LE, Coebergh JW et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *Journal of Clinical Oncology* 2006;**24**:5216-22.

73 Flossmann E, Rothwell PM, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies.[see comment]. [Review] [84 refs]. *Lancet* 2007;**369**:1603-13.

74 Terry MB, Gammon MD, Zhang FF et al. Association of Frequency and Duration of Aspirin Use and Hormone Receptor Status With Breast Cancer Risk. *JAMA: The Journal of the American Medical Association* 2004;**291**:2433-40.

75 Franklin J, Lunt M, Bunn D et al. Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. [Review] [33 refs]. *Ann Rheum Dis* 2006;**65**:617-22.

76 Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis & Rheumatism* 1988;**31**:315-24.

77 Swerdlow SH, Campo E, Harris NL et al. WHO classification of tumours of haematopoietic and lymphoid tissues. IARC: Lyon 2008

78 Roman E, Smith AG. Epidemiology of lymphomas. *Histopathology* 2011;**58**:4-14.

79 Smedby KE, Hjalgrim H, Askling J et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *Journal of the National Cancer Institute* 2006;**98**:51-60.

80 Zintzaras E, Voulgarelis M, Moutsopoulos HM. The Risk of Lymphoma Development in Autoimmune Diseases: A Meta-analysis. *Arch Intern Med* 2005;**165**:2337-44.

81 Goldin LR, Landgren O. Autoimmunity and lymphomagenesis. *Int J Cancer* 2009;**124**:1497-502.

82 Baecklund E, Sundstrom C, Ekbom A et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. *Arthritis & Rheumatism* 2003;**48**:1543-50.

83 Conde L, Bracci PM, Halperin E et al. A search for overlapping genetic susceptibility loci between non-Hodgkin lymphoma and autoimmune diseases. *Genomics* 2011;**98**:9-14.

84 Mellemkjaer L, Pfeiffer RM, Engels EA et al. Autoimmune disease in individuals and close family members and susceptibility to non-Hodgkin's lymphoma. *Arthritis & Rheumatism* 2008;**58**:657-66.

85 Hellgren K, Smedby KE, Feltelius N et al. Do rheumatoid arthritis and lymphoma share risk factors?: A comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. *Arthritis & Rheumatism* 2010;**62**:1252-58.

86 Baecklund E, Iliadou A, Askling J et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis.[see comment]. *Arthritis & Rheumatism* 2006;**54**:692-701.

87 Hellgren K, Iliadou A, Rosenquist R et al. Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: results from a case-control study. *Ann Rheum Dis* 2010;**69**:654-59.

88 Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. [Review] [110 refs]. *Oncogene* 2003;**22**:5108-21.

89 Nalesnik MA, Jaffe R, Starzl TE et al. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. *American Journal of Pathology* 1988;**133**:173-92.

90 Kamel OW. Lymphomas during long-term methotrexate therapy. *Arch Dermatol* 1997;**133**:903-4.

91 Bachman TR, Sawitzke AD, Perkins SL et al. Methotrexate-associated lymphoma in patients with rheumatoid arthritis: report of two cases. *Arthritis & Rheumatism* 1996;**39**:325-29.

92 Suzuki M, Hirano S, Ito H et al. Pulmonary lymphoma developed during long-term methotrexate therapy for psoriasis. *Respirology* 2007;**12**:774-76.

93 Liote F, Pertuiset E, Cochand-Priollet B et al. Methotrexate related B lymphoproliferative disease in a patient with rheumatoid arthritis. Role of Epstein-Barr virus infection. *Journal of Rheumatology* 1995;**22**:1174-78.

94 Thomason RW, Craig FE, Banks PM et al. Epstein-Barr virus and lymphoproliferation in methotrexate-treated rheumatoid arthritis. *Modern Pathology* 1996;**9**:261-66.

95 Georgescu L, Quinn CG, Schwartzman S et al. Lymphoma in patients with rheumatoid arthritis: Association with the disease state or methotrexate treatment. *Semin Arthritis Rheum* 1997;**26**:794-804.

96 Grulich AE, van Leeuwen MT, Falster MO et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.[see comment]. [Review] [30 refs]. *Lancet* 2007;**370**:59-67.

97 Salloum E, Cooper DL, Howe G et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases.[see comment]. [Review] [56 refs]. *Journal of Clinical Oncology* 1996;**14**:1943-49.

98 Rojo-Contreras W, Olivas-Flores EM, Gamez-Nava JI et al. Cervical human papillomavirus infection in Mexican women with systemic lupus erythematosus or rheumatoid arthritis. *Lupus* 2012;**21**:365-72.

99 Tam LS, Chan AY, Chan PK et al. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. *Arthritis & Rheumatism* 2004;**50**:3619-25.

100 Nath R, Mant C, Luxton J et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. *Arthritis & Rheumatism* 2007;**57**:619-25.

101 Dhar JP, Kmak D, Bhan R et al. Abnormal cervicovaginal cytology in women with lupus: a retrospective cohort study. *Gynecologic Oncology* 2001;**82**:4-6.

102 Bateman H, Yazici Y, Leff L et al. Increased cervical dysplasia in intravenous cyclophosphamide-treated patients with SLE: a preliminary study. *Lupus* 2000;**9**:542-44.

103 Mattey DL, Thomson W, Ollier WE et al. Association of DRB1 shared epitope genotypes with early mortality in rheumatoid arthritis: results of eighteen years of followup from the early rheumatoid arthritis study. *Arthritis & Rheumatism* 2007;**56**:1408-16.

104 Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C et al. Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. *Seminars in Arthritis & Rheumatism* 2007;**37**:31-38.

105 Panoulas VF, Smith JP, Nightingale P et al. Association of the TRAF1/C5 locus with increased mortality, particularly from malignancy or sepsis, in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 2009;**60**:39-46.

106 Zapata JM, Krajewska M, Krajewski S et al. TNFR-associated factor family protein expression in normal tissues and lymphoid malignancies. *Journal of Immunology* 2000;**165**:5084-96.

107 MacLean CH, Louie R, Leake B et al. Quality of care for patients with rheumatoid arthritis.[see comment]. *JAMA* 2000;**284**:984-92.

108 Solomon DH, Karlson EW, Curhan GC. Cardiovascular care and cancer screening in female nurses with and without rheumatoid arthritis. *Arthritis & Rheumatism* 2004;**51**:429-32.

109 Kim SC, Schneeweiss S, Myers JA et al. Cancer screening rates in patients with rheumatoid arthritis: No different than the general population. *Arthritis & Rheumatism* 2012;n/a.

110 Bernatsky SR, Cooper GS, Mill C et al. Cancer screening in patients with systemic lupus erythematosus.[see comment]. *Journal of Rheumatology* 2006;**33**:45-49.

111 Virchow R. Aetiologie der neoplastischen Geschwülste/Pathogenie der neoplastischen Geschwülste. Berlin: Verlag von August Hirschwald 1863:57-101.

112 Schmidt A, Weber OF. In memoriam of Rudolf Virchow: a historical retrospective including aspects of inflammation, infection and neoplasia. *Contributions to Microbiology* 2006;**13**:1-15.

113 Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. [Review] [83 refs]. *Cancer Cell* 2005;**7**:211-17.

114 Sylvester RJ, van der Meijden AP, Witjes JA et al. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *Journal of Urology* 1991;**174**:86-91.

115 Harris RE, Chlebowski RT, Jackson RD et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. *Cancer Research* 2003;**63**:6096-101.

116 Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. *British Journal of Cancer* 2001;**84**:1188-92.

117 Castelao JE, Yuan JM, Gago-Dominguez M et al. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *British Journal of Cancer* 2000;**82**:1364-69.

118 Habel LA, Zhao W, Stanford JL. Daily aspirin use and prostate cancer risk in a large, multiracial cohort in the US. *Cancer Causes & Control* 2002;**13**:427-34.

119 Harris RE, Beebe-Donk J, Namboodiri KK. Inverse association of non-steroidal anti-inflammatory drugs and malignant melanoma among women. *Oncology Reports* 2001;**8**:655-57.

120 Harris RE, Beebe-Donk J, Alshafie GA. Reduced risk of human lung cancer by selective cyclooxygenase 2 (COX-2) blockade: results of a case control study. *International Journal of Biological Sciences [Electronic Resource]* 2007;**3**:328-34.

121 Pereg D, Lishner M. Non-steroidal anti-inflammatory drugs for the prevention and treatment of cancer. [Review] [98 refs]. *Journal of Internal Medicine* 2005;**258**:115-23.

122 Cerhan JR, Anderson KE, Janney CA et al. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma.[see comment]. *Int J Cancer* 2003;**106**:784-88.

123 Kato I, Koenig KL, Shore RE et al. Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-Hodgkin's lymphoma (NHL) (United States). *Cancer Causes & Control* 2002;**13**:965-74.

124 Penn I. Malignant melanoma in organ allograft recipients. *Transplantation* 1996;**61**:274-78.

125 Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *Journal of Rheumatology* 1999;**26**:1705-14.

126 Matteson EL, Hickey AR, Maguire L et al. Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD Registry. Rheumatoid Arthritis Azathioprine Registry Steering Committee. *Journal of Rheumatology* 1991;**18**:809-14.

127 Jones M, Symmons D, Finn J et al. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. *British Journal of Rheumatology 35(8)()(pp 738-745), 1996 Date of Publication: 1996* 1996;738-45.

128 Blohme I, Brynger H. Malignant disease in renal transplant patients. *Transplantation* 1985;**39**:23-25.

129 Arellano F, Krupp P. Malignancies in rheumatoid arthritis patients treated with cyclosporin A. *British Journal of Rheumatology* 1993;**32**:Suppl-5.

130 van den Borne BE, Landewe RB, Houkes I et al. No increased risk of malignancies and mortality in cyclosporin A-treated patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1998;**41**:1930-1937.

131 Radis CD, Kahl LE, Baker GL et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year followup study. *Arthritis & Rheumatism* 1995;**38**:1120-1127.

132 Bernatsky S, Clarke A, Suissa S. Lung cancer after exposure to disease modifying anti-rheumatic drugs. *Lung Cancer* 2008;**59**:266-69.

133 Bologna C, Picot MC, Jorgensen C et al. Study of eight cases of cancer in 426 rheumatoid arthritis patients treated with methotrexate. *Ann Rheum Dis* 1997;**56**:97-102.

134 Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis & Rheumatism* 2007;**56**:1433-39.

135 Mariette X, Cazals-Hatem D, Warszawki J et al. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002;**99**:3909-15.

136 Bernatsky S, Clarke AE, Suissa S. Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis. *Arch Intern Med* 2008;**168**:378-81.

137 Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis.[see comment]. *Arthritis & Rheumatism* 2003;**48**:313-18.

138 Zink A, Strangfeld A, Schneider M et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to

their eligibility for major randomized clinical trials. *Arthritis & Rheumatism* 2006;**54**:3399-407.

139 Kievit W, Fransen J, Oerlemans AJ et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. [Review] [27 refs]. *Ann Rheum Dis* 2007;**66**:1473-78.

140 St Clair EW, van der Heijde DM, Smolen JS et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis & Rheumatism* 2004;**50**:3432-43.

141 Keystone EC, Kavanaugh AF, Sharp JT et al. 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 & Rheumatism* 2004;**50**:1400-1411.

142 Combe B, Codreanu C, Fiocco U et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis* 2006;**65**:1357-62.

143 Bathon JM, Martin RW, Fleischmann RM et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.[see comment][erratum appears in N Engl J Med 2001 Jan 18;344(3):240]. *New England Journal of Medicine* 2000;**343**:1586-93.

144 Keystone EC, Schiff MH, Kremer JM et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis & Rheumatism* 2004;**50**:353-63.

145 Moreland LW, Schiff MH, Baumgartner SW et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Annals of Internal Medicine* 1999;**130**:478-86.

146 Furst DE, Schiff MH, Fleischmann RM et al. 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).[see comment]. *Journal of Rheumatology* 2003;**30**:2563-71.

147 van de Putte LB, Rau R, Breedveld FC et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003;**62**:1168-77.

148 Breedveld FC, Weisman MH, Kavanaugh AF et al. 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 & Rheumatism* 2006;**54**:26-37.

149 Bongartz T, Sutton AJ, Sweeting MJ et al. 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.[see comment][erratum appears in JAMA. 2006 Jun 7;295(21):2482]. [Review] [58 refs]. *JAMA* 2006;**295**:2275-85.

150 Bongartz T, Warren FC, Mines D et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies. A systematic review and individual patient data meta-analysis of Randomized Controlled Trials. *Ann Rheum Dis* 2008;ard.

151 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. [Review] [64 refs]. *Ann Rheum Dis* 2009;**68**:1136-45.

152 Askling J, Fahrbach K, Nordstrom B et al. Cancer risk with tumour necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiology & Drug Safety* 2010;**19**:1-11.

153 Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis & Rheumatism* 2011;**63**:1479-85.

154 Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al.[see comment]. *Arthritis Research & Therapy* 2006;**8**:111.

155 Costenbader KH, Glass R, Cui J et al. Risk of Serious Infections and Malignancies With Anti-TNF Antibody Therapy in Rheumatoid Arthritis. *JAMA: The Journal of the American Medical Association* 2006;**296**:2201.

156 Brown SL, Greene MH, Gershon SK et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration.[see comment]. *Arthritis & Rheumatism* 2002;**46**:3151-58.

157 Meyboom RH, Star K, Bate J et al. TNF-alpha inhibitors and leukaemia: international pharmacovigilance reports. *Drug Safety* 2008;**31**:445-47.

158 US Food and Drug Administration. FDA Drug Safety Communication: Safety review update on reports of hepatosplenic T-cell lymphoma in adolescents and young adults receiving tumor necrosis factor (TNF) blockers, azathioprine and/or mercaptopurine. http://www.fda.gov/Drugs/DrugSafety/ucm250913.htm. 14 Apr 2011. (Accessed:Aug 2012).

159 Ochenrider MG, Patterson DJ, Aboulafia DM. Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review. [Review] [24 refs]. *Clinical lymphoma, myeloma & leukemia* 2010;**10**:144-48.

160 Tubach F, Dougados M, Falissard B et al. Feeling good rather than feeling better matters more to patients. *Arthritis & Rheumatism* 2006;**55**:526-30.

161 Wolfe F, Michaud K, Dewitt EM. Why results of clinical trials and observational studies of antitumour necrosis factor (anti-TNF) therapy differ: methodological and interpretive issues. *Ann Rheum Dis* 2004;**63**:Suppl-ii17.

162 About MEDLINE. The John Rylands University Library, The University of Manchester. 2008. (Accessed:Oct 2008).

163 Askling J, Fored CM, Baecklund E et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis* 2005;**64**:1414-20.

164 Askling J, van Vollenhoven RF, Granath F et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis & Rheumatism* 2009;**60**:3180-3189.

165 Askling J, Baecklund E, Granath F et al. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. *Ann Rheum Dis* 2009;**68**:648-53.

166 Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients.[see comment]. *Arthritis & Rheumatism* 2004;**50**:1740-1751.

167 Geborek P, Bladstrom A, Turesson C et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas.[see comment]. *Ann Rheum Dis* 2005;**64**:699-703.

168 Pallavicini FB, Caporali R, Sarzi-Puttini P et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. *Autoimmunity Reviews* 2010;**9**:175-80.

169 Strangfeld A, Hierse F, Rau R et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Research & Therapy* 2010;**12**:R5.

170 Setoguchi S, Solomon DH, Weinblatt ME et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis.[see comment][erratum appears in Arthritis Rheum. 2006 Oct;54(10):3134]. *Arthritis & Rheumatism* 2006;**54**:2757-64.

171 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis & Rheumatism* 2007;**56**:2886-95.

172 Amari W, Zeringue AL, McDonald JR et al. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. *Rheumatology* 2011.

173 Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *Journal of Rheumatology* 2005;**32**:2130-2135.

174 Mariette X, Tubach F, Bagheri H et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2010;**69**:400-408.

175 Dixon WG, Watson KD, Lunt M et al. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: Results from the British Society for rheumatology biologics register. *Arthritis Care Res* 2010;**62**:755-63.

176 van Vollenhoven RF, Askling J. Rheumatoid arthritis registries in Sweden. *Clinical & Experimental Rheumatology* 2005;**23**:Suppl-200.

177 Patel S, Farragher T, Berry J et al. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. *Arthritis & Rheumatism* 2007;**56**:2143-49.

178 Lienard D, Eggermont AM, Koops HS et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. *Melanoma Research* 1999;**9**:491-502.

179 Franklin JP, Symmons DPM, Silman AJ. Risk of lymphoma in patients with RA treated with anti-TNF{alpha} agents. *Ann Rheum Dis* 2005;**64**:657-58.

180 Ledingham J, Deighton C, on behalf of the British Society for Rheumatology Standards GaAWG. Update on the British Society for Rheumatology guidelines for prescribing TNF{alpha} blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology* 2005;**44**:157-63.

181 Raaschou P, Simard JF, Neovius M et al. Does cancer that occurs during or after anti-tumor necrosis factor therapy have a worse prognosis? A national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents. *Arthritis & Rheumatism* 2011;**63**:1812-22.

182 Adamson P, Bray F, Costantini AS et al. Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. *European Journal of Cancer* 2007;**43**:391-401.

183 Britton A, McKee M, Black N et al. Choosing between randomised and non-randomised studies: a systematic review. [Review] [204 refs]. *Health Technology Assessment (Winchester, England)* 2001;**2**:i-iv.

184 British Society for Rheumatology. Guidelines for prescribing TNF-a blockers in adults with Rheumatoid Arthritis. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/p/prescribing_tnfalpha_blockers_in_adults_with_rheumatoid_arthritis_april_2001.pdf. British Socieity for Rheumatology. Apr 2001. (Accessed:Oct 2012).

185 Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. National Institute for Health and Clinical Excellence. 1 Mar 2002. (Accessed:Oct 2008).

186 BSR Biologics Register. BSRBR: MREC documents. http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bsrbr/healthprofessionals/MRECDocuments/. 2012. (Accessed:Aug 2012).

187 BSR Biologics Register. Forms for registering patients on biologic therapy. Consultant baseline questionnaire version 8. http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bsrbr/healthprofessionals/forms/rheumatoidarthritis/AntiTNFCohortForms. 2012. (Accessed:Aug 12 A.D.).

188 Prevoo ML, Van 't Hof MA, Kuper HH et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1995;**38**:44-48.

189 Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *Journal of Rheumatology* 1982;**9**:789-93.

190 United Kingdon Association of Cancer Registries. UK Association of Cancer Registries homepage. http://www.ukacr.org/. 2012. (Accessed:Aug 12 A.D.).

191 BSR Biologics Register. Events of Special Interest. http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bsrbr/healthprofessionals/forms/EventsofSpecialInterest/. 2012. (Accessed:Aug 12 A.D.).

192 Galloway JB, Hyrich KL, Mercer LK et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2010.

193 Dixon WG, Symmons DP, Lunt M et al. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis & Rheumatism* 2007;**56**:2896-904.

194 RUBIN DB. Inference and missing data. *Biometrika* 1976;**63**:581-92.

195 Wayman, J. C. Multiple imputation for missing data: What is it and how can I use it? http://www.csos.jhu.edu/contact/staff/jwayman_pub/wayman_multimp_aera2003.pdf. Paper presentd at the 2003 Annual Meeting of the American Educational Research Association, Chicago, IL. 2003. (Accessed:Aug 2012).

196 Brookhart MA, Schneeweiss S, Rothman KJ et al. Variable selection for propensity score models. *American Journal of Epidemiology* 2006;**163**:1149-56.

197 Rachet B, Ellis L, Maringe C et al. Socioeconomic inequalities in cancer survival in England after the NHS cancer plan. *Br J Cancer* 2010;**103**:446-53.

198 Ward E, Jemal A, Cokkinides V et al. Cancer disparities by race/ethnicity and socioeconomic status. [Review] [52 refs]. *CA: a Cancer Journal for Clinicians* 2004;**54**:78-93.

199 HM Government. Index of Multiple Deprivation. http://data.gov.uk/dataset/index-of-multiple-deprivation. 20 Apr 2012. (Accessed:Sep 2012).

200 Saag KG, Cerhan JR, Kolluri S et al. Cigarette smoking and rheumatoid arthritis severity. *Ann Rheum Dis* 1997;**56**:463-69.

201 Glynn RJ, Schneeweiss S, St++rmer T. Indications for Propensity Scores and Review of their Use in Pharmacoepidemiology. *Basic & Clinical Pharmacology & Toxicology* 2006;**98**:253-59.

202 Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology* 2008;**168**:656-64.

203 Cochran WG. The effectiveness of adjustment by subclassification in removing bias in observational studies. *Biometrics* 1968;**24**:295-313.

204 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studeis for causal effects. *Biometrika* 1996;**70**:41-55.

205 Centres for Disease Control and Prevention. Breast cancer rates by race and ethnicity. http://www.cdc.gov/cancer/breast/statistics/race.htm. 2012. (Accessed:Aug 2012).

206 Northern Ireland Cancer Registry. Incidence and Survival 1993-2010; Table 2 All cancers. http://www.qub.ac.uk/research-centres/nicr/CancerData/OnlineStatistics/. 2011. (Accessed:Aug 2012).

207 ISD Scotland. Cancer Incidence 2009; All Cancers. http://www.isdscotland.org/Health-Topics/Cancer/Publications/data-tables.asp?id=605#605. 2010. (Accessed:Aug 2012).

208 Welsh Cancer Intelligence and Surveillance Unit. Cancer incidence in Wales 2005-2009; Annual Publication No. SA11/01.

http://www.wales.nhs.uk/sites3/page.cfm?orgid=242&pid=51358. 27 Jan 2011. (Accessed:Aug 2012).

209 Piccirillo JF, Tierney RM, Costas I et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004;**291**:2441-47.

210 Wolfe F, Michaud K, Strand V. Expanding the definition of clinical differences: from minimally clinically important differences to really important differences. Analyses in 8931 patients with rheumatoid arthritis. *Journal of Rheumatology* 2005;**32**:583-89.

211 Wells GA, Tugwell P, Kraag GR et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *Journal of Rheumatology* 1993;**20**:557-60.

212 Hyrich KL, Watson KD, Silman AJ et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* 2006;**45**:1558-65.

213 Lunt M, Watson KD, Dixon WG et al. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis & Rheumatism* 2010;**62**:3145-53.

214 Hyrich KL, Watson KD, Lunt M et al. Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology* 2011;**50**:117-23.

215 Luqmani R, Hennell S, Estrach C et al. British Society for Rheumatology and british health professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). *Rheumatology* 2006;**45**:1167-69.

216 Luqmani R, Hennell S, Estrach C et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). *Rheumatology* 2009;**48**:436-39.

217 Office for National Statistics. Cancer Statistics: Registrations Series MB1. http://ons.gov.uk/ons/datasets-and-tables/search/index.html?newquery=mb1. 1 Jan 2010. (Accessed:Jun 2012).

218 World Health Organisation. International statistical classification of diseases and related health problems; 10th revision. http://apps.who.int/classifications/apps/icd/icd10online/. 5 Apr 2006. (Accessed:Jun 2010).

219 Salinas CA, Kwon EM, FitzGerald LM et al. Use of aspirin and other nonsteroidal antiinflammatory medications in relation to prostate cancer risk. *American Journal of Epidemiology* 2010;**172**:578-90.

220 Prizment AE, Folsom AR, Anderson KE. Nonsteroidal anti-inflammatory drugs and risk for ovarian and endometrial cancers in the Iowa Women's Health Study. *Cancer Epidemiology, Biomarkers & Prevention* 2010;**19**:435-42.

221 Murad AS, Down L, Davey SG et al. Associations of aspirin, nonsteroidal anti-inflammatory drug and paracetamol use with PSA-detected prostate cancer: findings from a large, population-based, case-control study (the ProtecT study). *Int J Cancer* 2011;**128**:1442-48.

222 Brasky TM, Velicer CM, Kristal AR et al. Nonsteroidal anti-inflammatory drugs and prostate cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Cancer Epidemiology, Biomarkers & Prevention* 2010;**19**:3185-88.

223 Takkouche B, Regueira-Mendez C, Etminan M. Breast Cancer and Use of Nonsteroidal Anti-inflammatory Drugs: A Meta-analysis. *Journal of the National Cancer Institute* 2008;**100**:1439-47.

224 Jensen P, Hansen S, Moller B et al. Are renal transplant recipients on CsA-based immunosuppressive regimens more likely to develop skin cancer than those on azathioprine and prednisolone? *Transplantation Proceedings***31**:1120-1Mar.

225 Glover MT, Deeks JJ, Raftery MJ et al. Immunosuppression and risk of non-melanoma skin cancer in renal transplant recipients. *Lancet* 1997;**349**:398.

226 Dantal J, Hourmant M, Cantarovich D et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998;**351**:623-28.

227 Fairchild WV, Spence CR, Solomon HD et al. The incidence of bladder cancer after cyclophosphamide therapy. *Journal of Urology* 1979;**122**:163-64.

228 Office for National Statistics. Cancer Statistics: Registrations Series MB1 - No. 39, 2008 http://ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-198611. 1 Aug 2010. (Accessed:Jul 2011).

229 Baecklund E, Backlin C, Iliadou A et al. Characteristics of diffuse large B cell lymphomas in rheumatoid arthritis. *Arthritis & Rheumatism* 2006;**54**:3774-81.

230 Rosenwald A, Wright G, Chan WC et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *New England Journal of Medicine* 2002;**346**:1937-47.

231 Callan MF. Epstein-Barr virus, arthritis, and the development of lymphoma in arthritis patients. [Review] [49 refs]. *Current Opinion in Rheumatology* 2004;**16**:399-405.

232 Miceli-Richard C, Mariette X. EBV-specific T-cell response and immunosuppression by methotrexate and TNF[alpha] antagonists in patients with chronic inflammatory joint disease. *Joint Bone Spine* 2007;**74**:560-562.

233 Goldberg JE, Schwertfeger KL. Proinflammatory cytokines in breast cancer: mechanisms of action and potential targets for therapeutics. [Review]. *Current Drug Targets* 2010;**11**:1133-46.

234 Su K, Tian Y, Wang J et al. HIF-1alpha acts downstream of TNF-alpha to inhibit vasodilator-stimulated phosphoprotein expression and modulates the adhesion and proliferation of breast cancer cells. *DNA & Cell Biology* 2012;**31**:1078-87.

235 Madhusudan S, Foster M, Muthuramalingam SR et al. A phase II study of etanercept (Enbrel), a tumor necrosis factor alpha inhibitor in patients with metastatic breast cancer. *Clinical Cancer Research* 2004;**10**:6528-34.

236 Baxter JM, Patel AN, Varma S. Facial basal cell carcinoma. *British Medical Journal* 2012;**345**:37-42.

237 Clouser MC, Roe DJ, Foote JA et al. Effect of non-steroidal anti-inflammatory drugs on non-melanoma skin cancer incidence in the SKICAP-AK trial. *Pharmacoepidemiology & Drug Safety* 2009;**18**:276-83.

238 Nunes AP, Lapane KL, Weinstock MA et al. Association between non-steroidal anti-inflammatory drugs and keratinocyte carcinomas of the skin among participants in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Pharmacoepidemiol Drug Saf* 2011;**20**:922-29.

239 Sterne JA, Hernan MA, Ledergerber B et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005;**366**:378-84.

240 Verstappen SM, Watson KD, Lunt M et al. Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* 2010;**49**:1570-1577.

241 Office for National Statistics. UK indices of multiple deprivation - a way to make comparisons across constituent countries easier? http://www.ons.gov.uk/ons/rel/hsq/health-statistics-quarterly/no--53--spring-2012/uk-indices-of-multiple-deprivation.html?format=print. 21 Feb 2012. (Accessed:Sep 12 A.D.).

242 British Society for Rheumatology. Guidelines for prescribing TNF-a blockers in adults with Rheumatoid Arthritis. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/p/prescribing_tnfalpha_blockers_in_adults_with_rheumatoid_arthritis_april_2001.pdf. British Socieity for Rheumatology. Apr 2001. (Accessed:Oct 2012).

243 Popa C, Leandro MJ, Cambridge G et al. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. *Rheumatology* 2007;**46**:626-30.

244 Mellemkjaer L, Hammarstrom L, Andersen V et al. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clinical & Experimental Immunology* 2002;**130**:495-500.

245 Simard, J. F., Raaschou, P., Neovius, M. et al. RA, anti-TNF therapy, and risk of malignant melanoma - a nationawide population-based study from Sweden. https://www.rheumatology.org/about/newsroom/2011/2011_ASM_07_anti_tnf_therapies.asp. 8 Nov 2011. (Accessed:Sep 2012).

Appendices

Appendix 1. OVID Medline search strategy to identify all cancers in observational studies of anti-TNF in RA

	Searches	Results
1	exp Receptors, Tumor Necrosis Factor/ or exp Tumor Necrosis Factor-alpha/ or etanercept.mp.	94231
2	exp Antibodies, Monoclonal/ or infliximab.mp.	161637
3	adalimumab.mp.	2398
4	golimumab.mp.	159
5	certolizumab.mp.	303
6	1 or 2 or 3 or 4 or 5	247976
7	exp Arthritis, Rheumatoid/	77156
8	exp Neoplasms/	248865
9	6 and 4 and 5	86
10	limit 7 to (english language and humans and last 20 years)	63

Appendix 2. Documentation relating to ethical approval for the lymphoma histology work

NHS

National Research Ethics Service

North West 5 Research Ethics Committee - Haydock Park

NHS North West
Room 155 - Gateway House
Piccadilly South
Manchester
M60 7LP

Tel: 0161 237 2394 / 2152
Fax: 0161 237 2383

04 September 2009

Professor Deborah Symmons
The University of Manchester
arc Epidemiology Unit
School of Medicine
Oxford Road
Manchester M13 9PT

Dear Professor Symmons

Study title: **Prospective observational study of the long-term hazards of anti-TNF therapy in rheumatiod arthritis**

REC reference: **00/8/053**
Amendment number: ***N/A***
Amendment date: **14 August 2009**

The above amendment was reviewed at the meeting of the Sub-Committee held on 25 August 2009.

Ethical opinion

RECEIVED

The British Society for Rheumatology Biologics Register (BSRBR) has been collecting data on patients receiving biologic therapy (including the anti-TNF drugs etanercept, infliximab and adalimumab) for rheumatoid arthritis (RA) during routine clinical care since 2001. One of the main reasons for setting up the study was to determine whether or not treatment with these drugs increased the risk of cancer, and in particular lymphoproliferative cancers including lymphoma. The amendment (dated 14 August 2009) sought approval for a number of changes to the current approved study protocol, as follows: -

1. To ascertain the prevalence and incidence rates of patients with lymphoma who are already taking part in the BSRBR.
2. To determine the subtypes of lymphoma in the biologics cohort by reclassifying them in accordance with the World Health Organisation classification.
3. To examine the factors predicting development and outcome of lymphoma in the biologics treated cohort, and in particular the influence of disease activity.

There are currently 49 patients registered with the BSRBR, who have been treated with biologic drugs for RA and had been diagnosed with lymphoma during the course of the study. It was anticipated that this number would increase as patients continued to be followed via the registry.

A comprehensive, clear and well written rationale had been submitted in support of the amendment.

The Sub-Committee had no ethical difficulties with the proposed amendment.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter: From Dr Kimme Hyrich	1	14 August 2009
Notice of Substantial Amendment (non-CTIMPs)		14 August 2009
Appendix A: Letter to Consultant	1	10 August 2009
Appendix B: Letter to Patient	1	10 August 2009
Appendix C: Letter to Pathologist	1	10 August 2009
Appendix D: Patient Information Sheet	1	10 August 2009
Appendix E: Patient Consent Form	1	10 August 2009

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

00/8/053: **Please quote this number on all correspondence**

Yours sincerely

Noel Graham
Committee Co-ordinator

E-mail: noel.graham@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

This Research Ethics Committee is an advisory committee to North West Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within

NHS
National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:

Name: Professor Deborah Symmons
Address: arc Epidemiology Unit
Stopford Building
The University of Manchester
Oxford Road
Manchester
M13 9PT

Telephone: 0161 275 5044
E-mail: deborah.symmons@manchester.ac.uk
Fax: 0161 275 1640

Full title of study:	Prospective Observational Study of the Long Term Hazards of Anti-TNF Therapy in Rheumatoid Arthritis
Name of main REC:	North West MREC
REC reference number:	MREC 00/8/53
Date study commenced:	October 2001
Protocol reference *(if applicable)*,	Protocol dated 06/10/2003
current version and date:	
Amendment number and date:	

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC application form

Yes *No*

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes ***No***

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The British Society for Rheumatology Biologics Register (BRSBR) has been collecting data on patients receiving biologic therapy (including the anti-TNF drugs etanercept, infliximab and adalimumab) for rheumatoid arthritis (RA) during routine clinical care since October 2001. One of the main reasons for setting up this study was to determine whether or not treatment with these drugs increases the risk of cancer, and in particular lymphoproliferative

cancers, including lymphoma. This amendment outlines changes to the protocol to help us carry out a more detailed analysis of lymphoproliferative malignancies that have been reported to the BSRBR.

1. Incident lymphomas occurring in the biologics-treated cohort will be reclassified according to the World Health Organisation classification, to determine the subtypes of lymphoma seen in these patients. For these lymphomas the loan of representative paraffin blocks of tumour material and histology reports will be requested from the reporting pathologist. Sections will be cut from the tissue blocks for hematoxylin and eosin (H&E) staining and immunohistochemistry in order to classify all lymphomas in a standardised way. This work will be overseen by Dr Richard Byers, Consultant Pathologist and Senior Lecturer at the University of Manchester, and member of the Manchester Lymphoma Group. All material will be carefully stored at Manchester Royal Infirmary, and remaining tissue returned to the patient's pathologist. (See below under 'any other relevant information' regarding patient consent).
2. The effect of RA disease activity on lymphoma incidence will be explored. Each patient in the biologics cohort with an incident lymphoma will be matched individually to 4 controls from the biologics cohort. The case notes for these cases and controls will be reviewed to determine average and cumulative disease activity from the time of diagnosis with RA. Other supporting information will be collated.

Supporting Scientific Information

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease causing pain, swelling, stiffness and deformity. Patients with RA are known to have an increased risk of certain malignancies, including lymphoma (1). The increased risk of lymphoma may relate in part to chronic immune stimulation. However, duration of disease alone is not enough to account for this risk. Recent work from Sweden has shown that the severity of disease, in particular cumulative disease activity, may be a stronger predictor in patients with RA (2).

Recently, the biologic therapy, anti-tumour necrosis factor (TNF), has been shown to be very effective in treating severe RA (3-5). However, there is still anxiety about the long-term safety of anti-TNF agents, particularly a theoretical risk of cancer. TNF is a cytokine protein of the immune system and plays a critical role in tumour surveillance (6). TNF is being studied as an anti-cancer agent in many types of cancer, including malignant melanoma and soft-tissue sarcomas (7;8). It is also known to promote a T-cell cytotoxic response against certain lymphomas.

Unfortunately, patients who receive anti-TNF therapies are those with the most severe RA and are therefore, already at the highest risk of lymphoma. Therefore, any analysis of cancer risk with these new therapies must account for this background risk. The possibility also exists that those patients who respond to anti-TNF therapies, by way of improved RA disease control, may actually have a lower lymphoma risk over time compared to patients who do not receive the therapy, and therefore, any analysis must also account for changes in disease activity over time.

Patterns of lymphoma have already been studied in large cohorts of patients with RA. This has shown that around 80% of lymphomas are B cell lymphomas, and 50% diffuse large B cell lymphoma. Since it is possible that some types of lymphoma may be increased with anti-TNF drugs, and some decreased, the pattern of lymphoma seen in biologics treated patients may change.

Due to the large size of this national cohort and the recording of all serious adverse events, the BSRBR offers a unique opportunity to study the factors governing the occurrence and progression of lymphoma, including anti-TNF drugs and disease activity.

Hypothesis:
Anti-TNF therapy may increase the risk of developing lymphoma in patients with RA by inhibiting the role of TNF in tumour surveillance.

Aims:
To determine the influence of anti-TNF on incidence, subtype and outcome of lymphoma in RA.
To determine the influence of cumulative disease activity on incidence of lymphoma in patients with RA treated with anti-TNF.

Objectives:
1. To ascertain prevalence and incidence rates of patients with lymphoma who are already consented to take part in the BSRBR (a study to monitor the long-term safety of biologic agents in rheumatic diseases).
2. To determine the subtypes of lymphoma in the biologics cohort by reclassifying them according to the World Health Organisation classification.
3. To examine factors predicting development and outcome of lymphoma in the biologics treated cohort, and in particular the influence of disease activity.

Methods:
The BSRBR is an ongoing national prospective observational study assessing the medium- to long-term safety of biologic drugs in the treatment of rheumatic diseases. To 21/07/09, there have been 15418 biologic treated patients and 3775 DMARD treated controls registered. Extensive clinical information is collected at baseline and at six-monthly follow-up intervals. Patients with lymphoma reported by themselves, their consultant or the NHS Information Centre will be identified from the register.

Pathological classification
1. Rheumatology consultants of live patients with lymphoma diagnosed during follow up in the BSRBR will be contacted via letter (appendix A). This letter will ask that they send these patients a cover letter, an information sheet explaining our intention to review their medical notes and lymphoma pathology specimen and a patient consent form (Appendices B, D and E). Consent will not be sought from relatives of deceased patients (see below in 'Any other relevant information').
2. Once patient consent is received (in the case of live patients) the pathologist will be contacted to request the loan of the tumour tissue block with their accompanying report.
3. Tissue blocks will be reviewed and reported by a Histopathologist at the University of Manchester with an interest in lymphoma.
4. In addition, copies of histology reports and the name and address of the patient's Oncologist/Pathologist will be requested from Rheumatology consultants of all lymphoma patients.

Additional work for the consultant / rheumatology specialist nurse entails reviewing medical records for the above information and postage of this information to the BSRBR, as well as postage of letters with information sheets and consent forms to patients. Postage will be paid for by the University of Manchester

Nested case control study
1. The effect of RA disease activity on lymphoma incidence will be explored. Each patient with incident lymphoma will be matched individually to 4 controls from the

Notice of amendment (non-CTIMP), version 3.1, November 2005

biologics cohort. Controls must be alive and free of cancer at the time of matching. The case notes of these patients and controls will be reviewed to assess disease activity from time of diagnosis of RA. This will be done using information recorded in the patient's case notes including blood results, joint counts (where available), radiology reports and physician's opinion. Average disease activity and cumulative disease activity will be calculated, and categorised as absent, low, medium and high disease activity. At the time of their registration, patients have already consented to information form their medical file being disclosed to the BSRBR.

Sample sizes:
On 12/05/09 there were 49 patients, registered with the BSRBR, who had been treated with biologic drugs for RA and diagnosed with lymphoma during the study. This number will increase as patients continue to be followed in the register.
The study has 88% power to detect a 25% difference in the proportion of patients with high disease activity between 50 cases and 200 controls.

Time scale: It is estimated that it will take up to 2 months to reclassify lymphoma tissue blocks from 50 patients. It will take an estimated 12 months to review the casenotes of around 250 biologics treated patients, with and without lymphoma, in 40-50 hospitals to determine cumulative disease activity.

Additional work for the consultant / rheumatology specialist nurse entails retrieving case notes for the above patients.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.
Whilst it is not mandatory to obtain consent to review material collected prior to September 1st 2006, we intend to obtain written consent from all patients that are still alive at the time of requesting the pathological specimen. However, in patients that are deceased it is impractical for us to seek consent from the next of kin since we do not record their contact details. Furthermore, we feel that it may be distressing to the next of kin to seek permission.
Written consent will be requested from patients as detailed below:

1. **Live patients:** For use of retrospectively archived material we propose sending a letter to the patient's Rheumatology consultant, which they will then copy onto their own headed paper and send to patients on our behalf endorsing their approval of the project (Appendix B). An information leaflet explaining the project in detail and a consent form will be enclosed (see Appendices D and E) of the study protocol). Patients will be invited to contact Dr Louise Mercer or Dr Kimme Hyrich at the BSRBR, and are also advised they may discuss the project with their Rheumatologist or Specialist Nurse. Patients will be asked to give or withhold informed consent for use of their tissue on the enclosed consent form.
2. **Dead patients:** We do not wish to write to the relatives of dead patients for the following reasons:

    1. Request for written consent from relatives may provoke emotional distress, particularly if they were recently bereaved.
    2. Tests will be carried out on tumour tissue (not organs) previously removed at surgery for the purpose of patient assessment and management. This archived material is stored for future confirmation of diagnosis and comparison with secondary or other tumours that may develop; at completion of the proposed study, sufficient tissue will remain for this purpose.
    3. Patients will not be directly involved in the research.
    4. Tissue, including correlation of clinical and pathological findings, will be anonymised.
    5. The results of this research will not pose any risk of adverse effect on the patient or their relatives.
    6. We do not keep records of next of kin details.

The BSRBR includes the mortality status of patients. Where there is doubt, we will first contact the patient's consultant to establish whether the patient is still alive.

List of enclosed documents

Document	*Version*	*Date*
Appendix A: Letter to consultant	1	10th August 2009
Appendix B: Letter to patient	1	10th August 2009
Appendix C: Letter to Pathologist	1	10th August 2009
Appendix D: Patient information sheet	1	10th August 2009
Appendix E: Patient consent form	1	10th August 2009

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: .....

Notice of amendment (non-CTIMP), version 3.1, November 2005

Print name:	.....
Date of submission:	.....

Reference List

(1) Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis.[see comment]. Arthritis Research & Therapy 2008;10(2):R45.

(2) Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis.[see comment]. Arthritis & Rheumatism 2006 Mar;54(3):692-701.

(3) Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999 Dec 4;354(9194):1932-9.

(4) Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. 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.[see comment][erratum appears in Arthritis Rheum. 2003 Mar;48(3):855]. Arthritis & Rheumatism 2003 Jan;48(1):35-45.

(5) Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet 2004 Feb 28;363(9410):675-81.

(6) Balkwill F. Tumor necrosis factor or tumor promoting factor?. [Review] [89 refs]. Cytokine & Growth Factor Reviews 2002 Apr;13(2):135-41.

(7) Lienard D, Eggermont AM, Koops HS, Kroon B, Towse G, Hiemstra S, et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. Melanoma Research 1999 Oct;9(5):491-502.

(8) Eggermont AM, Schraffordt KH, Klausner JM, Kroon BB, Schlag PM, Lienard D, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Annals of Surgery 1996 May;224(6):756-64.

BSR Biologics Register
Biologic Studies Group
Unit 4 Rutherford House
Manchester Science Park
Manchester
M15 6SZ

17/05/2011

Helen Penistone
North West 5 REC - Haydock Park
North West Centre of Research Ethics Committees
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Dear Helen,

Re: MREC 08/8/53 PROSPECTIVE OBSERVATIONAL STUDY OF THE LONG-TERM HAZARDS OF BIOLOGIC THERAPY IN RHEUAMTIC CONDITIONS
Notification of Non-Substantial Amendment

I am writing to inform you of a non-substantial amendment to the above study. On 4th September 2009, a substantial amendment was approved to determine the subtypes of lymphoma in the biologics cohort by reclassifying them in accordance with the World Health Organisation classification. We would now like to extend this part of the study to also include patients that have not been treated with anti-TNF therapy. Doing so will allow us to make comparisons with the anti-TNF cohort to see what effect, if any, these drugs are having on subtypes of lymphoma.

Please find enclosed a copy of the substantial amendment approved in September 2009, approval letter and appendices containing letters and information to be sent to patients and clinicians involved:

Document	Version (if applicable) and Date
Notice_of_Substantial_Amendment_090810_lymphoma.doc	10/08/2009
Lymphoma MREC_SA_approval_Sept09.pdf	04/09/2009
Appendix A Letter to Rheumatologist (live patient)_110517.doc	1.1, 17/05/2011
Appendix B Letter to patient_110517.doc	1.1, 17/05/2011
Appendix C Letter to pathologist_090810.doc	1, 10/08/2009
Appendix D patient information sheet_110517.doc	1.1, 17/05/2011
Appendix E Patient consent form_090810.doc	1, 10/08/2009

Please do not hesitate to contact me if you have any questions regarding this non-substantial amendment.

Yours sincerely,

Dr Louise Mercer
Clinical Research Fellow
Louise.mercer@manchester.ac.uk
0161 275 7330

Dr Kath Watson
Manager of Pharmacovigilance Studies
kath.watson@manchester.ac.uk
0161 306 1898

BSRBR
The British Society for Rheumatology Biologics Register

Louise.Mercer@manchester.ac.uk
Date

Dear <constitle> <conssurname>

Many thanks for your ongoing support of the BSR Biologics Register. We are writing to you now because it has been reported that one of your patients with rheumatoid arthritis has developed a lymphoma. As you will know, the risk of lymphoma is increased in patients with RA, and this increased risk is related to cumulative disease activity. Any additional risk from treatment with anti-TNF therapy remains unknown. With the support of the BSR, we are planning an analysis to look at the rate and subtypes of lymphoma in the BSRBR. We will then be able to look at predictors of outcome and mortality by exploring factors such as disease activity and response to anti-TNF treatment. This will be of benefit to all of us who treat these patients as well as allowing us to provide better information to patients about the potential risks and benefits of these therapies.

This analysis will consist of two parts. In the first part, we are endeavouring to have all of the tissue blocks from patients on the biologics register with an incident lymphoma reviewed by an independent Histopathologist from the Manchester Lymphoma Group, at the University of Manchester. Remaining tissue blocks will then be returned after this review.

In the second part of the analysis, we want to determine the influence of cumulative disease activity on risk of lymphoma in anti-TNF treated patients. In order to do this, we will need to look at disease activity from diagnosis of RA until diagnosis of lymphoma. To establish this we are conducting a nested case-control study, and matching each anti-TNF-treated patient with lymphoma to 4 anti-TNF treated patients who have not developed a lymphoma (controls). To reduce confounding cases will be matched to controls treated by the same Rheumatology Department. Cumulative disease activity will be determined by case notes review. We would be grateful for your permission for access to patients' medical notes, in order to obtain clinically relevant information, which will be anonymously related to laboratory findings.

We will require consent to obtain tissue blocks from patients who are still alive. To facilitate this, we have enclosed details of patients who are still alive (according to our records) and under your care whom we wish, with your agreement, to include in our study. We have attached a covering letter which we would need you to send to your

Consultant letter, version 1.1 for MREC 17/05/2011

patient, a patient information sheet and a patient consent form. It would be very helpful for us if you could arrange to send this letter, printed on your stationary, together with a copy of the attached patient information leaflet, consent form and stamped addressed envelope in which each patient can send their completed consent form back to us directly. In this way we, and patients, can be assured of your support of the project. The patient information sheet contains additional contact information for two physicians at the BSR Biologics Register whom patients can also contact with any additional concerns or questions. If requested to, we will send you an electronic copy of the covering letter to be sent to your patient that can then we printed on your department's headed notepaper.

We will not need consent from relatives of deceased patients.

In order to facilitate the collection of the tissue block, we would be grateful if you could supply us with copies of any histology reports that are stored in the patient's case notes along with the contact details of the patient's oncologist, the reporting pathologist, or both. If necessary, we will arrange any additional ethics and R&D applications if the patient was treated at a different hospital. We have attached a short questionnaire which clarifies what additional information we will require. Please indicate on the form if "not known".

This amendment has been approved by North West MREC.

We appreciate that pulling files and chasing results is a time consuming process. We are most grateful to you for your ongoing support of the register and particularly with these additional requests for further information. We will contact you again in the near future with further details of our nested case-control study.

Many thanks for your help.

Yours sincerely,

Dr Louise Mercer
Clinical Research Fellow, BSRBR
0161 2751615

Dr Kimme Hyrich
Principal Investigator, BSRBR
0161 2755044 (Secretary)

Consultant letter, version 1.1 for MREC 17/05/2011

BSRBR
The British Society for Rheumatology Biologics Register

Please fax to Dr Louise Mercer, BSRBR on 0161 2751640 or post to BSR Biologics Register, Rutherford House, 40 Pencroft Way, Manchester Science Park, Manchester, M15 6SZ

If you have any questions regarding this form please call the Register office on 0161 275 1613

PATIENT:	**BSRBR ID:**
HRN:	**DOB:**
EVENT:	**EVENT DATE:**

At which hospital was the lymphoma diagnosed (tissue obtained)?

.....

What was the name of the reporting Pathologist?

.....

At which hospital was the lymphoma treated?

.....

What was the name of the treating Oncologist?

.....

If available, please would you also attach a copy of the histopathology report since this may provide additional information that may be helpful when requesting the lymphoma tissue block.

Patient letter, version 1.1 for MREC 17/05/2011

<Date>

Dear <patient name>

I am writing to you on behalf of clinical researchers at the British Society for Rheumatology (BSR) Biologics Register at The University of Manchester. Your participation in the BSR Biologics Register is very much valued. So far this study has already contributed considerably to our knowledge of the long term safety of drugs used to treat rheumatoid arthritis. One of the most important questions that we hope to answer is whether biologic treatments, including anti-TNF, might influence the risk of developing lymphoma. Researchers at the BSR Biologics Register are currently addressing this question and have asked me to contact you and ask whether you are willing to take part in this study.

It is important that you know that the investigators will not ask you to participate in the research directly, and that the results of the research will neither adversely affect you nor your future medical care, if you decide that you do not wish to be included.

I have given my permission for the study to include my patients, and have been asked to forward the enclosed 'Patient Information Leaflet', which gives more information. Please take a few moments to read this.

We hope that the study will help us understand more about lymphomas in patients with rheumatoid arthritis and by publishing the results of the study will help rheumatologists in treating patients with rheumatoid arthritis safely in the future.

If you have any questions or concerns, you can contact the Rheumatology Department. Alternatively, you may also contact either Dr Louise Mercer or Dr Kimme Hyrich at the BSR Biologics Register (contact details on the patient information sheet). You may also wish to discuss this with your GP.

Many thanks for your help.

Yours sincerely,

(Consultant name)

BSRBR
The British Society for Rheumatology Biologics Register

PATIENT INFORMATION SHEET

Study Title: Safety of long-term anti-TNF use, with respect to lymphoma, in the BSR Biologics Register

The BSR Biologics Register is the largest register of its kind worldwide and the information provided by patients and their consultants has contributed considerably to our knowledge of the biologic anti-TNF drugs. In addition to collecting information from yourself and your consultant we are now collecting further information on lymphomas that have occurred in patients who are registered with the BSR Biologics Register.

You are being invited to take part in this additional part of the BSR Biologics Register since our records show that you have had a lymphoma. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your Rheumatologist or Rheumatology Specialist Nurse if you wish. Ask us if there is anything that is not clear or if you would like more information. Take as much time as you need to decide whether you wish to take part.

What is the purpose of the study?

We already know that some people with rheumatoid arthritis have a small increased chance of developing a lymphoma compared to people without rheumatoid arthritis. We also know that in the majority of patients anti-TNF drugs such as etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade) are effective in controlling the symptoms of rheumatoid arthritis. The purpose of this study is to find out whether the anti-TNF drugs have any effect on the risk of developing lymphoma. There may be a decrease in risk, an increase in risk, or no change. Using the follow up forms you and your consultant send to us as part of the main study, we will also be looking to see if the way that patients respond to anti-TNF drugs affects this risk. There are many different types of lymphoma and we would also like to know if the types of lymphoma that develop in people with arthritis, or in those who have received anti-TNF drugs, are different from those who do not have arthritis. For this reason we will be looking at lymphomas that have occurred in patients that have not received anti-TNF drugs as well as those that have.

Why Have I been chosen?

We have identified your name from our files at the BSR Biologics Register as somebody who has had a lymphoma whilst registered with us.

Do I have to take part?

Your decision to take part is entirely your own. If you decide to take part you will be asked to sign and return a consent form in the pre paid envelope provided. Having decided to take part you are still free to withdraw your consent at any time without giving a reason. This will not affect your future care in any way.

Patient information sheet, version 1.1 for MREC 17/05/2011

What will happen if I take part?

Most importantly, you will not be directly participating in the study. All the tests we need to carry out will be performed by using small samples of your lymphoma which would have been removed at the time of biopsy/surgery and saved at the hospital. This tissue helped with your diagnosis and treatment at the time and is routinely stored for future reference. Only a small amount of tissue will be needed, and the rest of the tissue will be returned to storage as before. Sections of your medical notes will need to be looked at by responsible members of the research team to obtain information related to your tissue and your rheumatoid arthritis. We have written to your consultant informing them that we have contacted you for the study.

What tests will be performed?

Standard laboratory tests will be carried out on the tumour tissue so that we can learn about the types of lymphomas that people with rheumatoid arthritis get.

How will the results of the research affect me?

The results will not adversely affect or benefit you directly in any way, and will not impact on your current medical care. However, the results may benefit the management of rheumatoid arthritis in the future.

Will my participation in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the BSR Biologics Register will have your name and address removed so that you cannot be recognised from it. The results of the research will be kept separate from your medical records. Individuals from The University of Manchester, from regulatory authorities or from relevant NHS Trusts will have access to the personal data in order to monitor and audit the conduct of the study.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact details below). If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact the University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email too research-governance@manchester.ac.uk.

What will happen to the results of the research study?

The results will be analysed and presented for publication and possibly at scientific meetings in order to share useful information with colleagues in similar fields of work/study. Your personal details will not be identified in any reports, presentations or meetings. If you wish you may contact us at the end of the research. Neither you nor your doctor will be paid for including you in the study.

Who has reviewed the study?

Patient information sheet, version 1.1 for MREC 17/05/2011

The North West Research Ethics Committee has reviewed the study, and given appropriate ethical approval to proceed.

Please feel free to contact us at any time for further information

Dr Louise Mercer
Arc Epidemiology Unit
Stopford Building
University of Manchester
Oxford Road
Manchester M13 9PT
Tel 0161 2751615

Dr Kimme Hyrich
Arc Epidemiology Unit
Stopford Building
University of Manchester
Oxford Road
Manchester M13 9PT
Tel 0161 2755044 (secretary)

Consent form, version 1.1 for MREC 17/05/11

BSRBR
The British Society for Rheumatology Biologics Register

CONSENT FORM

Title of Project: **Safety of long term anti-TNF use, with respect to lymphoma, in the BSR Biologics Register**

Name of Researchers: Dr Louise Mercer, Dr Kimme Hyrich, Dr Richard Byers, Prof Deborah Symmons

Please initial box

1. I confirm I have read and understand the information sheet dated May 2011 (version 1.1) for the above study and have had the opportunity to ask questions ☐

2. I understand that giving my permission to use my tissue (lymph node, blood and bone marrow) is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I give permission for my tissue to be used in the above study. ☐

4. I understand that personal data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

Name of patient	Date	Signature
----------	----------	----------

Please keep one copy for your own record and return 2 copies in the stamped addressed envelope enclosed (1 for BSR Biologics Register researcher, 1 for hospital notes).

(BSRBR headed paper)

Louise.Mercer@manchester.ac.uk
Date

Dear (Pathologist)

The BSR Biologics Register (BSRBR) is a longitudinal observational study that was established in 2001 by the British Society for Rheumatology (BSR) to develop an extensive register of 12000 patients receiving anti-TNF therapy for RA, as well as 4000 patients treated with traditional drugs (DMARDs). Detailed information is collected on each patient regarding serious adverse events in order to determine the longterm safety of the drugs. One of the main outcomes of this study is the occurrence of lymphoma.

It is known that there is a two fold increase in lymphoma in patients with RA. There is a suggestion from previously published work that large B cell lymphomas may be over represented in RA. The BSRBR provides a unique opportunity to determine the influence of anti-TNF drugs on lymphoma rate, subtype and outcome. We are endeavouring to have all of the lymphomas reported in our study reviewed by an independent Histopathologist in order to ensure consistent reporting within our study.

We are writing to you now about the possible loan of a tissue block on a patient who was diagnosed with lymphoma in your institution.

Details of patients treated in your hospital and included in our study are given on the enclosed forms. We would be grateful for the loan of representative paraffin blocks of tumour material and histology reports. We have obtained patient consent from those patients who were still alive at the time of this analysis. Sections will be cut from the blocks for H&E staining, immunohistochemistry and tested for EBV. All material will be handled with care, and returned to you upon completion of our analysis.

The project is being conducted at the University of Manchester by Dr Louise Mercer, Clinical Research Fellow, and Dr Kimme Hyrich, Senior Lecturer, for the BSRBR, in conjunction with Dr Richard Byers, Senior Lecturer in Pathology, University of Manchester.

Please contact Dr Louise Mercer, or either of the other investigators, if you have any questions or concerns regarding the proposed project, any suggestions or comments.

Pathologist letter, version 1 for MREC 10/08/09

Many thanks for your help.

Yours sincerely,

Dr Louise Mercer
Arc Epidemiology Unit
Stopford Building
University of Manchester
Oxford Road
Manchester M13 9PT

0161 2751615

Dr Kimme Hyrich
Arc Epidemiology Unit
Stopford Building
University of Manchester
Oxford Road
Manchester M13 9PT

0161 275 1642 (secretary)

Dr Richard Byers
Department of Histopathology
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

0161 276 8816

Details of the patient for whom we are requesting the loan of a lymphoma tissue block

Name: BSRBR Study number:

Date of birth:

Hospital number:

Date of removal of lymphoma tissue from the patient:

Tissue block number (if known):

Please complete the section below indicating to whom you wish the remaining tissue block to be returned on completion of the study.

Name:

Hospital address, including department:

Please send the tissue block with this form to:

Dr Richard Byers

Department of Histopathology

Manchester Royal Infirmary

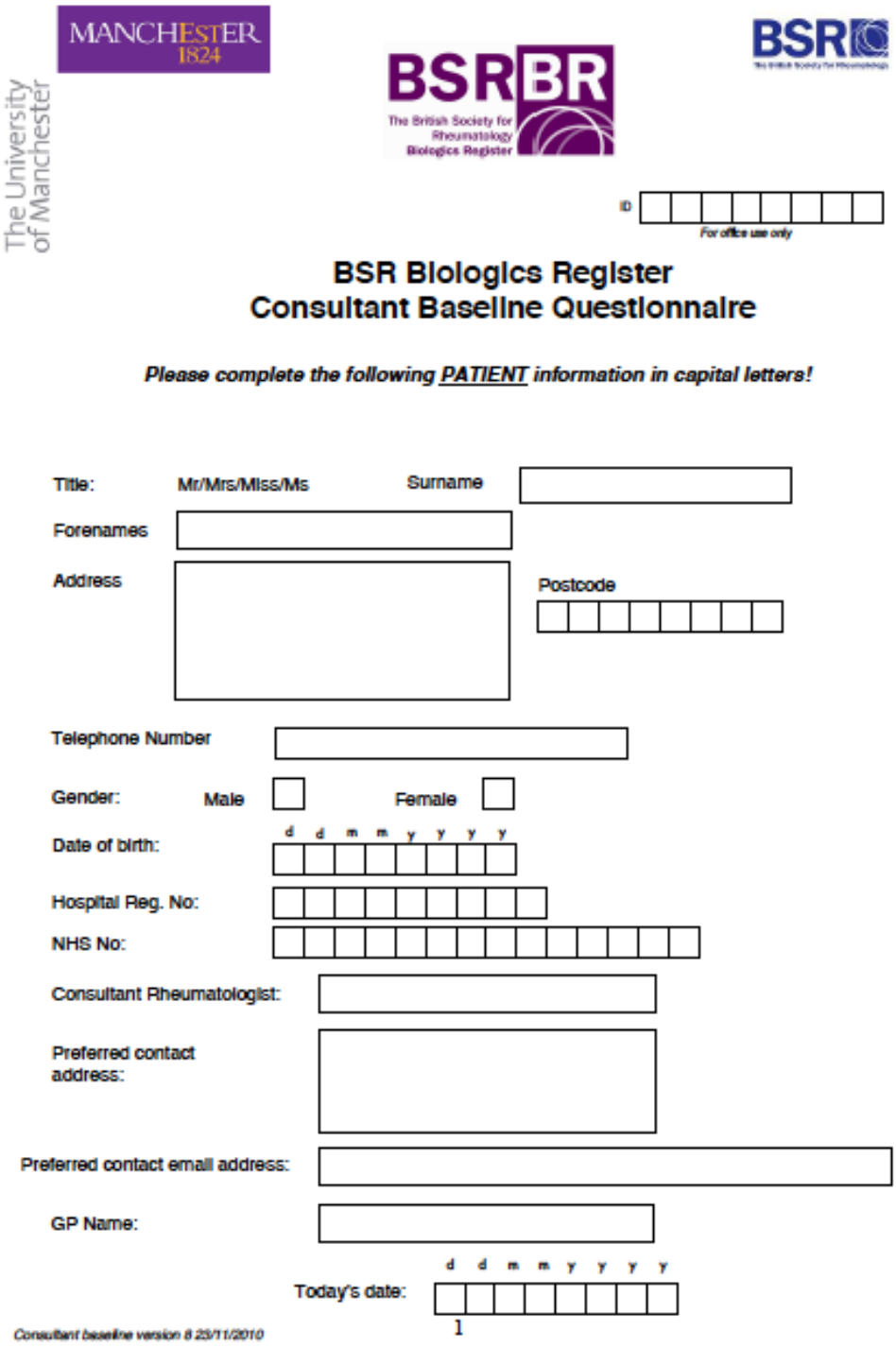
Oxford Road

Manchester M13 9WL

Appendix 3. The BSRBR Control Centre Consortium

The BSRBR Control Centre Consortium consisted of the following institutions at the time of commencing this research (all in the UK): Antrim Area Hospital, Antrim (Dr Nicola Maiden), Cannock Chase Hospital, Cannock Chase (Dr Tom Price), Christchurch Hospital, Christchurch (Dr Neil Hopkinson), Royal Derby Hospital, Derby (Dr Sheila O'Reilly), Dewsbury and District Hospital, Dewsbury (Dr Lesley Hordon), Freeman Hospital, Newcastle-upon-Tyne (Dr Ian Griffiths), Gartnavel General Hospital, Glasgow (Dr Duncan Porter), Glasgow Royal Infirmary, Glasgow (Prof Hilary Capell), Haywood Hospital, Stoke-on-Trent (Dr Andy Hassell), Hope Hospital, Salford (Dr Romela Benitha), King's College Hospital, London (Dr Ernest Choy), Kings Mill Centre, Sutton-In Ashfield (Dr David Walsh), Leeds General Infirmary, Leeds (Prof Paul Emery), Macclesfield District General Hospital, Macclesfield (Dr Susan Knight), Manchester Royal Infirmary, Manchester (Prof Ian Bruce), Musgrave Park Hospital, Belfast (Dr Allister Taggart), Norfolk and Norwich University Hospital, Norwich (Prof David Scott), Poole General Hospital, Poole (Dr Paul Thompson), Queen Alexandra Hospital, Portsmouth (Dr Fiona McCrae), Royal Glamorgan Hospital, Glamorgan (Dr Rhian Goodfellow), Russells Hall Hospital, Dudley (Prof George Kitas), Selly Oak Hospital, Selly Oak (Dr Ronald Jubb), St Helens Hospital, St Helens (Dr Rikki Abernethy), Weston General Hospital, Weston-super-Mare (Dr Shane Clarke/Dr Sandra Green), Wythenshawe Hospital, Manchester (Dr Paul Sanders), Withybush General Hospital, Haverfordwest (Dr Amanda Coulson), North Manchester General Hospital (Dr Bev Harrison), Royal Lancaster Infirmary (Dr Marwan Bukhari) and The Royal Oldham Hospital (Dr Peter Klimiuk).

Appendix 4. Consultant baseline questionnaire



MANCHESTER 1824

The University of Manchester

BSRBR The British Society for Rheumatology Biologics Register

BSR

ID

For office use only

BSR Biologics Register
Consultant Baseline Questionnaire

Please complete the following PATIENT information in capital letters!

Title: Mr/Mrs/Miss/Ms Surname

Forenames

Address

Postcode

Telephone Number

Gender: Male Female

Date of birth: d d m m y y y y

Hospital Reg. No:

NHS No:

Consultant Rheumatologist:

Preferred contact address:

Preferred contact email address:

GP Name:

Today's date: d d m m y y y y

1

Consultant baseline version 8 23/11/2010

1. Does the patient have rheumatoid arthritis? Yes ☐ No ☐

If NO, can you specify the other diagnosis? ☐

2. Please complete the following details:

Year of diagnosis ☐☐☐☐ (y y y y)

Year first seen by a rheumatologist ☐☐☐☐ (y y y y)

3. ACR Criteria (please tick all that apply)

☐ Morning stiffness >1 hour (ever)

☐ Arthritis or deformity/damage of three or more joint areas (PIP, MCP, wrist, elbow, knee, ankle, MTP) (now)

☐ Arthritis/deformity of hand/joint (now)

☐ Symmetry

☐ Nodules (ever)

☐ Rheumatoid factor positive (≥ 1/40) (ever)

☐ Erosions on hand or feet x-ray

4. Systemic features: Has the patient ever had any of the following? (please tick all that apply)

☐ Sicca syndrome

☐ Serosal involvement (pleurisy/pericarditis)

☐ Eye involvement

☐ Systemic vasculitis

☐ Nailfold vasculitis

☐ Pulmonary fibrosis

☐ Other (please specify) _____

5. Joint replacements/surgery: Has the patient ever had any of the following?

	Unilateral	Bilateral
Total knee replacement		
Total hip replacement		
Total shoulder replacement		
Total elbow replacement		
Wrist/hand/ankle/foot surgery		
Neck surgery		

Id ☐☐☐☐☐☐☐☐

For office use only

6. Please indicate the current disease activity (i.e. at the time the patient started the new drug)

28 tender joint count		
28 swollen joint count		
ESR <u>OR</u>		
CRP		
Patient global assessment (VAS) (out of 100)		mm

7. Drug therapy: Please list all the patient's <u>current</u> treatment, for any indication

8. New drug therapy: Is the patient about to start/ has just started:

Biologic therapy? Yes ☐ ⇨ Go to 8a) / No ☐ ⇨ Go to 9

8a) Which biologic has the patient started?

Etanercept ☐ 1 | Infliximab ☐ 2 | Anakinra ☐ 3 | Adalimumab ☐ 4 | Rituximab ☐ 5 | Tocilizumab ☐ 6 | Certolizumab ☐ 7

Other ☐ Please specify _____

Please indicate the date of first biologic therapy dose: d d m m y y ☐☐☐☐☐☐

Please also indicate the average dose: ☐ mg ☐ Frequency

Is the patient still on biologic therapy? Yes ☐ 1 / No ☐ 0 — If NO, please give details on a separate sheet

Is this the patient's first exposure to a biologic agent? Yes ☐ / No ☐ — If NO, please give details on a separate sheet

9. New drug therapy: Is the patient about to start/ has just started/ or is continuing:

New DMARD therapy? Yes ☐ ⇨ Go to 9a) / No ☐ ⇨ Go to 10

9a) If yes, please indicate which DMARD(s) and current dose

DMARD Started	(Please Tick)	mg	Frequency	Date Started (d d m m y y)
Methotrexate				
Azathioprine				
Cyclophosphamide				
Cyclosporine				
Leflunomide				
Other_____				
Other _____				

10. Previous second-line drug therapy:

Has the patient EVER had any of the following drugs?

	Yes	No	Don't know
IM Gold			
Auranofin			
Penicillamine			
Sulphasalazine			
Chlor/HCQ			
Steroids			

We would now like to know more details about certain drugs:

	Yes	No	Don't know	1st Course Date started: Month	1st Course Date started: Year	1st Course Date stopped: Month	1st Course Date stopped: Year	2nd Course Date started: Month	2nd Course Date started: Year	2nd Course Date stopped: Month	2nd Course Date stopped: Year
Methotrexate											
Azathioprine											
Cyclophosphamide											
Cyclosporine											
Leflunomide											
Other, please specify											

If patient has started or stopped the same drug more than twice please give details on an additional sheet
(Do not include stopping a drug for less than three months)

For psoriatic arthritis patients only:

Has the patient EVER had PUVA therapy? Yes ☐ No ☐

If yes please record cumulative dose: ☐ joules/cm²

11. Co-morbidity:

Has the patient ever had (i.e. required treatment for) any of the following illnesses? Please tick all that apply

	Yes	No	Don't know	Year of onset
High blood pressure				
Angina				
Heart attack				
Stroke				
Epilepsy				
Asthma				
Chronic bronchitis/emphysema				
Peptic ulcer				
Liver disease				
Renal disease				
TB				
Demyelination				
Diabetes[¶]				
Hyperthyroidism				
Depression				
Cancer[‡]				

Other co-morbidity not listed _____

_____

_____

[‡]If the patient has cancer please specify site(s):

[¶]If the patient is diabetic is (s)he:

Insulin dependent ☐ Tablet controlled ☐ Diet controlled ☐

ID

For office use only

12. Smoking status: is the patient a:

Current smoker	☐
Ex-smoker	☐
Never-smoked	☐

13. Blood pressure: what is the patient's current (i.e. at the time that the biologic agent was started) blood pressure?

Systolic	☐☐☐	mm
Diastolic	☐☐☐	mm

14. Height and weight: what is the patient's current (i.e. at the time that the biologic agent was started) height and weight?

Weight	☐☐☐	kg
Height	☐☐☐	cm

15. Did the patient have a chest x-ray prior to starting the new therapy?

Yes	☐
No	☐

This form should be accompanied by the following pre-biologic agent patient completed questionnaires:

HAQ	☐
EQ-5D	☐

Thank you for completing this questionnaire - we will never ask this many questions again!

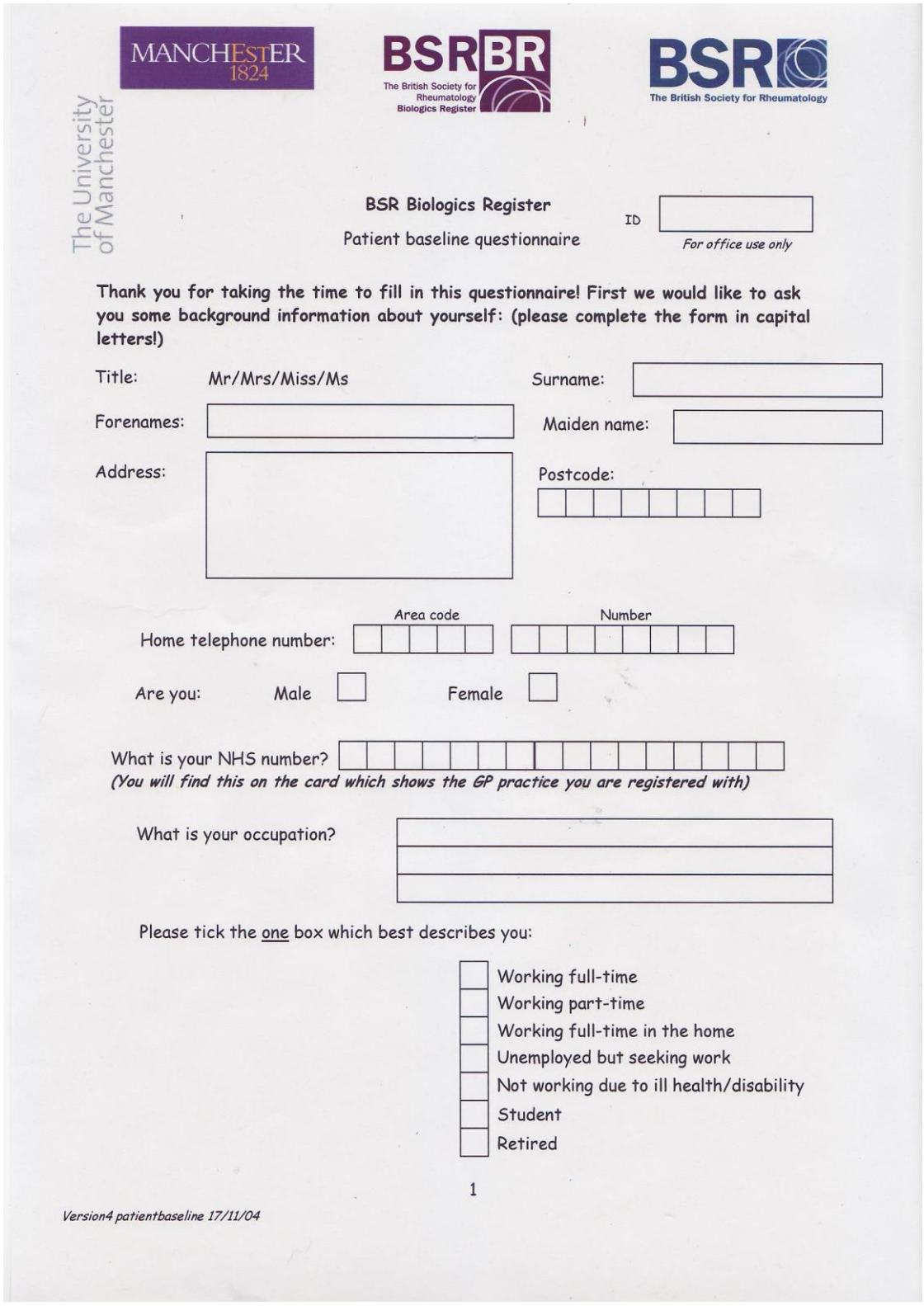
Please return to:

BSRBR
Arthritis Research UK Epidemiology Unit
Unit 4 Rutherford House
Manchester Science Park
40 Pencroft Way
Manchester
M15 6SZ

Ib ☐☐☐☐☐☐☐☐☐

For office use only

Appendix 5. Patient baseline questionnaire



MANCHESTER 1824

The University of Manchester

BSRBR The British Society for Rheumatology Biologics Register

BSR The British Society for Rheumatology

BSR Biologics Register

Patient baseline questionnaire

ID

For office use only

Thank you for taking the time to fill in this questionnaire! First we would like to ask you some background information about yourself: (please complete the form in capital letters!)

Title: Mr/Mrs/Miss/Ms

Surname:

Forenames:

Maiden name:

Address:

Postcode:

Home telephone number: Area code Number

Are you: Male Female

What is your NHS number?

(You will find this on the card which shows the GP practice you are registered with)

What is your occupation?

Please tick the one box which best describes you:

- Working full-time
- Working part-time
- Working full-time in the home
- Unemployed but seeking work
- Not working due to ill health/disability
- Student
- Retired

1

Version4 patientbaseline 17/11/04

What is your date of birth? d d m m y y y y

Where were you born?

Town: Country:

Which of these ethnic groups do you belong to?

- White
- Black-African
- Black-Caribbean
- Black-British
- Black-other
- Indian
- Pakistani
- Bangladeshi
- Chinese
- Other — Please specify

Have you EVER smoked more than one cigarette a day? Yes 1 / No 0

If you have <u>ever</u> smoked, what was the average number of cigarettes /day? cigarettes/day

Age started smoking years

Age stopped smoking years

Do you CURRENTLY smoke more than one cigarette a day? Yes 1 / No 0

If YES, how many cigarettes do you smoke each day? cigarettes/day

How many of the following do you drink in an <u>average week</u>?

Pints of beer / lager

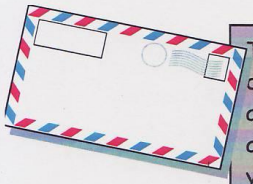
Glasses of wine

Glasses of spirits

The following question is for patients with Psoriatic Arthritis <u>ONLY</u>:

Have you <u>EVER</u> had PUVA (Psoralens & Ultraviolet A) therapy? Yes 1 / No 0

If yes, how many sessions have you had (if known)?



This study will continue for five years. It is important that we keep in touch with you during that time. We have enclosed a post card for you to send us to tell us your new address if you move. It would be helpful if you could give us the name and address of a close relative or friend who is likely to know your new address if you move (in case you forget!) We will not contact them for any other reason.

Close relative/friend details:

Title: Mr/Mrs/Miss/Ms Surname

Forenames

Address

Postcode

Your signature:

Today's date: d d m m y y y y

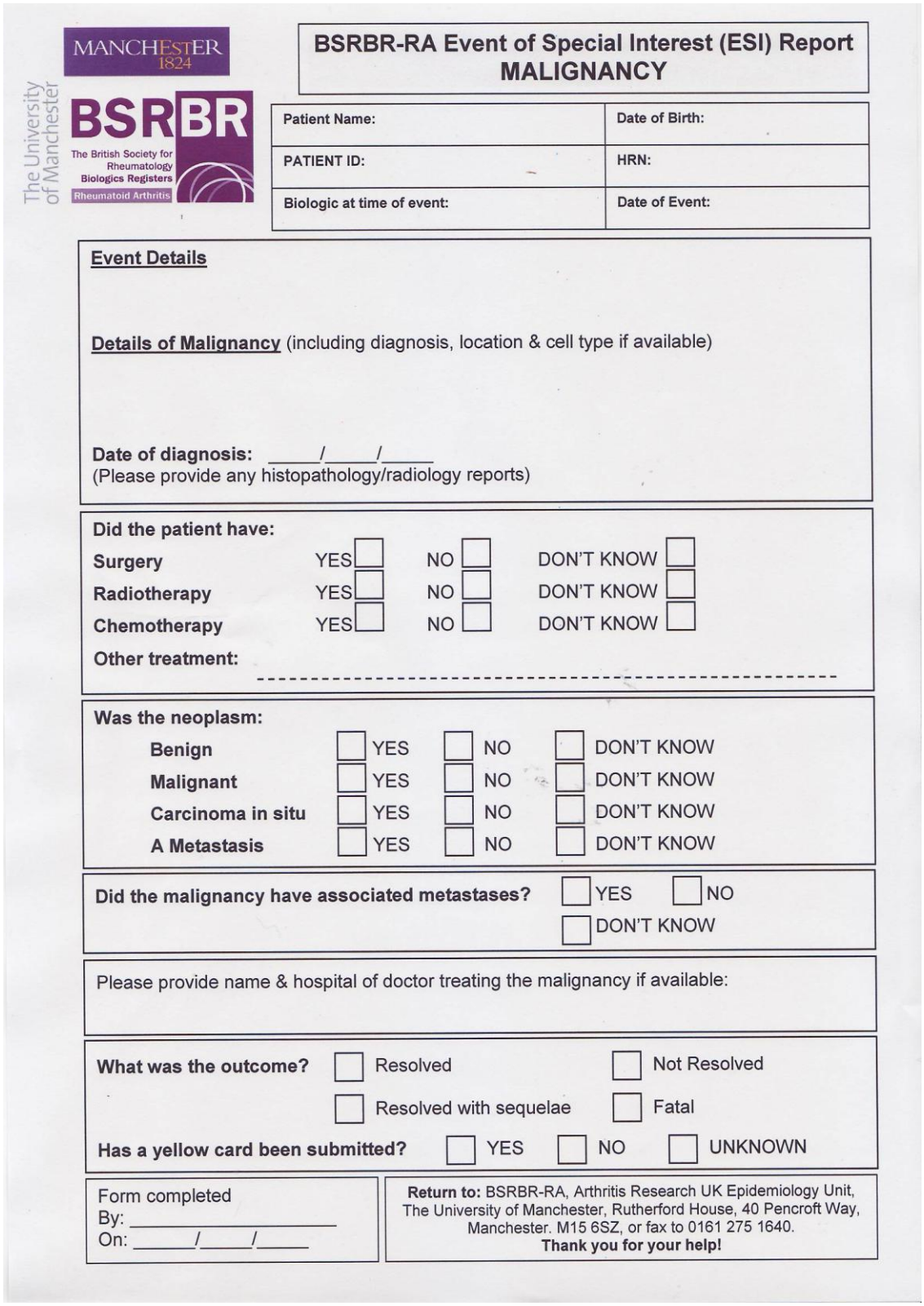
Thank you for taking the time to fill in this questionnaire. Please return it now to: (in the pre-paid envelope provided)

Kath Watson: BSRBR Study Co-ordinator
ARC Epidemiology Unit
Stopford Building
The University of Manchester
Oxford Road
Manchester
M13 9PT

ID

For office use only

Appendix 6. Event of special interest forms for malignancy and lymphoproliferative malignancy



MANCHESTER 1824

The University of Manchester

BSRBR

The British Society for Rheumatology Biologics Registers

Rheumatoid Arthritis

BSRBR-RA Event of Special Interest (ESI) Report
MALIGNANCY

Patient Name:	**Date of Birth:**
PATIENT ID:	**HRN:**
Biologic at time of event:	**Date of Event:**

Event Details

Details of Malignancy (including diagnosis, location & cell type if available)

Date of diagnosis: _____/_____/_____
(Please provide any histopathology/radiology reports)

Did the patient have:

Surgery	YES ☐	NO ☐	DON'T KNOW ☐
Radiotherapy	YES ☐	NO ☐	DON'T KNOW ☐
Chemotherapy	YES ☐	NO ☐	DON'T KNOW ☐

Other treatment: ----------

Was the neoplasm:

Benign	☐ YES	☐ NO	☐ DON'T KNOW
Malignant	☐ YES	☐ NO	☐ DON'T KNOW
Carcinoma in situ	☐ YES	☐ NO	☐ DON'T KNOW
A Metastasis	☐ YES	☐ NO	☐ DON'T KNOW

Did the malignancy have associated metastases? ☐ YES ☐ NO ☐ DON'T KNOW

Please provide name & hospital of doctor treating the malignancy if available:

What was the outcome? ☐ Resolved ☐ Not Resolved ☐ Resolved with sequelae ☐ Fatal

Has a yellow card been submitted? ☐ YES ☐ NO ☐ UNKNOWN

Form completed
By: _____
On: _____/_____/_____

Return to: BSRBR-RA, Arthritis Research UK Epidemiology Unit, The University of Manchester, Rutherford House, 40 Pencroft Way, Manchester. M15 6SZ, or fax to 0161 275 1640.
Thank you for your help!

MANCHESTER 1824

The University of Manchester

BSRBR
The British Society for Rheumatology Biologics Registers
Rheumatoid Arthritis

BSRBR-RA Event of Special Interest (ESI) Report
LYMPHOPROLIFERATIVE MALIGNANCY

Patient Name:	**Date of Birth:**
PATIENT ID:	**HRN:**
Biologic at time of event:	**Date of Event:**

Event Details (please annotate with any additional information)

What was the diagnosis? (Please include site)

Histopathological classification & Staging/ Radiology: (If known, please enclose a copy of the results)

Treatment Regime:

Withdrawal of MTX, no other treatment given ☐

Withdrawal of Anti TNF, no other treatment given ☐

☐ Surgery ☐ Chemo regime ☐ Rituximab ☐ Radiotherapy

Tissue EBV Status: ☐ Positive ☐ Negative ☐ Unknown

Past history of Sjögren's disease? ☐ YES ☐ NO ☐ DON'T KNOW

Please provide name & hospital of doctor treating the malignancy if available:

Positive family history of cancer? ☐ YES ☐ NO ☐ DON'T KNOW

What was the outcome? ☐ Resolved ☐ Not Resolved

☐ Resolved with sequelae ☐ Fatal

Has a yellow card been submitted? ☐ YES ☐ NO ☐ UNKNOWN

Form completed
By: _____
On: _____/_____/_____

Return to: BSRBR-RA, Arthritis Research UK Epidemiology Unit, The University of Manchester, Rutherford House, 40 Pencroft Way, Manchester. M15 6SZ, or fax to 0161 275 1640.
Thank you for your help!