An Investigation into the Risk of Cancer in Patients with Psoriasis treated with Biologic Therapy

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Contents

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List of Abbreviations

BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic and Immunomodulators Register
BMI	Body Mass Index
BSA	Body Surface Area
CPRD	Clinical Practice Research Datalink
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
ESI	Event of Special Interest
FAEs	Fumaric Acid Esters
HLGT	Higher Level Group Term
HLT	Higher Level Term
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
IBD	Inflammatory Bowel Disease
IL	Interleukin
IQR	Interquartile Range
IRR	Incidence Rate Ratio
KC	Keratinocyte Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio

PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PsA	Psoriatic Arthritis
PSD	Propensity Score Decile
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PT	Preferred Term
PUVA	Psoralen plus Ultraviolet A
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
ROI	Republic of Ireland
RR	Relative Risk
SIGN	Scottish Intercollegiate Guidelines Network
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality ratio
SOC	System Organ Class
Th	T-helper
TNF	Tumour Necrosis Factor
TNFi	Tumour Necrosis Factor inhibitor
UK	United Kingdom
USA	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B
WHO	World Health Organisation

Abstract

Aims: The broad aim of this thesis was to explore the risk of cancer in patients with psoriasis treated with biologic therapy, who were previously treated with non-biologic systemic therapy, compared with patients treated with non-biologic systemic therapy only.

Methods: Cohort studies of patients with chronic-plaque psoriasis treated with biologic therapy compared with patients with psoriasis treated with only non-biologic systemic therapy registered to the British Association of Dermatologists Biologic and Immunomodulators Register were performed. Risk of the following cancer outcomes were explored: all cancer (excluding keratinocyte carcinoma [KC]), cancers of infectious origin, common site-specific cancer (lung, breast, prostate), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Propensity-score decile adjusted Cox-proportional hazards models were performed to compare risk of developing the cancer outcomes between the biologic cohort and the non-biologic systemic cohort, adjusting for differences in baseline confounders.

Results: Patients treated with biologic therapies were found to have no statistically significant increase or decrease in their risk of developing all cancer (excluding KC) (adjusted hazard ratio [aHR] 0.96 [95% Confidence Interval [CI] 0.70-1.30]) and cancers of infectious origin (aHR 0.95 [95% CI]) compared with patients treated with non-biologic systemic therapy only. Biologic-treated patients were also found to have no statistically significant increase or decrease in risk of developing lung cancer (aHR 0.83 [95% CI 0.86-1.94]), breast cancer (aHR 1.02 [95% CI 0.46-2.26]), prostate cancer (aHR 0.53 [95% CI 0.19-1.50]), BCC (aHR 1.27 [95% CI 0.70-2.32]) and SCC (aHR 0.93 [95% CI 0.42-2.07]).

Conclusion: Treatment with biologic therapy in patients with psoriasis was not associated with an increased risk of developing all cancer (excluding KC), cancers of infectious origin and some of the site-specific cancers compared with patients treated with non-biologic systemic therapy only. While the results are reassuring, the potentially long latency between exposure to these relatively new therapies and cancer development means that the long-term risk of incident or recurrent cancer still needs to be clarified.

Declaration

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Preface

Shamarke Esse graduated with a bachelor's degree in pharmacology (2:1) in 2014. After spending two years working as an information analyst in the NHS, he enrolled on to a Masters of Research (MRes) degree programme at the University of Manchester in 2016. He graduated from the University of Manchester in 2017 with an MRes in Public Health (merit). As part of this degree, he completed a thesis entitled: 'Comparing and contrasting the efficacy of deep anterior lamellar keratoplasty to penetrating keratoplasty in the treatment of keratoconus: a systematic review and meta-analysis'. Following the completion of the MRes in Public Health, he was awarded a PhD studentship by the Psoriasis Association. In 2018, he commenced a PhD programme in epidemiology, exploring the risk of cancer in patients with psoriasis, in the Division of Musculoskeletal and Dermatological Sciences at the University of Manchester. He is currently working as a public health analyst in a local authority.

Publications

Published paper

i. Esse S, Mason KJ, Green AC, Warren RB. Melanoma Risk in Patients Treated with Biologic Therapy for Common Inflammatory Diseases: A Systematic Review and Meta-analysis. JAMA Dermatology. 2020; 156(7):787–794. doi:10.1001/jamadermatol.2020.1300

Conference abstracts

i. Esse S, Mason KJ, Green AC, Warren RB. Risk of melanoma in patients with immune-mediated inflammatory diseases exposed to biological therapies: systematic review and meta-analysis [Poster]. 24th World Congress of Dermatology; 2019 June 10-15; Milan, Italy.

ii. Esse S, Mason KJ, Green AC, Warren RB. Risk of melanoma in patients with immune-mediated inflammatory diseases exposed to biological therapies: systematic review and meta-analysis [Poster]. In 99th Annual Meeting of the British Association of Dermatologists; 2019 July 2-4; Liverpool. Abstract No.P078

Planned publications

There are two papers for submission related to this thesis. The first paper will present the results of the risk of all cancer (excluding keratinocyte carcinoma) and common site-specific cancers (lung, breast and prostate) analyses. The second paper will present the results of the cancers of infectious origin analyses. These papers will be submitted to dermatology journals.

1 Introduction and literature review

1.1 Chapter outline

This chapter introduces the disease psoriasis, its epidemiology, presentation and pathogenesis. The treatment of the disease is then discussed with a focus on systemic therapies. Following a brief introduction of cancer, its incidence, burden and associated risk factors, a literature review of the evidence to date concerning risk of cancer in psoriasis populations will be presented. The final section of this chapter will provide the rationale for this thesis project.

1.2 Psoriasis

Psoriasis is a chronic, non-contagious, immune-mediated inflammatory skin disease which occurs as a result of the hyper-proliferation and abnormal differentiation of the epidermis (Camisa, 2008). It can occur at any point during life with the majority of patients being diagnosed before the age of 40, also known as early onset psoriasis, with those with onset after age 40 known as late-onset psoriasis. (Henseler and Christophers, 1985; Queiro et al., 2013). This notion of early onset and late onset psoriasis was supported by a cohort study of primary care records in the United Kingdom (UK) demonstrating a strong bi-modal pattern in the incidence of psoriasis for both men and women (Springate et al., 2017b).

Psoriasis is diagnosed clinically through examination of the scalp, skin and nails with clinical subtypes classified on features, pattern of distribution, morphology, and anatomical site (Raychaudhuri et al., 2014). Psoriasis can present in a number of distinct clinical subtypes collectively referred to as psoriasis vulgaris of which chronic plaque psoriasis is the most common, accounting for approximately 90% of all cases (Griffiths et al., 2007). Chronic plaque psoriasis is the form of psoriasis that has been the focus of drug therapy intervention studies and therefore the focus of this thesis. It will be referred to as psoriasis from Section 1.2.3 onwards unless specified otherwise.

1.2.1 Epidemiology

Psoriasis is one of the most common immune-mediated inflammatory conditions, estimated to affect over 60 million people worldwide (WHO, 2016). Global estimates of the incidence (number of new cases in a population) and prevalence (total number of new and existing cases in a population) of psoriasis, obtained from systematic reviews published in 2013 and 2014, vary considerably between age groups and geographic regions but not between the sexes (Hay et al., 2014; Parisi et al., 2013). Establishing the global epidemiology of psoriasis is difficult as studies were carried out in primarily North-American, European and other developed nations with very few studies conducted in developing nations.

Establishing the global epidemiology of psoriasis is further complicated by a lack of uniformity in these studies in terms of defining what would constitute an incident case (physician diagnosed versus patient reported), how prevalence is estimated (point prevalence versus lifetime) and the manner in which studies were performed (Griffiths et al., 2017). In 2014, the World Health Organisation (WHO) recognised psoriasis as a serious non-communicable disease with a subsequent report, published in 2016, calling for greater understanding of the epidemiology of the disease (WHO, 2016).

A recently published systematic review and meta-analysis of 168 studies examining the incidence (23 studies) and prevalence (159 studies) of psoriasis globally aimed to address these concerns by estimating the physician diagnosed global, regional, and country specific prevalence of psoriasis (Parisi et al., 2020). They found that the incidence of psoriasis in adults varied from 30.3 cases per 100,000 person years (95% confidence intervals [CI] 26.6 - 34.1) in Taiwan to 321.0 per 100,000 person years (95% CI 291.0 - 357.0) in Italy (Parisi et al., 2020). Studies examining the incidence of psoriasis in children (aged <18) have been scarce. The only evidence to date emanates from two population-based cohort studies conducted in the United States of America (USA) and Italy (children aged <14 years) reporting incidence rates of 40.8 per 100,000 person years (95% CI 36.6 - 45.1) and 57.0 per 100,000 person years (95% CI 40.0 – 80.0), respectively (Cantarutti et al., 2015; Tollefson et al., 2010).

The prevalence of psoriasis in adults varied globally with regional estimates ranging between 0.14% in East Asia (China, South Korea and Taiwan) to 1.99% in Australasia

(Australia and New Zealand) with prevalence also significant in Western Europe (1.92%), Central Europe (1.83%) and North America (1.50%) (Parisi et al., 2020). The USA is estimated to have the highest number of adults with physician diagnosed psoriasis (3.4 million) followed by India (2.9 million) and then China (2.3 million); (Parisi et al., 2020). Psoriasis occurred more frequently in adults with the prevalence of psoriasis in children varying between 0.02% in East Asia and 0.21% in Western Europe and 0.22% in Australasia (Parisi et al., 2020).

The incidence and prevalence of psoriasis in the UK, in the period 1999 to 2013, has been estimated by a 2017 study of the Clinical Practice Research Datalink (CPRD) consisting of clinical practice data for 15,346,637 primary care patients (Springate et al., 2017b). The reported incidence of psoriasis in the UK in 2013, adjusted for age and sex differences, was 129 cases per 100,000 person years (95% CI 126 – 133), down from 159 cases per 100,000 person-year in 1999 (Springate et al., 2017b). The prevalence of psoriasis in the UK in 2013 was 2.8%, up from 2.3% in 1999 (Springate et al., 2017b). The upward trend of increased prevalence of psoriasis mirrors that seen in Norway (4.8% in 1980 to 11.4% in 2008) and Spain (1.43% in 1998 to 2.31% in 2013), respectively (Danielsen et al., 2013; Ferrándiz et al., 2001; Ferrándiz et al., 2014).

1.2.2 Clinical features and subtypes

Chronic plaque psoriasis is characterised by the development of raised and well demarcated erythematous lesions, varying in size, shape and thickness, which appear red or pink in colour and are covered by adherent silvery-white scales (Figure 1.1A-1C) (Griffiths and Barker, 2007). Psoriatic plaques are most active at the edge, sometimes becoming annular, leaving uninvolved skin at the centre of the original plaque (Griffiths et al., 2007). Individual plaques range in size and thickness ranging from small (≤3 centimetres (cm) in diameter) and thin (≤0.75 millimetres (mm) in elevation) plaques to large plaques ((>3cm; 0.75mm) (Griffiths et al., 2007). Psoriatic plaques are often symmetrical in their distribution and typically develop on the extensor surfaces of the limbs, the scalp and torso (Griffiths and Barker, 2007).

Site-specific variants of plaque psoriasis have specific features. Flexural or inverse psoriasis is confined to the inguinal folds, armpits and external genitalia Figure 1.1D). Lesions that

develop in those areas have shiny surfaces and display minimal scaling relative to general plaque psoriasis due to the moist nature of such sites (Meier and Sheth, 2009). ***Seborrhoeic psoriasis*** *or* ***sebopsoriasis***, so called because of its resemblance to seborrhoeic dermatitis, is characterised by thin, red and well demarcated lesion covered by greasy scales. These lesions develop primarily on the nasolabial folds, scalp, eyebrows and other sebum rich areas of the body (Griffiths and Barker, 2007).

Scalp psoriasis is often the initial site of presentation with up to 80% of patients developing involvement at this site (Figure 1.1E) (Griffiths and Barker, 2007). It may occur in isolation or in conjunction with other forms of psoriasis. Scalp psoriasis is characterised by sharply demarcated erythematous lesions with silver-white scaling (Papp et al., 2007). These lesions often advance beyond the hair margins on to the face or retro-auricular area (van de Kerkhof and Franssen, 2001). Nail manifestation or ***nail psoriasis*** is common in patients with psoriasis, occurring in approximately 50% of patients (Figure 1.1F) (Reich, 2009). Nail psoriasis is characterised by the following nail changes occurring singly or in combination in one or multiple nails: pitting of the nail plate (70% of patients); separation of the distal nail plate from the nail bed; oil spots (light-brown discolouration under the nail plate); subungual hyperkeratosis (excessive thickening of the nail plate) (Griffiths et al., 2007; Reich, 2009)

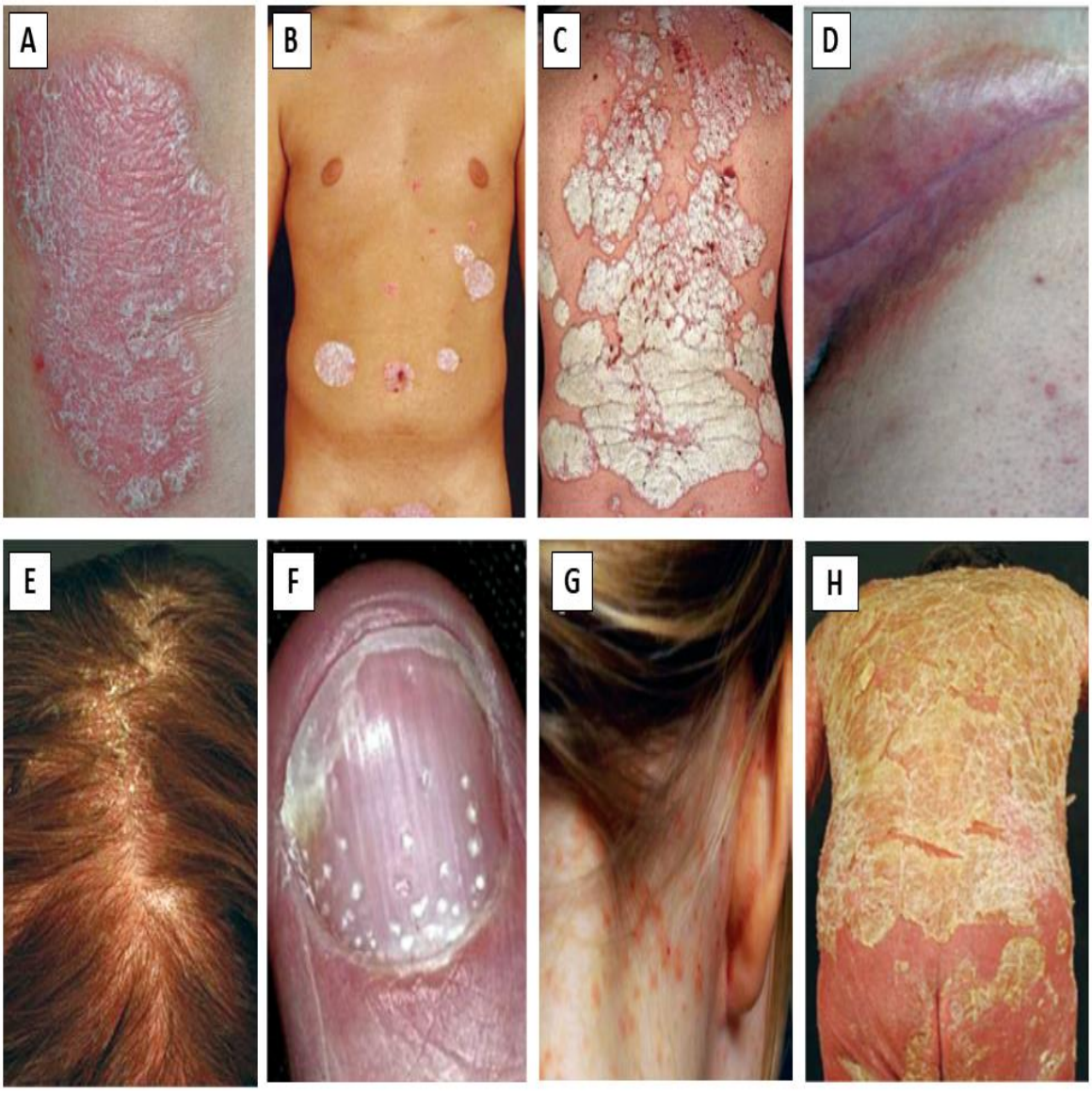
1.2.2.1 Other phenotypes

Guttate psoriasis affects around 2% of patients, primarily children and adolescents (Figure 1.1G) (Langley et al., 2005). It is characterised by the acute eruption of teardrop like papules measuring less than 1cm in diameter on the trunk over a period of one month (Griffiths et al., 2007). Streptococcal infections such as pharyngitis, have been implicated in the pathogenesis of guttate psoriasis with evidence of papules erupting two weeks after initial infection (Griffiths and Barker, 2007). Generally, there are three outcomes for patients with this phenotype: a third of patients recover after a single acute episode; a third of patient recover after a few weeks; a third of patients go on to develop chronic plaque psoriasis (Ko et al., 2010; Martin et al., 1996).

Erythrodermic psoriasis is a rare but severe form of psoriasis characterised by involvement of at least 90% of the body surface area and is sometimes accompanied by serious

metabolic dysfunction (Singh et al., 2016). It usually develops in patients with extensive and poorly controlled chronic plaque psoriasis with precipitating factors including withdrawal of systemic corticosteroids, severe emotional stress and systemic illness (Figure 1.1H) (Singh et al., 2016).

Figure 1.1: Clinical manifestations of psoriasis



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1.2.2.2 Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic, inflammatory arthritic condition closely associated with psoriasis. Usually patients with psoriasis will develop PsA 7-10 years after the first appearance of cutaneous lesions (Sankowski et al., 2013). PsA most commonly presents as an asymmetric polyarticular arthritis, although there are 5 different patterns described (Helliwell and Taylor, 2005). PsA is typically characterized by pain, swelling and inflammation of the joints and tendons and can results in radiographic damage and joint deformations (Warren and Menter, 2016). Given that psoriasis usually precedes PsA, it is routinely screened for in clinical practice as timely diagnosis and treatment can slow it's progression (NICE, 2017a). Global estimates for the prevalence of PsA in the general population range between 0.3% and 1.0% with the prevalence of PsA in psoriasis populations ranging from 7.7% to 36.0% (Catanoso et al., 2012). A cross-sectional study of The Health Improvement Network (THIN), a population based database of primary care medical records of 4.8 million patients in the UK, for the period 1994 to 2010, reported an overall prevalence of 0.19% (95% CI 0.185-0.193) and 8.6% in patients with psoriasis (95% CI 7.7-9.5) (Ogdie et al., 2013).

1.2.3 Aetiology and pathogenesis

The aetiology of psoriasis is multifactorial. The disease occurs in individuals with genetic predisposition in which a dysregulated immune response occurs following exposure to environmental triggers Figure 1.2. Genetic susceptibility is the most significant risk factor for psoriasis with many of the genes implicated also involved in the in the innate and adaptive immune system (Di Meglio et al., 2014). Population-based studies have demonstrated that the incidence of psoriasis is significantly greater in first and second degree relatives of patients with psoriasis compared with the general population (Rahman and Elder, 2005). This was further supported by twin studies demonstrating a two to three-fold increased risk in monozygotic twins compared with dizygotic twins (Gupta et al., 2014; Lønnberg et al., 2013). Advances in genotyping technology and the advent of genome-wide association studies have led to the identification of over 80 susceptibility loci with the majority of the corresponding genes clustering to a small number of immune pathways (Rendon and Schäkel, 2019). These include genes involved in antigen presentation (human leukocyte antigen (HLA)-C and endoplasmic reticulum aminopeptidase (ERAP)1), innate antiviral

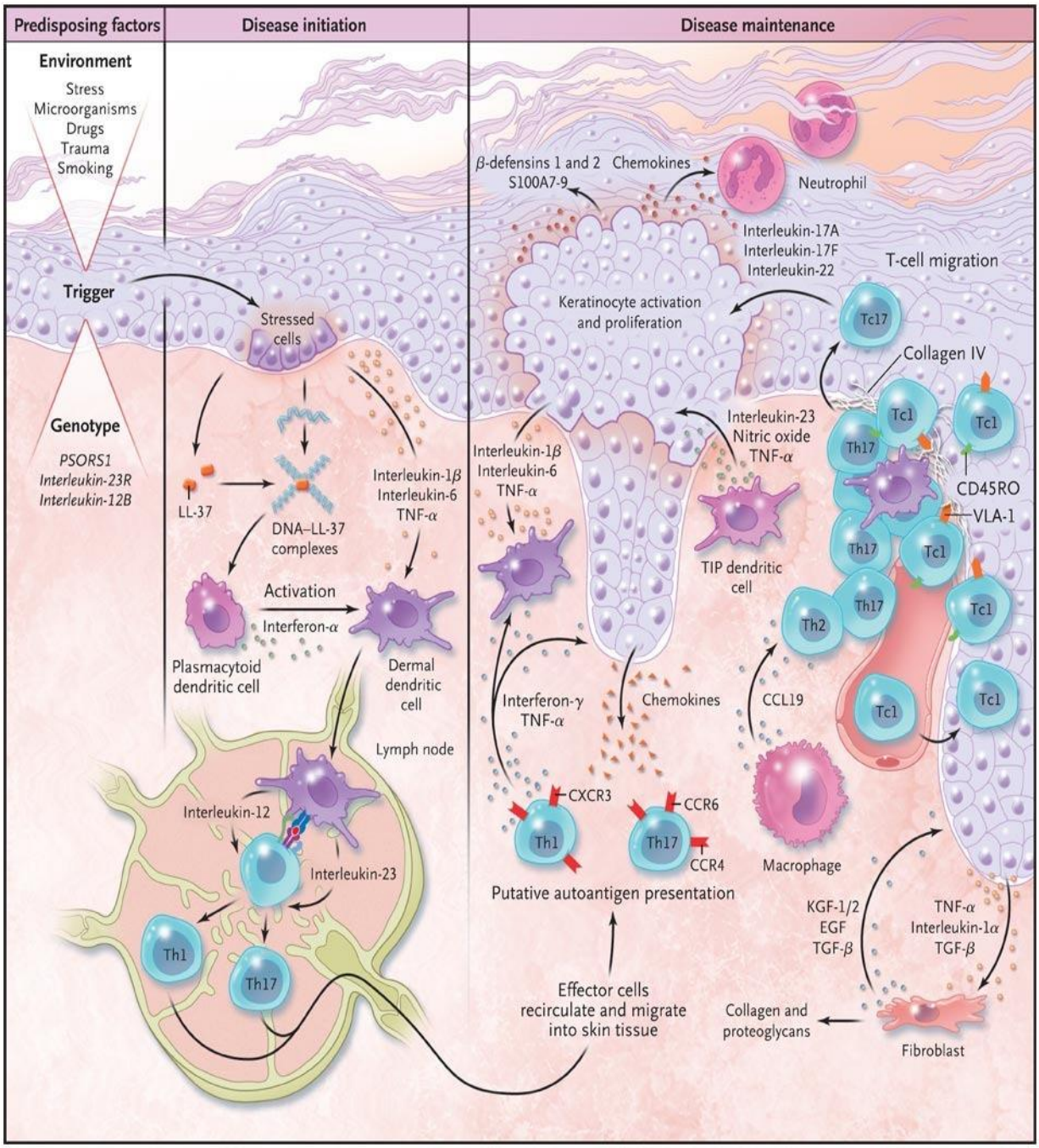
signalling (DDX58 and TYK2) and most notably T-helper cell (Th) - 17 cell activation (Interleukin (IL)12B and IL23A) (Rendon and Schäkel, 2019).

Several environmental risk factors have also been associated with initiating and exacerbating psoriasis in genetically predisposed individuals (Di Meglio et al., 2014). Cutaneous trauma such as tattoos and surgical incisions, can lead to the development of psoriatic lesions on previously uninvolved skin - known as the Koebner phenomenon (Eyre and Krueger, 1982; Weiss et al., 2002). Certain medicines can exacerbate psoriasis including lithium, Beta (β)-blockers) and anti-malarial drugs (Basavaraj et al., 2010). Streptococcal throat infections have long been associated with psoriasis, specifically guttate psoriasis (Prinz, 2001). Streptococcal antigens are thought to initiate the activation and expansion of T-cells in psoriatic lesions with some evidence implicating the streptococcal M protein, a virulence factor found in the bacterial cell membrane closely resembling human epidermal keratin in structure (Gudjonsson et al., 2003; Valdimarsson et al., 2009). There is some evidence suggesting that modifiable lifestyle factors such obesity, alcohol consumption and smoking, may also play a role in triggering or worsening of psoriasis in individuals (Jensen and Skov, 2016; Naldi et al., 2005; Qureshi et al., 2010). However, further studies are required to elucidate the exact role of these risk factors in the aetiopathogenesis of psoriasis (Naldi, 2013).

The pathogenesis of psoriasis is complex, involving both the innate and adaptive immune systems and can be conceptualised as consisting of two phases; the initiation phase and the maintenance phase. The initiation phase is triggered by the disruption of keratinocytes in genetically susceptible individuals by environmental factors, including physical trauma, leading to the release of self-nucleotides and the antimicrobial peptide LL-37 forming a complex (Nestle et al., 2005). This complex binds to toll-like receptors on the surface of plasmacytoid dendritic cells, activating it, leading to the production of interferon (IFN)-α & β, along with tumour necrosis factor (TNF)-α, IL-6 and IL-1β (Rendon and Schäkel, 2019). Myeloid dendritic cells are stimulated to migrate to the resting lymph nodes where they secrete the cytokines TNF-α, IL-12 and IL-23 and induce the resting naïve T-cells to differentiate into mature T-helper (Th) 1, Th17 and Th22 cells. Th17 cells migrate to the epidermis where they release inflammatory cytokines stimulating keratinocyte proliferation and altering differentiation (Mahil et al., 2016). Activated keratinocytes play a role in

disease maintenance producing antimicrobial peptides, pro-inflammatory cytokines (IL-1β, TNF, and IL-6), and various chemokines that contribute to the amplification of cutaneous inflammation (Mahil et al., 2016).

Figure 1.2: Schema of cells and cytokines involved in the pathogenesis of psoriasis



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1.3 Management of psoriasis

In the UK, the management of psoriasis is informed by guidance from the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the British Association of Dermatologists (BAD) (NICE, 2017a; SIGN, 2010; Smith et al., 2020). Treatment options for patients with psoriasis are dependent upon a number of factors which include disease severity, impact of the disease on the physical, psychological and social wellbeing of the patient, presence of comorbidities including PsA and patient preference. Psoriasis treatment is stepwise and can be broadly divided in to three categories; topical therapy; phototherapy; systemic therapy. Systemic therapy is further divided in to two subcategories, namely conventional systemic therapy and biologic therapy Figure 1.3. These treatments can be prescribed as monotherapy or in combination with each other, with treatments from one category often used in combination with treatments belonging to another category. Although patients with psoriasis are not required to transition from one treatment category to another, they are required to meet certain criteria for some therapies.

Figure 1.3: Overview of the NICE treatment pathway for patients with psoriasis in the United Kingdom

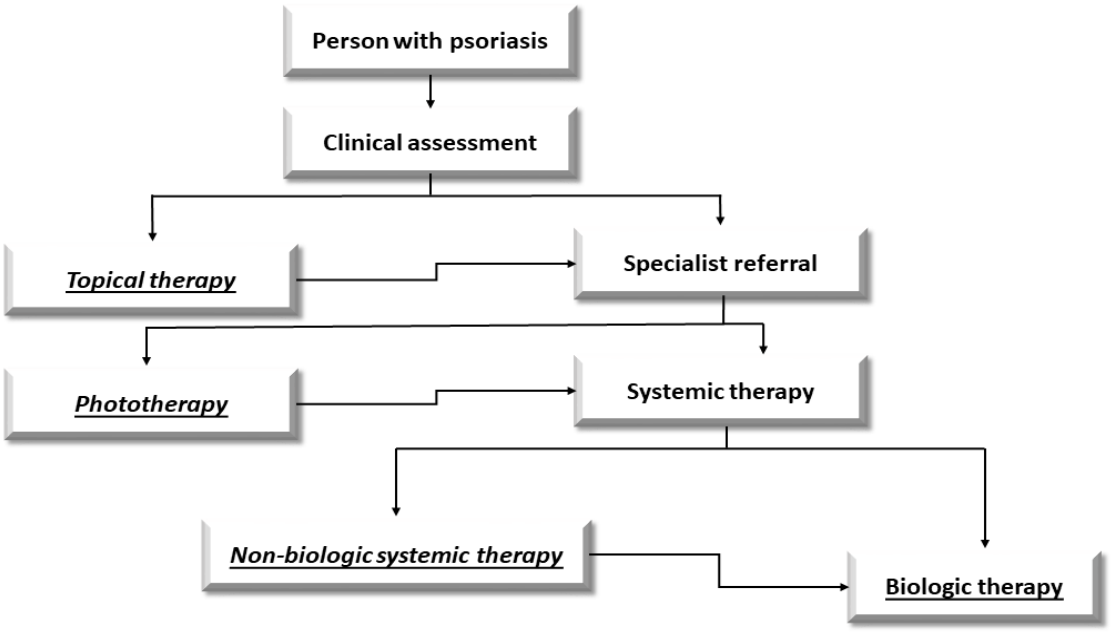


Figure 1.3 has been adapted from the National Institute of Clinical Excellence (NICE) pathways (NICE, 2019a)

1.3.1 Measures of disease impact and severity

A number of different measures are used to determine the severity of psoriasis and its impact on patient's quality of life. As the therapeutic aim of psoriasis therapy is to achieve skin clearance and to reduce the impact of the disease on the patient's quality of life, assessment of disease severity considers clinical manifestations and impact on quality of life (Strober et al., 2019). The most commonly used tools used to quantify the clinical severity of psoriasis in specialist and clinical settings are the psoriasis area and severity index (PASI), body surface area involved and physician's global assessment (PGA). The most commonly used quality of life questionnaire is the dermatology life quality index (DLQI).

1.3.1.1 Psoriasis area and severity Index

In the PASI method plaques in each region – head and neck, trunk, upper extremities and lower extremities - are assessed and scored for % affected body surface area involvement, induration, and erythema and scaling. The scores for each region are then combined to produce a total maximum score of 72 (Spuls et al., 2010). When evaluating treatment efficacy, the proportion of patients achieving a 75% or 90% reduction from their baseline measure, known as (PASI75) and (PASI90), respectively are now common primary end points in clinical trials (Schmitt and Wozel, 2005). Despite the widespread adoption of PASI in clinical and observational studies, it is limited by a number of factors which deem it insufficient as standalone measure. PASI lacks sensitivity as erythema, induration and scaling are given equal weights in each body region with commensurate changes in different regions producing the same PASI score (Ashcroft et al., 1999). As a uniform measure of disease severity, PASI does not take into account the disproportionate impact of plaques in sensitive areas of the bodies such as the face, hands, nails and genitalia on patient quality of life (Robinson et al., 2012).

1.3.1.2 Body surface area affected

The body surface area (BSA) method is used to estimate the extent of skin involvement in patients with psoriasis where the surface of the palm is equivalent to 1% of total body surface area (Finlay, 2005). Although this method is easy to use, differences in the understanding of what the palm refers to, the actual palm or full palmar aspect which included the fingers and thumb, could lead a 50% overestimations of BSA involvement if only the actual palm is used (Finlay, 2005). Furthermore, the use of the full palmer aspect

has been demonstrated to only equate to 0.76% and 0.70% of total BSA for male and female patients, respectively (Long et al., 1992).

1.3.1.3 Physician's global assessment

The PGA is a 5-7 point ordinal scale used to provide an overall assessment of the erythema, scale and induration of all the psoriatic lesions. Unlike the PASI and BSA methods, the PGA does not quantify body surface area involved nor does it evaluate individual lesions (Robinson et al., 2012). There are different forms of the PGA with the most prominent ones being the static PGA and the dynamic PGA (Spuls et al., 2010). The static PGA measures the physician's impression of the disease at a single point whereas the dynamic PGA assess the improvement of the disease compared with baseline (Robinson et al., 2012). The dynamic PGA is less reliable and less commonly used than the static PGA, the notion of baseline severity is entirely dependent on the researcher's ability to accurately recall baseline severity whereas the static PGA does not rely on recall of baseline severity (Robinson et al., 2012; Spuls et al., 2010). Although the PGA is easy to use and is found to correlate well with PASI in clinical trials, the variation in scales uses and definitions used for each point on the scale might complicate comparing results across studies (Robinson et al., 2012; Spuls et al., 2010).

1.3.1.4 Dermatology life quality index

The DLQI, developed in 1994, is the most commonly used dermatology-specific quality of life measure in observational studies (Nijsten, 2012). The DLQI questionnaire consists of ten questions concerning the patient's perceived impact of the condition over the past week and encompasses aspects such as symptoms, side effects of treatment, daily activity, work and personal relationships. Each individual question is allocated scores ranging between 0 and 3 based on the provided answer (yes; no; not relevant; not at all; a little; a lot; very much). Total scores range from 0 to 30 with greater scores denoting greater impairment on patient quality of life (Basra et al., 2012). Although limited by its focus on assessing the physical rather than psychological impact of psoriasis, the DLQI is easy to use, and reproduce so is widely used in clinical practice (Basra et al., 2012; Nijsten, 2012).

1.3.1.5 Defining disease severity

Historically, a number of different definitions have been used in clinical practice and clinical trials to define categories of disease severity, often guided by measures of clinical manifestations such as BSA and PASI (Langley and Ellis, 2004). These standalone measures may lead to an underestimation of disease severity as they don't consider the location of lesions in specific areas such as the face and scalp and the impact on quality life. Other definitions include a combination of these clinical manifestation measures with DLQI e.g. 'the rule of ten' which defined severe psoriasis as BSA>10%/PASI>10 and DLQI>10 (Mrowietz et al., 2011).

The international psoriasis council, a global collective of psoriasis experts, have proposed, through consensus, a new dichotomous definition for psoriasis severity based on the patient's treatment needs (Strober et al., 2020). Patients are classified as either eligible for topical therapy or candidates for systemic therapy if they meet at least one of the following criteria: BSA>10%; failure of topical therapy; disease involving the scalp, face, palms, soles or genitalia (Strober et al., 2020).

1.3.2 Topical therapy

Topical therapies are considered first-line therapy for patients with mild to moderate disease severity and are commonly used second-line in combination with phototherapy or systemic therapy in patients with moderate-severe disease (NICE, 2017a). Topical treatments come in a variety of strengths and formulations which include gels, lotions and ointments depending on the affected area. Topical treatments are typically reviewed 4 week after the start of treatment with the next treatment option considered if response is inadequate (NICE, 2017a; SIGN, 2010).

1.3.2.1 Vitamin D_3 analogues

Vitamin D3 analogues, which include calcitriol, calcipotriene (also known as calcipotriol) and tacalcitol, are first line therapy for patients with psoriasis of the trunk and limbs requiring topical treatment and come in the form of ointments and creams (Menter and Griffiths, 2007). Vitamin D3 analogues attach to vitamin D receptors which than bind to the vitamin D response element gene on target genes facilitating the inhibition of inflammation, cellular proliferation and differentiation of keratinocytes (Trémezaygues and Reichrath, 2011). The efficacy of vitamin D_3 analogues was demonstrated in a systematic review and meta-analysis of 177 randomised controlled trials (RCTs) consisting of 34,808 participants in which treatment with calcitriol (SMD -0.92, 95% CI -1.54 to -0.29), calcipotriol (SMD -0.96, 95% CI -1.12 to -0.77) or tacalcitol (SMD -0.73, 95% CI -1.09 to -0.37) lead to greater improvement in PASI compared with participants treated with placebo (Mason et al., 2013). According to a census paper consisting of 21 clinical trials exploring the clinical evidence for long term treatment with topical therapies in psoriasis “Best clinical evidence for long-term treatment of psoriasis is available for the two-compound-formation of calcipotriol and betamethasone” (Augustin et al., 2014).

1.3.2.2 Topical corticosteroids

Topical corticosteroids (TCS) are the most widely prescribed topical treatment for patients with psoriasis worldwide (Kim et al., 2017). TCS are categorised by potency (mild; moderate; potent; very potent) with potent and very potent TCS demonstrating greater efficacy than TCS with lower potency in a systematic review of 28 randomised head-to-head clinical trials (Mason et al., 2002). TCS enact their anti-inflammatory response though a number of mechanisms. TCS decreases the number of inflammatory mediators being delivered to the

site of plaques through vasoconstriction of blood vessels within the upper dermis (Ahluwalia, 1998). TCS also act directly at the DNA level where they increases the expression of anti-inflammatory genes and indirectly decreases the expression of pro-inflammatory genes through the inhibition of pro-inflammatory transcription factors (Uva et al., 2012).

TCS are recommended first line for patients with psoriasis affecting the scalp, face, flexures and genitals (NICE, 2017a). TCS in the form of shampoos, gels and sprays are used when treating the scalp while ointments and creams are used when treating the face, torso and extremities (NICE, 2017a). Affected areas sensitive to steroids such as the face and intertriginous areas are typically treated with agents of mild to moderate potency agents while areas with thicker skin such as the soles, elbows and knees can be treated with more potent corticosteroids (Lebwohl et al., 2005).

1.3.2.3 Other topical treatments

There are a number of other topical treatments that were once first-line for patients with plaque psoriasis have been relegated by TCS and Vitamin D3 analogues in the treatment ladder owing to their superior efficacy, tolerability and practicality. These topical treatments are worth mentioning as they still available to patients when deemed therapeutically necessary.

Coal Tar

Coal tar has been used for the treatment of dermatological conditions including psoriasis for over a century and comes in the form of ointment, solution, shampoo and crude coal tar. The acceptance of coal tar is generally low due to the colour and odour of the preparations with the availability of superior and more tolerable topical treatments reducing the use of coal tar as monotherapy (Warren and Menter, 2016). Coal tar was traditionally used to increase the effectiveness of phototherapy as part of the Goeckerman regimen in which crude coal tar was applied to the affected parts of the skin prior to treatment with ultraviolet B (UVB) phototherapy (Gupta et al., 2013). Coal tar as monotherapy is now only reserved for use in patients with refractory chronic plaque psoriasis, after failing treatment with Vitamin D3 and/or TCS (NICE, 2017).

Dithranol

Also known as anthralin, dithranol was the most commonly prescribed topical treatment for plaque psoriasis in Europe until the 1980's and comes in the form of creams and ointments (Warren and Menter, 2016). Since then, these treatments have been largely replaced by TCS and vitamin D_3 analogues owing not only to the superior efficacy of these newer topical treatments but also their superior tolerability as dithranol causes marked skin irritation, including burning sensations and skin discoloration, leading to discomfort and patient dissatisfaction (Mason et al., 2002; Menter and Griffiths, 2007). Short-contact (30 minute exposure) dithranol is considered for patients with psoriasis of trunks and limbs who do not respond treatment with Vitamin D_3 monotherapy or in combination with TCS, potent TCS monotherapy or coal tar (NICE, 2017).

1.3.3 Phototherapy

Phototherapy is offered to patients with psoriasis that cannot be controlled with just topical treatments (NICE, 2017a; SIGN, 2010). The anti-inflammatory effects of phototherapies include the inhibition of T-lymphocyte activation, the induction of apoptosis of various cutaneous cells and the inhibition of epidermal hyper-proliferation through interactions with keratinocyte DNA synthesis (Wong et al., 2013). The earliest form of UVB phototherapy saw patients exposed to the broad spectrum of UVB radiation (wavelengths 280 to 320 nanometres [nm]) (Lebwohl et al., 2005). In the 1980's, the observation that treatment with a more narrow spectrum of UVB radiation was more effective in clearing psoriasis led to the development of narrowband UVB therapy (311 to 313nm) (Lebwohl et al., 2005). Narrowband UVB is now the main form of phototherapy for patients with plaque psoriasis and can be administered 2 to 3 times a week depending on patient preference (NICE, 2017a; SIGN, 2010)

Psoralen plus UVA (PUVA) is a form of photo-chemotherapy, combining the photosensitising agent 8-methoxypsoralen with ultraviolet A (UVA) phototherapy (Lebwohl et al., 2005). Psoralen can be administered systemically, as oral PUVA, or topically as a bath or cream (Lebwohl et al., 2005). PUVA has been used to treat psoriasis since the 1950's but is now rarely used due to its association with cancer (Stern, 2012).

1.3.4 Conventional systemic and small molecule immunomodulatory therapy

NICE recommends non-biologic systemic therapy to patients with moderate-severe psoriasis that is considered extensive i.e. affecting BSA of more than 10% or a PASI greater than 10 that cannot be controlled with just topical therapy or in whom phototherapy has proved to be ineffective or has resulted in rapid relapse (Figure 1.4) (NICE, 2020b). Non-biologic systemic therapies available for patients in the UK are the conventional systemic therapies (methotrexate; ciclosporin; acitretin) and the small molecule immunomodulatory therapies (apremilast; dimethyl fumarate). The mechanisms of action of non-biologic systemic therapies as they related to cancer risk and cancer safety data are presented in Sections 1.4.3 and 1.5.2, respectively.

Figure 1.4: NICE treatment pathway for patients with psoriasis requiring systemic non-biologic therapy

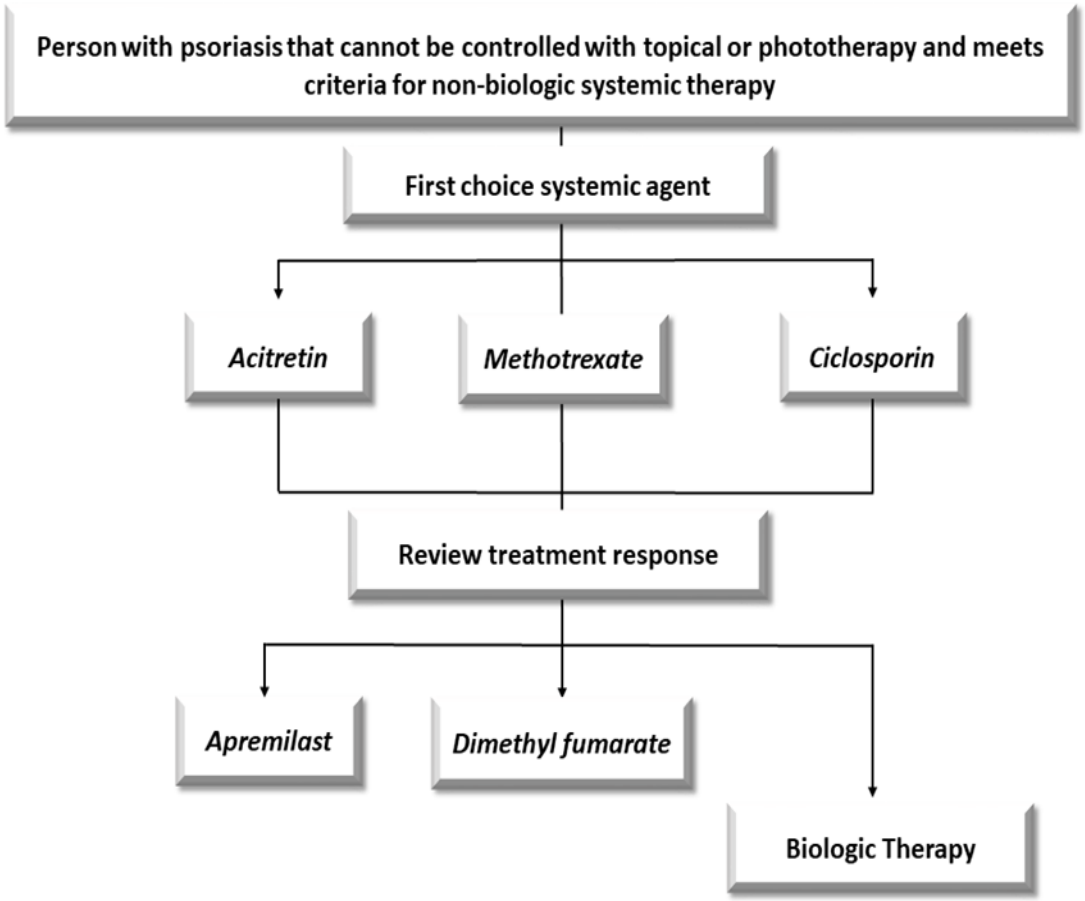


Figure 1.4 has been adapted from the National Institute for Clinical Excellence (NICE) pathways for systemic non-biologic therapy for psoriasis (NICE, 2020b).

1.3.4.1 Methotrexate

Methotrexate is the first-line therapy of choice for patients requiring systemic therapy (NICE, 2020b). The anti-inflammatory mechanism of methotrexate, a dihydrofolate reductase inhibitor, involves the mediation of the adenosine pathways resulting in reinforcement of activated T cell apoptosis and the downregulation of pro-inflammatory cytokines (Czarnecka-Operacz and Sadowska-Przytocka, 2014). Methotrexate is prescribed once-weekly through oral or parenteral routes with dosage starting at 5-7.5 milligram (mg) and, if appropriate, increasing to a maximum dose of 25mg (Warren et al., 2008). The efficacy of subcutaneous methotrexate relative to placebo has been demonstrated in a multicentre RCT conducted in the UK, France, Germany and the Netherlands involving 120 patients, 41% of patients in the methotrexate group achieved PASI75 at week 16 compared to only 10% of patients in the placebo group (Warren et al., 2017). Treatment response is assessed after 16 weeks and stopped if response is considered inadequate. Methotrexate is associated with a number of side-effects so it necessary to carefully select and monitor patients. Clinicians are recommended to evaluate patients for potential risk of hepatoxicity before and during methotrexate treatment (NICE, 2020b). Other side-effects include myelosuppression, stomatitis and gastrointestinal symptoms (nausea and vomiting) (Lebwohl et al., 2005).

1.3.4.2 Ciclosporin

Ciclosporin is prescribed as first-line therapy for patients who, in addition to fulfilling the requirements for systemic therapy, are in need of need rapid disease control (e.g. a psoriasis flare) or are considering conception (NICE, 2020b). Ciclosporin, a macrocyclic immunosuppressant, was found to be effective for the treatment of psoriasis in 1979 confirming that psoriasis was an immune-mediated condition (Griffiths and Barker, 2007). Ciclosporin exhibits its antipsoriatic effect by binding to immunophilin and inhibiting calcineurin phosphate-initiated activation of T-cells (Russell et al., 1992). Ciclosporin is administered orally at a daily dose of 2.5-3mg/kilogram (kg) and escalated to 5mg/kg where patients are found to not be responding to the lower dose. Ciclosporin was demonstrated to be more effective than methotrexate at 12 weeks of treatment in a multicentre RCT conducted in Sweden with (Flytström et al., 2008). However, after 12 weeks no significant difference was seen suggesting that both treatments are equally effective in the medium-

term (Flytström et al., 2008; Sandhu et al., 2003). Ciclosporin is recommended for induction therapy with long-term therapy limited to between 6 months and 12 months unless other treatments cannot be used due to the potential of long-term side effects, particularly nephrotoxicity, hypertension (Warren and Menter, 2016).

1.3.4.3 Acitretin

Acitretin, a synthetic oral retinoid, has been used in the treatment of psoriasis since the late 1980's (Ormerod et al., 2010). The precise mechanism of action is unclear, however acitretin is associated with normalisation of epidermal differentiation and proliferation, with some evidence that it interferes with expression of epidermal growth factor genes and neutrophil migration (Bécherel et al., 1994; Harper, 1988; Tong et al., 1990). Within the hierarchy of conventional systemic therapy, acitretin is considered effective in the management of erythrodermic and pustular forms of psoriasis (Warren and Griffiths, 2008). It is also considered for maintenance therapy for patients with plaque psoriasis requiring systemic therapy after failing both methotrexate and ciclosporin (NICE, 2020b). The initial dosing regimen for acitretin is between 10-20mg a day for 4 weeks with the maintenance regiment ranging between 25-50mg a day (Warren and Menter, 2016). Treatment response in patients with plaque psoriasis is reviewed after 4 months at the optimum dose with treatment stop if response is considered inadequate (NICE, 2020b).

1.3.4.4 Apremilast

Apremilast is a small molecule phosphodiesterase-4 inhibitor approved for the treatment of moderate severe psoriasis in the U.K under the brand name Otezla® in 2016 (NICE, 2016b). NICE recommends apremilast is considered for treatment in patients with severe psoriasis (PASI≥10 and DLQI>10) who have failed to respond to or who have a contraindication to, or are intolerant to other conventional systemic therapy including ciclosporin and methotrexate (NICE, 2016a). Apremilast acts by preventing the breakdown of cyclic adenosine monophosphate (cAMP). Elevated levels of cellular cAMP down-regulates the expression of a number of inflammatory cytokines involved in the pathogenesis of psoriasis such as TNFα, IL-17 and IL-23 (Torres and Filipe, 2015). Apremilast has been demonstrated to be efficacious in two, phase three, 52 week RCTs compared with placebo (Kim Papp et al., 2015; Paul et al., 2015). The recommended dosage regime for apremilast is 30mg a twice daily after an initial titration schedule in which a single 10mg dose is given on the first the

day of treatment followed by an increase to the maintenance dose after day 5 of treatment (NICE, 2016b).

1.3.4.5 Fumaric acid esters

Fumaric acid esters (FAEs) are a group of compounds first approved for the treatment of psoriasis in Europe and used off label in dermatology centres in the UK until 2017 (Atwan et al., 2016). The first FAEs approved in Germany for treatment of psoriasis was Fumaderm®, a combination of the compounds dimethyl fumarate and mono-ethyl fumarate (Reich et al., 2009). The exact mechanism of action of these compounds is not entirely clear, but there is evidence that dimethyl fumarate, the active component in these compounds, reduces inflammation within psoriatic plaques normalising epidermal hyperproliferation and keratinisation (Bovenschen et al., 2010). Since 2017, Skilarence®, a single agent dimethyl fumarate, has been approved for the treatment of moderate-severe plaque psoriasis in the UK (NICE, 2017b). As is the case with apremilast, it is considered for treatment in patients with severe psoriasis (PASI≥10 an DLQI>10) who have failed to respond to, are contraindicated or intolerant to conventional systemic therapy (NICE, 2020b).

1.3.5 Biologic therapy

Biologics are manufactured molecules designed to modify biological pathways that regulate pivotal immunological processes (Mustafa and Al-Hoqail, 2013). Major advances in the understanding of the pathogenesis of psoriasis has led to the introduction of a number of biologic therapies that directly target cytokine pathways that are overexpressed (Figure 1.5). NICE recommends biologic therapies, with the exception of infliximab, be offered to patients with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed are not tolerated or are contraindicated and; psoriasis is considered extensive (BSA >10% or PASI≥10) and having a large impact on their physical, psychological or social functions (DLQI>10) (NICE, 2020a). Infliximab is reserved for patients with very severe disease (PASI≥20 and DLQI>18) (NICE, 2020a). Biologic therapies, with the exception of infliximab, are administered subcutaneously via injection. A general overview of biologic therapies approved for the treatment of psoriasis in the UK are described below and summarised in Table 1.1. The mechanisms of action of biologic therapies as they related to cancer risk and cancer safety data are presented in Sections 1.4.3.3 and 1.5.3, respectively.

1.3.5.1 Tumour necrosis factor inhibitors

Tumour necrosis factor inhibitors (TNFi) were one of the first classes of biologics investigated for the treatment of psoriasis (Rønholt and Iversen, 2017). TNF-α is a pro-inflammatory cytokine, found in high levels in psoriatic plaques, and is involved in multiple inflammatory pathways in the pathogenesis of psoriasis (Sivamani et al., 2013). TNFi neutralises TNF activity by binding to it and preventing it from interacting with its receptors; TNF receptor-1 (TNFR1) and TNF receptor-2 (TNFR2). This in turn prevents the activation of nuclear factor kappa-B1, a transcription factor which regulates genes controlling cell proliferation and the secretion of pro-inflammatory cytokines (Sivamani et al., 2013).

Etanercept, a recombinant human TNF receptor p75 fusion protein, was the first approved for the treatment of adults with moderate-severe (chronic plaque) psoriasis in Europe by the European Medicines Agency (EMA) in 2004 (EMA, 2009a). Etanercept inhibits the activity of TNF by mimicking the action of natural TNF receptors and competitively binding to TNF which stops it from interacting with its receptors and prevents the activation of the inflammatory cascade (Nguyen and Koo, 2009). The clinical efficacy of etanercept monotherapy was first demonstrated in a 24-week double blind study in 2003: 34% of

patients treated with 25mg twice weekly etanercept achieved PASI75 improvement at week 12 compared with just 4% of patients in the placebo group (Leonardi et al., 2003). Etanercept is administered at a dose of 50mg twice weekly with treatment discontinued if patients show no response after 12 weeks (Smith et al., 2020). The most common side effects reported for etanercept are injection site reactions and upper respiratory tract infections (Papp, 2007).

Infliximab, a murine-human chimeric Immunoglobulin (Ig)G monoclonal antibody, was approved for treatment of psoriasis in 2005 (EMA, 2009c). It binds to soluble and membrane bound TNFα in a dose-dependent manner before it interacts with the cell surface TNF receptors thereby blocking the pro-inflammatory activities of the cytokine (Gall and Kalb, 2008). Infliximab, unlike the other biologic therapies, is administered intravenously leading to a rapid onset of action and high response rates (Reich et al., 2005). Following an initial infusion of 5mg/kg, infliximab is administered at weeks 2 and 6 followed by an infusion every 8 weeks with treatment stopped if no response is seen after 10 weeks (Smith et al., 2020). The efficacy of infliximab in psoriasis was first demonstrated in a phase 3, multicentre double-blind trial where 80% of patients achieved PASI75 at week 10 compared with 3% of placebo-treated patients (Reich et al., 2005). Infliximab has also been demonstrated in a RCT to have a greater level of efficacy at week 24 than etanercept with 72% of patients achieving PASI75 at that point compared with only 35% of patients treated with etanercept (de Vries et al., 2017). Treatment with infliximab have been demonstrated to carry a greater risk of serious infections compared with conventional systemic therapy (Yiu et al., 2018a).

Adalimumab is a murine-human IgG1 monoclonal antibody which binds with high affinity and specificity to TNF (Menter et al., 2008b). First approved in 2007, adalimumab is the recommend treatment option by NICE for patients for whom TNFi treatment is considered and is thus the most commonly prescribed biologic (EMA, 2009b; NICE, 2020a). Similarly to infliximab, the mechanism of action involves the neutralisation of TNF bioactivity by binding to it, preventing interaction between TNF- α with surface TNF receptors (Vena and Cassano, 2007). Adalimumab is administered to adults at an initial dose of 80mg followed by 40mg every other week or 40mg every week if patients don't respond after 16 weeks (Smith et al., 2020). The efficacy of adalimumab has been demonstrated in a number of clinical trials. A 52-week, phase 3 multicentre RCTs demonstrated that, at week 16, 71% of adalimumab-

treated patients achieved PASI75 compared with 7% of placebo-treated patients (Menter et al., 2008b). Treatment with adalimumab was also found to yield superior efficacy at week 16 compared with patients randomised to treatment with methotrexate (80% PASI75 versus 36% PASI75) (Saurat et al., 2008). The safety profile of adalimumab is comparable with etanercept with common side effects including injection site reactions and upper respiratory tract infections (Burness and McKeage, 2015).

Certolizumab pegol (CZP) , a PEGylated recombinant humanised monoclonal antibody, was approved for treatment in adults with moderate-severe psoriasis in 2018 (EMA, 2018a). CZP has emerged as a promising treatment option for women of child bearing potential (Mariette et al., 2018). Biologic therapy is stopped discontinued after the first trimester in some pregnant patients due to fears of placental transfer of drug to foetus but unlike other TNFi, CZP has no Fc domain and is thus not actively transported across the placenta (Smith et al., 2017). A study of patients with chronic inflammatory diseases, including psoriasis, demonstrated minimal-to-no placental transfer after treatment with CZP (Mariette et al., 2018). CZP is administrated at a loading dosage of 200mg at weeks 0, 2 and 4 followed by maintenance at 200mg every 2 weeks with response reviewed after 16 weeks. (Smith et al., 2020). The efficacy of CZP compared with placebo and etanercept was demonstrated in three, phase 3 multicentre trials; CIMPASI-1-and-2 and CIMPACT (Gottlieb et al., 2018; M. Lebwohl et al., 2018). CZP PASI75 responder rates at week 16 for patients randomised to 200mg (CIMPASI1, 66.5%; CIMPASI2, 81.4%) and 400mg (CIMPASI1, 75.8%: CIMPASI2, 82.6%) were higher than placebo patients (CIMPASI1, 6.5%; CIMPASI2, 11.6%) (Gottlieb et al., 2018). Superior efficacy (PASI75) was also demonstrated for CZP at both 200mg (61.3%) and 400mg (66.7%) compared with etanercept at 50mg (53.3%) (M. Lebwohl et al., 2018).

1.3.5.2 Interleukin-12/23 inhibitor

The earliest studies of the role of IL-12 and IL-23 pathways in psoriasis discovered that these proteins played a key role in the disease's pathogenesis in part due to their role in the differentiation of naïve T-cells in to Th1 and Th17 cells (Murphy and Reiner, 2002; Tesmer et al., 2008). IL-12 is responsible for mediating Th1 differentiation and the subsequent production of the inflammatory cytokines IFN-γ, TNF-α and IL-2 (Harrington et al., 2005). IL-23 stimulates the proliferation of Th17 cells, a key cell involved in the regulating the production of inflammatory cytokines (IL-6, IL-17, IL-21 IL-22) (Stockinger and Veldhoen,

2007). The p40 subunit, shared by IL-12 and IL-23, has been identified as a target to inhibit the Th1 and Th17 signalling necessary to activate the cascade of these inflammatory cells responsible for the disease manifestation (Lee et al., 2004).

Ustekinumab, a recombinant human IgG1 monoclonal antibody, was approved for the treatment of psoriasis in Europe in 2010 (EMA, 2009d). Ustekinumab binds to the IL-12/23 shared p40 subunit which inhibits their interaction with the IL-12Rβ1 receptor on natural killer cells and T-lymphocytes and decreases Th1 and Th17 activation (Warren and Menter, 2016). Ustekinumab is administered at 45mg (90mg if kg ≥ 100kg body weight) at week 0, 4 and then every 12 weeks with treatment discontinued if no response is seen up to 28 weeks (Smith et al., 2020). The efficacy of ustekinumab for both 45mg and 90mg compared with placebo at week 12 was established by the PHOENIX 1 and PHOENIX 2 phase 3 RCTs (Leonardi et al., 2008; Papp et al., 2008). Ustekinumab at 45mg (67.5% PASI75) and 90mg (73.8% PASI75) has also been demonstrated to have greater efficacy than etanercept (56.8% PASI75) at week 12 in the ACCEPT trial (Griffiths et al., 2010). Long-term follow-up of patients in phase 2 and 3 ustekinumab trials have demonstrated no increases risk of adverse events compared with other biologic therapies and the general population (Lebwohl et al., 2012; Papp et al., 2013; Reich et al., 2012).

1.3.5.3 Interleukin 17-A/F and interleukin 17 receptor A inhibitors.

As more recent studies of the pathogenesis of psoriasis established the condition as one that is mediated by IL-17, a new range of biologic therapies targeting the IL-23/IL-17 pathway were introduced into the treatment of psoriasis. IL-17A, the primary effector cytokine of the Th17 cell lineage, plays a key role in the pathogenesis of psoriasis. IL-17A exerts it pro-inflammatory effects by binding to the IL-17A receptor expressed on the surface of keratinocytes leading to epidermal hyper-proliferation and skin barrier dysfunction (Frieder et al., 2018). The synergistic effects of IL-17A and TNFα on keratinocytes sustain an inflammatory feedback loop, upregulating the production of inflammatory mediators leading to the maintenance of chronic inflammation (Chiricozzi et al., 2011). Expression of IL-17A messenger RNA (mRNA) is higher in psoriatic plaques than in uninvolved skin with higher serum levels of IL-17A levels correlating with greater disease severity (Arican et al., 2005; Li et al., 2007).

Secukinumab was the first IL-17A inhibitor approved for the treatment of psoriasis and was introduced to clinical practice in 2015 (EMA, 2015). Its mechanism of action involves the neutralisation of the biologic activity of IL-17A by binding to it and preventing its interaction with the IL-17A receptor (Fala, 2016). Secukinumab is administered at an initial dose of 300mg for the first four weeks followed by monthly maintenance dosing with treatment response reviewed after 12 weeks (Smith et al., 2020). The efficacy of secukinumab has been compared with placebo, etanercept and ustekinumab in three multicentre, phase 3, RCTs (Langley et al., 2014; Thaçi et al., 2015). Greater proportions of patients treated with 150mg and 300mg of secukinumab respectively (71.6%, ERASURE; 67.0% FIXTURE), (81.6%, ERASURE; 77.1%, FIXTURE) achieved PASI75 at week 12 than those in the placebo (4.5%, ERASURE; 4.9% FIXTURE) and etanercept (44.0%, FIXTURE) groups (Langley et al., 2014). Secukinumab was also more efficacious than ustekinumab in the CLEAR study with 79% of patients achieving PASI90 at week 16 compared with 57.6% of patients randomised to ustekinumab (Thaçi et al., 2015). Secukinumab has been well tolerated in studies with pooled safety analyses of phase 2 and 3 clinical studies reporting nasopharyngitis, headache and upper respiratory tract infections as the most commonly reported adverse events for these patients (van de Kerkhof et al., 2016). A specific adverse event related to IL-17 blockade is candida infections which are usually mild to moderate

The second IL-17A inhibitor introduced to the treatment of psoriasis was ***Ixekizumab,*** a humanised IgG4 monoclonal antibody approved by the EMA in 2016 (EMA, 2016).The mechanism of action is similar to secukinumab involving the inhibition of IL-17A by selectively binding to it and blocking its interaction with the IL17-A receptor (Syed, 2017). Ixekizumab is administered at an initial dose of 160mg followed by 80mg every two weeks until week 12; maintenance is at 80mg every four week after week 12 (Smith et al., 2020). The efficacy of ixekizumab compared with placebo and etanercept was studied in an integrated efficacy analyses of three phase 3 RCTs (UNCOVER-1-3) (Gordon et al., 2016; Papp et al., 2018). At week 12, PASI75 responder rates for ixekizumab-treatment at 80mg every 2 weeks (88.7%) or every 4 weeks (81.6%) were greater than the placebo (4.4%) and etanercept (47.7%) treatment groups (Papp et al., 2018). Treatment with ixekizumab was also demonstrated to have superior efficacy to ustekinumab in the IXORA-S phase 3 head-to-head RCT with 72.8% of patients randomised to ixekizumab achieving PASI90 at week 12

compared with 42.2% of ustekinumab-treated patients (Reich et al., 2017c). Long-term extension (268 weeks) of the UNCOVER-3 trial found ixekizumab treatment to be well tolerated with the most common treatment emergent adverse events consisting of candidiasis, nasopharyngitis and upper respiratory tract infection (Blauvelt et al., 2020).

Brodalumab*,* a fully human IgG2 monoclonal antibody, was the first IL-17 receptor antagonist approved for the treatment of psoriasis (EMA, 2017a). Brodalumab achieves its therapeutic effect by inhibiting the biologic activity of not only IL-17A but also IL-17E and Il-17F through selectively binding, with high affinity, to the IL-17 receptor A (Roman and Chiu, 2017). Brodalumab is administered at 210mg weekly for the first three weeks and fortnightly thereafter with response reviewed after 12 weeks (Smith et al., 2020). The efficacy of brodalumab compared with placebo and ustekinumab was demonstrated in three large multicentre phase 3 clinical trials (AMAGINE-1-3) (Lebwohl et al., 2015; Papp et al., 2016). In the AMAGINE-1 trial, 60% and 83% of patients treated with 140mg or 210mg of brodalumab achieved PASI75 at week 12 compare just 3% of patients randomised to placebo (Papp et al., 2016). In the AMAGINE-2 and AMAGINE-3 trials, PASI75 response at week 12 was also greater for patients treated with brodalumab at 140mg doses (67% and 69%) and at 210mg doses (86% and 85%) compared with placebo (8% and 6%) (Lebwohl et al., 2015). PASI100 response rates at week 12 for brodalumab at 140mg doses (26% and 27%) and 210mg doses (44% and 37%) were also significantly higher than ustekinumab (22% and 19%) in the AMAGINE-2 and AMAGINE-3 trials, respectively (Lebwohl et al., 2015). Concerns were raised regarding the safety of brodalumab after 6 patients, of which 4 had psoriasis, enrolled in long-term open label trials committed suicide developed suicidal ideations and behaviours (Foulkes and Warren, 2019). However, a subsequent analysis of psychiatric adverse events in 5 clinical trials reported no causal relationship between suicidal ideations and behaviours and treatment with brodalumab (M. G. Lebwohl et al., 2018). However, this has impacted the clinical update of brodalumab with many doctors and patients cautious about using this therapy.

Bimekizumab, a humanised igG1 monoclonal antibody, is the latest member of the IL-17 inhibitor class of biologics approved for the treatment of psoriasis (EMA, 2021). It has a novel mechanism of action consisting of the selective dual inhibition of IL-17A and IL-17F (Adams et al., 2020). IL-17F shares many of the same biological properties as IL-17A and

shares signalling pathways with IL-17A through the IL-17 Receptor A and C heterodimer complex (Freitas and Torres, 2021). Although IL-17A is more biologically active, both cytokines are found at increased levels in psoriatic skin. Thus, dual inhibition of IL-17A and IL-17F could potentially lead to better disease control than that seen in IL-17A inhibition only (Reis et al., 2019).

Bimekizumab is administered to patients at 320mg, given in two 160mg doses, at weeks 0, 4, 8, 12, 16 and every 8 weeks thereafter with treatment response reviewed after week 16 (EMA, 2021). The clinical efficacy of bimekizumab compared with placebo, ustekinumab, secukinumab and adalimumab was evaluated in three Phase 3, multicentre RCTs published in 2021. The BE READY trial, conducted across 77 clinical sites in nine countries, was the first to report the clinical efficacy of bimekizumab at 320mg every 4 weeks in patients with psoriasis (Gordon et al., 2021). At week 16, PASI90 was achieved by 91% of bimekizumab-treated patients compared with just 1% of placebo patients (Gordon et al., 2021). The BE VIVID trial also demonstrated the superior efficacy of bimekizumab compared with the IL-12/23 inhibitor ustekinumab (Reich et al., 2021a). Significantly greater proportion of patients randomised to bimekizumab (85%) achieved PASI90 at week 16 than those randomised to 45mg or 90mg of ustekinumab (50%) (Reich et al., 2021a). The BE RADIANT trial demonstrated greater short-term and long-term efficacy for bimekizumab than secukinumab giving credence to the theory that selective inhibition of IL-17A and IL-17F leads to a more potent anti-inflammatory effect than selective inhibition of IL-17A only (Reich et al., 2021b). Greater proportion of bimekizumab patients achieved PASI100 at week 16 (62% versus 49%) and week 48 (67.0% versus 46.2%) compared to secukinumab (Reich et al., 2021b). Similarly, Bimekizumab was also demonstrated to produce superior clinical response (PASI90) compared with the TNFI adalimumab (86% versus 47%) at week 16 in the BE SURE trial (Warren et al., 2021a). Safety assessments from the four trials concluded that bimekizumab was well tolerated with an acceptable safety profile. The most common side-effect observed in patients across these trials treated with bimekizumab were nasopharyngitis, upper-respiratory tract infections and oral candidiasis (Gordon et al., 2021; Reich et al., 2021a; Reich et al., 2021b; Warren et al., 2021a).

1.3.5.4 Interleukin 23 inhibitors

The importance of IL-23 over IL-12 in the biologic activity of the IL-12/23 p40 subunit was first highlighted by the discovery that, along with p40 subunit mRNA, IL-23's p19 subunit mRNA was significantly elevated in psoriatic plaques whereas IL-12's p35 mRNA was not (Levin and Gottlieb, 2014). This built on the findings of genome wide association studies demonstrating an association between the genetic loci of IL23p19 and IL23p40 subunits but not IL-12p35 subunit (Nair et al., 2010). Before these important findings, the pro-inflammatory role of the IL-12/23 p40 subunit was attributed primarily to IL-12 (Section 1.3.5.2). These findings raised the potential for the development of a new class of biologic therapies inhibiting the biologic activity of IL-12/23 p40 subunit. These therapies would in theory produce efficacy results analogous to the IL-12/23 inhibitor ustekinumab while also preserving the IL-12 mediated Th1 response against pathogens leading to a better safety profile.

Guselkumab, a fully human IgG1λ monoclonal antibody, blocks the initiation of the IL-23 pathway and subsequent release of pro-inflammatory cytokines by selectively binding to its p19 subunit (Nogueira and Torres, 2019). Guselkumab, first approved for use in Europe in 2017, is administered at 100mg at week 0 and week 4 followed a maintenance dose every 8 weeks with response reviewed after 16 weeks of treatment (EMA, 2017b; Smith et al., 2020). Guselkumab has been demonstrated have superior efficacy at weeks 16, 24 and 48 compared to adalimumab in two prominent, phase 3, RCTs, namely VOYAGE-1 and VOYAGE-2 (Blauvelt et al., 2017; Reich et al., 2017a). PASI75 responder rates for guselkumab-treated patients at week 16 were 91.2% (VOYAGE-1) and 86.3% (VOYAGE-2) compared with just 73.1% (VOYAGE-1) and 68.5% (VOYAGE-2 for patients randomised to adalimumab (Blauvelt et al., 2017; Reich et al., 2017a). Adverse event rates for guselkumab-treated patients are comparable with patients treated with other biologic therapies; nasopharyngitis, upper-respiratory tract infections and injection site reactions were the most commonly reported adverse events in clinical trials (Blauvelt et al., 2017; Reich et al., 2017a).

Tildrakizumab, a humanised IgG1κ monoclonal antibody, was approved for the treatment of psoriasis in Europe (EMA, 2018b). Its mechanism of action, like guselkumab, involves the blocking of IL-23 downstream signalling by selectively binding to the p19 subunit of IL-23 cytokine (Nogueira and Torres, 2019). Tildrakizumab is administered to patients at 100mg at

weeks 0, 4 and every 12 weeks thereafter with response reviewed after 28 weeks (Smith et al., 2020). Treatment with tildrakizumab was demonstrated to more efficacious than placebo and treatment with etanercept in two phase 3 RCTs (Reich et al., 2017b). At week 12, 64% of patients randomised to tildrakizumab at 100mg and 62% of patients randomised to 200mg achieved PASI75 at week 12 compared with just 6% in the placebo group in the reSURFACE-1 trial (Reich et al., 2017b). In the reSURFACE-2 trial, week 12 PASI75 responder rates for patients randomised at 100mg and 200mg were 66% and 61% compared to only 48% of patients randomised to etanercept (Reich et al., 2017b). Long-term follow-up (148 weeks) of patients in reSURFACE trials has demonstrated that tildrakizumab an acceptable long-term safety profile with the most common side-effects consisting of nasopharyngitis and upper respiratory tract infections (Reich et al., 2020).

Risankizumab, a humanised IgG1 monoclonal antibody, is the latest IL-23 inhibitor approved for the treatment for psoriasis (EMA, 2019). Risankizumab is administered to patients at 150mg, in two 75mg injections, at weeks 0, 4 and then every 12 weeks thereafter with response reviewed after week 16 (Smith et al., 2020). The efficacy of risankizumab compared with placebo, ustekinumab and adalimumab was demonstrated in three multicentre, phase 3 RCTs (Gordon et al., 2018; Reich et al., 2019). In the UltIMMA-1 trial PASI90 was achieved by 75.3% of patients randomised to 150mg of risankizumab, 4.9% of patients receiving placebo and 42% of patients receiving ustekinumab at week 16 (Gordon et al., 2018). PASI90 responder rates were also more favourable for risankizumab-treated patients (74.8%) in the ultIMMA-2 trial compared with placebo (2%) and ustekinumab (47.5%) (Gordon et al., 2018). Similarly, in the IMMvent active-comparator-controlled trial, PASI90 responder rates at week 16 were 72% for risankizumab-treated patients compared with only 47% of adalimumab-treated patients (Reich et al., 2019). Treatment with risankizumab has also demonstrated to be more efficacious in clearing psoriasis than secukinumab. The IMMerge study, a phase 3 multicentre RCT conducted in nine countries, reported that 73.8% of patients randomised to risankizumab achieved PASI90 at week 16 compared with 66% of patients randomised to secukinumab (Warren et al., 2021b). Safety data from these four RCTs indicate that treatment with risankizumab is well tolerated with the most commonly reported adverse events consisting of

nasopharyngitis and upper respiratory tract infections (Gordon et al., 2018; Reich et al., 2019; Warren et al., 2021b).

1.3.5.5 Biosimilars

The expiration of patents for the originator product for the TNFi's etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira) has led to the introduction of the cost-effect biosimilars to clinical practice in the UK (Smith et al., 2020). Biosimilars, as defined by the EMA, are "biological medicinal products that contain a version of the active substance of an already authorised biological medicinal product…" (EMA, 2014). Biosimilars are only approved by the EMA if "similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy" are established (EMA, 2014). NICE clinical guidelines for biologic therapy recommend that, where a biosimilar product is available, clinicians start treatment with the least expensive option after taking in to account product and administrative costs (NICE, 2020a). TNFi biosimilars approved at the time of writing this thesis are summarised in Table 1.1.

1.3.5.6 Treatment pathway

Through the course of this PhD project, spanning 2018 to 2021, the guidelines pertaining to the prescribing of biologic therapy have changed. Guidance from the BAD published in 2017, separate from NICE who base their decision to approve therapies on cost-effectiveness, recommend ustekinumab and secukinumab as first-line therapy with adalimumab as alternative first-line therapy in adult patients if they also present with active PsA (Smith et al., 2017). Clinicians were recommended to treat patients with any other approved biologic therapies should they fail first-line therapy (Smith et al., 2017). However, the latest guidelines for biologic therapy, published in March 2020, recommend that clinicians offer any of the currently licensed biologic therapies as first-line therapy to adults who fulfil the criteria for biologic therapy with infliximab still reserved for patients with very severe disease (Smith et al., 2020).

Figure 1.5: Site of action of biologic therapies for psoriasis

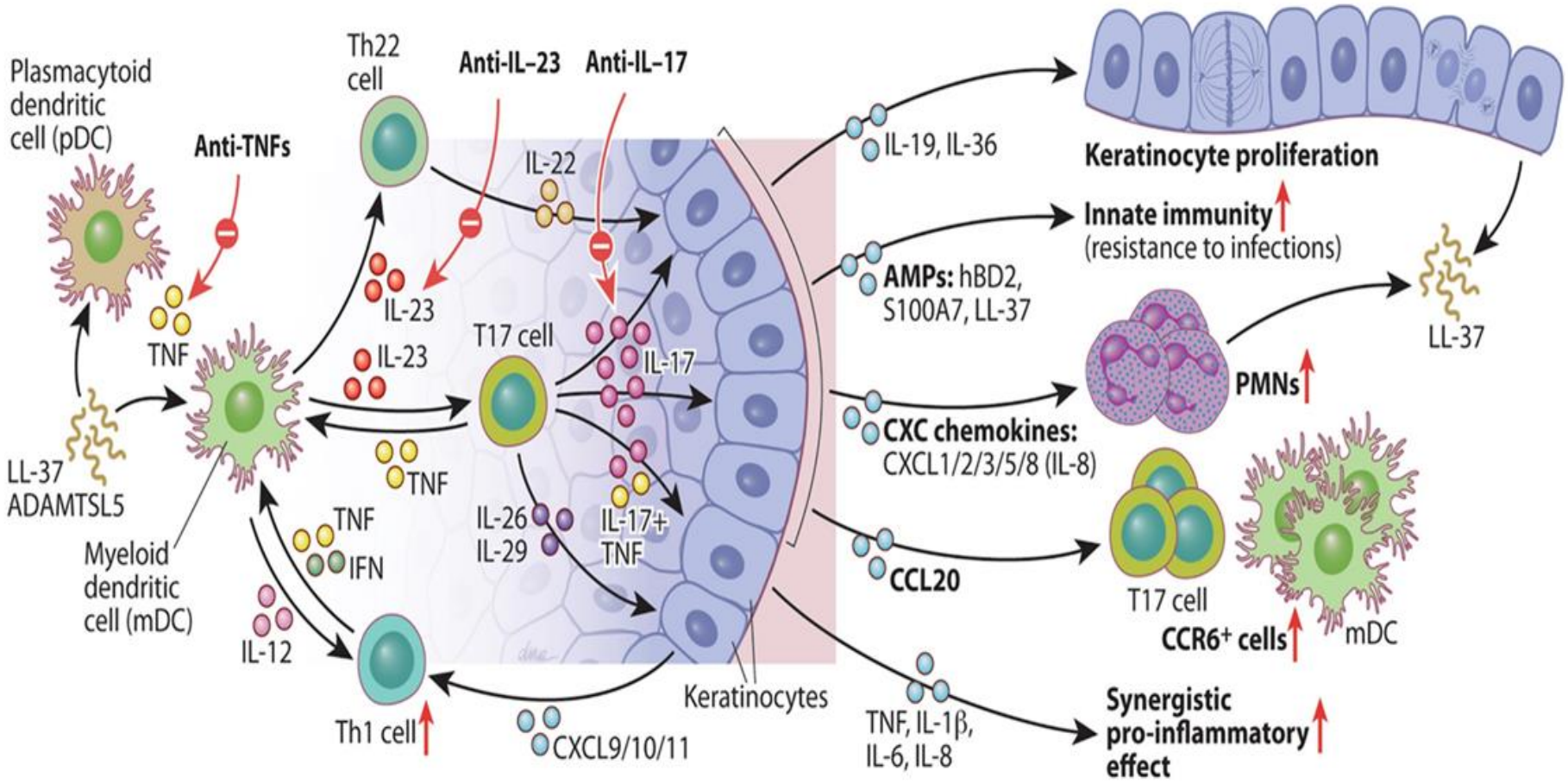


Figure 1.5 was adapted from (Hawkes et al., 2017) with permission from Elsevier via Rightslink copyright clearance centre (License number: 5001900971780).

Table 1.1: Summary of biologic therapies approved for the treatment of psoriasis

Biological target	Reference drug (authorisation year*)	Tradename (category)	Indication		Dosing regimen		NICE treatment response evaluation	Clinical effectiveness demonstrated
			Adults	Children	Adults	Children		
TNF-α	Etanercept (2004)	Enbrel (originator) *Benepali (biosimilar)* *Erelzi (biosimilar)*	Moderate-severe chronic plaque psoriasis	Severe chronic plaque psoriasis	50mg once weekly SC (alternative twice weekly for up to 12 weeks after which reduced to once weekly)	0.8mg/kg (up to 50mg) SC once weekly for up to 24 weeks	12 weeks	Leonardi et al., 2003
TNF-α	Infliximab (2005)	Remicade (originator) *Inflectra (biosimilar)* *Remsima (biosimilar)* *Zessly (biosimilar)* *Flixabi (biosimilar*)	Severe chronic plaque psoriasis	Not licensed	5mg/kg IV at week 0, 2 and 6, then once every 8 weeks	N/A	10 weeks	Reich et al., 2005
TNF-α	Adalimumab (2007)	Humira (originator) *Amgevita (biosimilar)*	Moderate-severe chronic plaque psoriasis	Not licensed	Initial dose of 80mg SC at week 0, followed by 40mg every other week starting from week 1	N/A	16 weeks	Menter et al., 2008b
TNF-α	Certolizumab Pegol	Cimzia (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	400mg SC (two 200mg doses) at week 0, 2 and 4. 200mg (up to maximum of 400mg) every two weeks.	N/A	16 weeks	Gottlieb et al., 2018; M. Lebwohl et al., 2018

Biological target	Reference drug (authorisation year*)	Tradename (category)	Indication		Dosing regimen		NICE treatment response evaluation	Evidence for clinical efficacy
			Adults	Children	Adults	Children		
IL-12/23 shared p40 subunit	Ustekinumab (2009)	Stelara (originator)	Moderate-severe chronic plaque psoriasis	Moderate-severe chronic plaque psoriasis aged 12 and over	45mg SC (90mg if body weight over 100kg) at week 0,4 and then every 12 weeks thereafter	0.75mg/kg SC If body weight under 60kg. Same dose as adults if greater than 60kg	16 weeks	Leonardi et al., 2008; Papp et al., 2008
IL-17A	Secukinumab (2015)	Cosentyx (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	300mg SC at week 0, 1, 2, and 3. Monthly maintenance from week 4.	N/A	12 weeks	Langley et al., 2014
IL-17A	Ixekizumab (2016)	Taltz (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	160mg SC at week 0, 80mg at weeks 2, 4, 6,8,10 and 12. 80mg maintenance every 4 weeks.	N/A	12 weeks	Gordon et al., 2016; Papp et al., 2018)
IL-17 Receptor A	Brodalumab (2017)	Kyntheum (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	210mg SC at weeks 0, 1 and 2 followed by 210mg every 2 weeks.	N/A	12 weeks	(Lebwohl et al., 2015; Papp et al., 2016
IL-17A/F	Bimekizumab (2021)	Bimzelx (Originator)	Moderate-severe chronic plaque psoriasis	Not licensed	320mg SC (2 doses at 160 mg) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter.	N/A	16 weeks	(Gordon et al., 2021; Reich et al., 2021a; Reich et al., 2021b; Warren et al., 2021a)

Biological target	Reference drug (authorisation year*)	Tradename (category)	Indication		Dosing regimen		NICE treatment response evaluation	Clinical effectiveness demonstrated
			Adults	Children	Adults	Children		
IL-23 p19 subunit	Guselkumab (2017)	Tremfya (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	100mg SC at weeks 0 and 4, followed by maintenance dose every 8 weeks.	N/A	16 weeks	Blauvelt et al., 2017; Reich et al., 2017a
IL-23 p19 subunit	Tildrakizumab (2018)	Ilumetri (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	100mg SC at weeks 0, 4 and then every 12 weeks thereafter.	N/A	12-28 weeks	Reich et al., 2017b
IL-23 p19 subunit	Risankizumab (2019)	Skyrizi (originator)	Moderate-severe chronic plaque psoriasis	Not licensed	150mg SC (two 75mg doses) at weeks 0, 4 and then every 12 weeks thereafter.	N/A	16 week	Gordon et al., 2018; Reich et al., 2019

Abbreviations: National Institute for Clinical Excellence (NICE); tumour necrosis factor (TNF); Intravenously (IV); Subcutaneously (SC); Not Applicable (N/A); Interleukin (IL)

* Year European Medicines Agency provided authorisation for the treatment of psoriasis in Europe.

1.4 Psoriasis and risk of cancer

1.4.1 Introduction to cancer

Cancer is a broad term used to describe a cluster of heterogeneous diseases with a common underlying pathology, genetic alterations in a single cell leading uncontrolled cellular growth, division and potential invasion or spread of abnormal cells to other sites in the body (Thun et al., 2018). A mass consisting of abnormal cells are referred to as a tumour, arising from virtual any cell type or tissue (Thun et al., 2018). Cancers develop through a multi-stage process referred to as carcinogenesis. The first stage, referred to as tumour initiation, involves mutations or epigenetic changes in genes that control for cell division (oncogenes) and programmed cell death (tumour suppressor genes) leading to uncontrolled cell proliferation (Thun et al., 2018). The tumour promotion stage is characterised by further division and proliferation of these cells (Thun et al., 2018). The tumour progression stage involves accelerated cell proliferation, escape from the immune system and the continued acquisition of mutations (Thun et al., 2018). At this point the tumours become malignant and is characterised by irregular borders and spreading to nearby sites (Patel, 2020). Malignant tumours are further defined by the potential of metastasis, the process in which tumour cells leave their primary site, circulate in the blood stream and establish themselves as a secondary tumour in another site far from the primary site (Fares 2020)

The WHO has developed a classification system in which the over 100 types of cancer are grouped by histological type and primary site called the International Classification of Disease for Oncology (Fritz, 2013). Classifications and relevant cell type include: carcinoma (epithelial cells), sarcoma (mesenchymal cells), leukaemia and lymphoma (haematopoietic cells) (SEER, 2021). Chemical, physical or viral agents implicated in causing or increasing the incidence of cancer are referred to as carcinogens (Hecht, 2002). The WHO International Agency for Research on Cancer (IARC), a body of experts evaluating the carcinogenicity of agents in humans and experimental animals, categorise these agents through the quantitative assessment of the scientific literature (Samet, 2015). To date, over 1,000 carcinogens have been assessed and categorised in one of the following four defined groups: Group 1 (carcinogenic to humans, 121 agents); Group 2A (probably carcinogenic to humans, 90 agents); Group 2B (possibly carcinogenic to humans, 322 agents); Group 3 (not classifiable as to its carcinogenicity to humans, 498 agents) (IARC, 2019).

1.4.2 Incidence and burden of cancer

Cancer is a common, chronic condition with an estimated 2.9 million people living in the UK in 2020 having had a diagnosis at some point in their life (Macmillan-NCRAS, 2020). The lifetime risk of developing cancer for people born after 1960 in the UK is estimated to be 45% for females and 50% for males (Ahmad et al., 2015). All time prevalence of cancer is projected to increase to 4 million and 5.3 million people in 2030 and 2040, respectively (Maddams et al., 2012). These projections are driven by year-on-year increases in cancer incidence and decreases in cancer mortality (Smittenaar et al., 2016). Cancer is associated with significant burden. A systematic analysis of the global burden of disease study, between 1990 and 2017, quantified the impact of cancer and other diseases using disability adjusted life-years (DALY), measured as the number of years of healthy life lost due to disability or premature death (Fitzmaurice et al., 2019). This study estimated that cancer caused a loss of 250 million years of healthy (95% Uncertainty Interval [UI] 235-264 million) with only cardiovascular disease causing a greater loss of number of years of healthy life (Fitzmaurice et al., 2019).

In 2018, a total of 375,400 new cases of cancer were reported for the UK (CRUK, 2021b). Eighty-three percent of all new cases were reported for England (312, 827) with the remaining 17% of cases reported for Scotland (33,180 cases, 9%), Wales (19,586, 5%) and Northern Ireland (9,807, 3%), respectively (CRUK, 2021b). The European age standardised incidence rate (SIR) for all cancer in the UK for this period was 835.5 cases (95% CI 603.9-606.1) per 100,000 population (CRUK, 2021b). Rates were highest in Scotland (SIR 627.9 [95% CI 624.0-631.8]) and the lowest in Northern Ireland (SIR 602.0 [95% CI 595.1-608.9]) (CRUK, 2021b). The incidence of all cancer was significantly greater in men (SIR 678.4 [95% CI 676.7-680.2]) than in women (SIR 549.7 [95% CI 548.2-551.1]) in 2018 (CRUK, 2021b).

Cancer is one of leading causes of mortality with an estimated 28% of all deaths in the UK attributed to the condition in 2019 (CRUK, 2021h).The European age standardised mortality rate (SMR) for all cancers in the UK was 265.3 (95% CI 264.0-266.5) per 100,000 population in 2018 (CRUK, 2021h). As was the case with the incidence of cancer, mortality rates varied between the countries in the UK with the highest rates reported for Scotland (SMR 308.2 [95% CI 303.4-312.9]) and lowest rates reported for England (SMR 259.8 [95% CI 258.4-261.1)] (CRUK, 2021h). Cancer mortality rates were higher in men (SMR 321.2 [95% CI

319.0-323.3]) than women (SMR 224.6 [95% CI 223.1-226.2]) in the UK, reflecting the difference in cancer incidence between the two sexes (CRUK, 2021h).

The most commonly diagnosed cancer in the UK population in 2018 was basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (CRUK, 2021b; Kwiatkowska et al., 2021). The most commonly diagnosed solid cancers in the UK were those of the breast, lung, prostate and colorectum and melanoma, combining for 53% of all new cancer cases in 2018 (CRUK, 2021b). Cancer overall and these common major site-specific cancers were the outcomes of interest in this thesis project. The common site-specific cancers and their associated risk factors are summarised in Table 1.2.

Table 1.2: Summary of the most common site-specific cancers in the United Kingdom

Cancer	Description	Risk factors	Evidence for an association with cancer
Basal cell carcinoma	• BCC presents as pinky, pearly papules or plaques and typically develop in the head and neck region in the absence of pre-cancerous lesions with metastasis rare (Cives et al., 2020). • BCC is the most common type of KC, estimated to represent 75%-80% of all cases (Nagarajan et al., 2019) • Incidence of BCC in the UK in 2018 ranged between 336.4 [95% CI CI 332.7-340.2] in Wales and 275.1 (95% CI 272.4-277.8) per 100,000 population in Scotland (Kwiatkowska et al., 2021).	Age	• Risk of KC (including BCC) is strongly associated with age. Incidence rises steeply from age 60 onwards with 48% of all cases occurring in people who are aged 75 and over (CRUK, 2021i; Kwiatkowska et al., 2021).
		Sex	• Overall incidence of BCC in the UK is higher in men than women (IRR 1.44 [95% CI 1.43-1.45]) (Kwiatkowska et al., 2021). However, incidence of BCC is lower in men under the age of 50 (IRR 0.78 [95% CI 0.77-0.80]) (Kwiatkowska et al., 2021).
		Exposure to UVR	• The IARC working group designated solar radiation or UV emitting tanning beds as a group 1 carcinogen for BCC (El Ghissassi et al., 2009). • Outdoor work is associated with an statistically significant increased risk of BCC (OR 1.43 [95% CI 1.23-1.66]) compared to indoor work (Bauer et al., 2011). • The use of sunbeds, at any age in life, is also associated with statisticaly significant increased risk of developing BCC (HR 1.29 [95% CI 1.08-1.53]) compared with people who have never used a sunbed (Wehner et al., 2012).

		Skin phenotype	• Eighty-two percent of patients diagnosed with any KC in England in 2018 were of white ethnicity with less than one percent identifying as 'non-white' (Kwiatkowska et al., 2021). • Individuals with Fitzpatrick skin type I/II have a 70% greater risk of BCC than those with skin type III/IV (OR 1.70 [95% CI 1.17-2.47]) (Khalesi et al., 2013). • Risk of developing BCC was also found to be twice as high in individuals who burn and never tan compared with those who tan and never burn (OR 2.03 [95% CI 1.73-2.38]) (Khalesi et al., 2013).
Squamous cell carcinoma	• SCC presents as scaly nodules or plaques and typically develop on the parts of the body most exposed to the sun (scalp, face and back of the hands) (Cives et al., 2020). • Bowen's disease (also referred to as SCC in situ) and actinic keratosis are the two premalignant forms of SCC (Small et al., 2016). • SCC is the second most common type of KC, representing 15%-20% of all cases (Nagarajan et al., 2019). • Incidence of SCC in the UK in 2018 ranged between 110.9 [95% CI 108.7-113.2]) in	Age	• Risk of KC (including SCC) is strongly associated with age. Incidence rises steeply from age 60 onwards with 48% of all cases occurring in people who are aged 75 and over (CRUK, 2021i; Kwiatkowska et al., 2021).
		Sex	• Overall incidence of SCC in the UK is higher in men than women (IRR 2.34 [95% CI 2.32-2.37]). Unlike BCC, incidence of SCC is also higher in males under the age of 50 (IRR 1.25 [95% CI 1.16-1.35]) (Kwiatkowska et al., 2021).
		Exposure to UVR	• The IARC working group designated solar radiation or UV emitting tanning beds as a group 1 carcinogen for SCC (El Ghissassi et al., 2009). • Outdoor work is associated with a statistically significant increased risk of SCC (OR 1.77 [95% CI 1.40-2.22]) compared to indoor work (Schmitt et al., 2011). • The use of sunbeds, at any age in life, is also associated with statistically significant increased risk of developing BCC (HR 1.67 [95% CI 1.29-2.17]) compared with people who have never used a sunbed (Wehner et al., 2012).

	Wales and 75.4 [95% CI 73.9-76.9]) per 100,000 population in Scotland (Kwiatkowska et al., 2021).	Skin phenotype	• Eighty-two percent of patients diagnosed with any KC in England in 2018 were of white ethnicity with less than one percent identifying as 'non-white' (Kwiatkowska et al., 2021). • KC (including SCC) is greater in individuals with fair skin versus dark skin (OR 1.75 [95% 1.42-2.15]) (Whiteman et al., 2016). • SCC was also found to be increased in individuals with red and light blond hair compared with individual with black hair suggesting a general greater risk in those with fairer skin (Rosso et al., 1996).
		Smoking	• Individuals who smoke have a statistically significant increased risk of SCC compared with individuals who never smoked (RR 1.32 [95% CI 1.15-1.52]) (Arafa et al., 2020)
Breast cancer	• Breast cancer can develop in different part of the breast tisues including the lobules, the cells lining the milk ducts, the stroma and nipple (Eliyatkın et al., 2015). • Malignant forms of breast cancer are ductal carcinoma no special type and lobular carcinoma while benign forms are are ductal carcinoma in situ and lobular carcinoma in situ (Momenimovahed and Salehiniya, 2019). • Breast cancer is also commonly classified based on tumour expression of oestrogen receptor (ER), progesterone receptor (PR)	Age	• Breast cancer risk if strongly associated with age. Breast cancer incidence increases steadily with age (CRUK, 2021a). Twenty-four percent of all new cases in 2018 were diagnosed in women aged 75 and over (CRUK, 2021a).
		Obesity (BMI] ≥ 30 kg/m^2)	• The IARC working group designated body fatness as a group 1 carcinogen for breast cancer (Lauby-Secretan et al., 2016). • Obese women (BMI≥30) have an increased riks of post-menopausal breast cancer than women who are not obese (RR 1.25 [95% CI 1.07-1.46]) (Dobbins et al., 2013). Obesity was also found to be associated with a 13% increase risk of developing breast cancer, for every 5 units of BMI increase, in post-menopausal women and an 8% decreased risk in pre-menopausal women (Kyrgiou et al., 2017)
		Alcohol consumption	• The IARC working group designated ethanol and acetaldehyde in alcoholic beverages as group 1 carcinogens for breast cancer (IARC, 2019). • A dose-response relationship between alcohol consumption and breast cancer at all levels has been demonstrated. Light drinkers (≤23.5 g per day) had a 4% increased risk (RR 1.04 [95% CI 1.01-1.07]) while heavy drinkers

	and human epidermal growth factor 2 receptor (HER-2) (Harbeck et al., 2019). • Breast cancer is the most common cancer in women and the second most cancer overal in the UK. The Incidence of breast cancer in 2018 was 169.0 (95% CI 168.2-169.8) per 100,000 population (CRUK, 2021a).		(>50 g per day) had a 61% increased risk [RR 1.61 [95% CI 1.33-1.94]) compared with non-drinkers (Bagnardi et al., 2015).
		Hormone replacement therapy	• The IARC working designated treatment with hormone replacement therapy (HRT) as group 1 carcinogen for breast cancer (IARC, 2019). • Breast cancer risk was significantly higher in women with long term treatment with oestrogen-only HRT (RR 1.33 [95% CI 1.28- 1.37] and oestrogen-progestogen combined HRT (RR 2.08 [95% CI 2.02-2.15]) compared to never-users (CGHFBC, 2019).
		Family history and genetic factors	• Breast cancer risk is significantly higher in women with one first-degree relative with breast cancer versus women with no first-degree relative (RR 1.80 [95% CI 1.69-1.91]) with the disease with risk increasing with increasing numbers of first-degree relatives (CGHFBC, 2001). • Risk is also greater in those who carry BRCA1 and BRCA2 mutations compared to those who do not in all age groups (Antoniou et al., 2003).
Lung cancer	• Lung cancer is a highly heterogenous disease that can arise in different sites of the bronchial tree. Non-small cell lung cancer (NSCLC) are the most common histological subtype, representing around 85% of all lung cancers with small cell lung cancer (SCLC) making up the remaining 15% (Gridelli et al., 2015). • NSCLC is subdivided in to non-squamous NSCLSC (70%) and squamous NSCLC (30%). Subtypes of non-squamous NSCLC include adenocarcinoma and large cell carcinoma (Gridelli et al., 2015).	Age	• Lung cancer risk is strongly related to age. Incidence of lung cancer rises steadily from age 45 to 49 peaking at ages 75 to 79 in women and ages 85 to 89 in men. Fourty-four percent of all new cases in the UK in 2018 were in people aged 75 and over(CRUK, 2021e).
		Sex	• The incidence of lung cancer in the UK in 2018 was higher in men (52% of new cases) than women (48% of new cases) (CRUK, 2021e). The lifetime risk of lung cancer diagnosis is 1 in 13 for men and 1 in 15 for women born after 1960 in the UK (Smittenaar et al., 2016).
		Family history	• Individuals with first-degree relative with lung cancer have 1.5-fold statistically significant increase in risk of developing lung cancer after adjusting for smoking and other potential confounders (OR 1.51 [95% CI 1.39-1.63]) (Coté et al., 2012).
			• Tobacco smoking and enviromental tobacco smoke (second-hand smoke) have been classified by the IARC as group 1 carcinogens for lung cancer

	• Lung cancer is the second most common cancer in both men and women in the UK and the overall leading cause of cancer-related mortality (CRUK, 2021f).The incidence of lung cancer in the UK in 2018 was 79.0 [95% CI 78.6-79.4]) per 100,000 population.	Smoking	(IARC, 2019). Tobacco smoking was estimated to be responsible for 72% of all lung cancer cases in the UK in 2015 (Brown et al., 2018). • Life time risk of developing lung cancer is 17 times higher in smokers compared with those who do not smoke (HR 17.66 [95% CI 14.65-21.29]) (Weber et al., 2021). • Lung cancer risk increases with the number of cigarettes smoked per day in both men and women. Risk is higher those who smoke ≥20 cigarettes per day (RR 13.70 [95% CI 7.40-25.50]; men) and (RR 24.10 [95% CI 12.70-45.90]; women) than those who smoke 1-9 cigarettes per day (RR 1.39 [95% CI 1.28-1.50); men) and (RR 1.49 [95% CI 1.37-1.61]; women]) (Gandini et al., 2008). • Smoking is more strongly to risk of developing small cell lung cancer and squamous cell lung cancer than other histological subtypes (Pesch et al., 2012).
Prostate cancer	• Prostate cancer develops in the prostate gland, located beneath the bladder and surrounding the urethra. The prostate is divided in to three zones; the central,	Age	• Prostate cancer risk increases is strongly asscoiated with age with incidence increasing steadily from age from age 45 to 49, peaking at ages 75 to 79. More than one in three of all new cases were diagnosed in men aged 75 and over in 2018 (CRUK, 2021j).

	transition and peripheral (Aaron et al., 2016). The peripheral zone makes up more than 70% of prostate glandular tissue with almost 80% of all prostate tumours arising from this site (Zlotta et al., 2013). • The most common type of prostate cancer in adenocarcinoma which can be divided up in to the subtypes acinar adenocarcinoma (the more common type) and ductal adenocarcinoma. Other types included transitional cell carcinoma which develop in the cells lining the urethra and neuroendocrine tumours and prostate sarcomas (Kaler et al., 2020). • Prostate cancer is the most common cancer in men in the UK. The incidence of prostate cancer in 2018 was 183.8 (95% CI 182.9-184.7) per 100,000 population (CRUK, 2021j).	Family history and genetics factors	• Prostate cancer is strongly associated with a family history of any cancer with an estimated 9% of men diagnoseed with prostate cancer having a family history of the disease (Hemminki, 2012) • Prostate cancer risk is 2.48 times higher in men with a first degree relative affected by prostate compared with men without a first degree relative with the disease (RR 2.48 [95% CI 2.25-2.74]) with risk highest in men with an affected brother (RR 3.14 [95% CI 2.37-4.15]) (Kiciński et al., 2011). • Prostate cancer risk is also higher in men with a first-degree female relative affected by breast cancer (RR 1.22 [95% CI 1.08-1.38]) compared to men without a female first-degree relative with the disease (Chen et al., 2008). • BRCA2 mutation carriers had a near 5-fold increase in risk of developing prostate cancer compared with men who were not carriers (RR 4.65 [95% CI 3.48-6.22]) (BCLC, 1999). • Men with Lynch syndrome have between a 2.13-fold (RR 2.13 [95% CI 1.45-2.80] and 2.5-fold (SIR 2.5 [95% CI 1.40-4.00]) statistally signifant increase in risk of prostate cancer compared with the general population (Haraldsdottir et al., 2014; Ryan et al., 2014).
		Ethnicity	• Life-time risk of developing prostate cancer varies by ethnicity. Black men (29.3%) were found to be more than twice as likely to be diagnosed with prostate cancer than White men (13.3%) and more than 7 times as likely than Asian men (4.2%) in the UK in 2010 (Lloyd et al., 2015).
Colorectal cancer	• Colorectal cancer consists of colon cancer and rectal cancer, considered a single entity due a number of shared features between the colon and the rectum. Colorectal cancers consist primarily of cancers in the colon (72%) (Alzahrani et	Age	• Colorectal cancer is strongly associated with age.Incidence of colorectal cancer rises steeply from age 55, peaking at age 85 in in both men and women. Fourty-three percent of all cases in the UK in 2018 occurred in people aged 75 and over (CRUK, 2021d).
		Sex	• The incidence of colorectal cancer in the UK in 2018 was higher in men (56% of all new cases) than in women (44% of all new cases) (CRUK,

	al., 2021). • The colon and rectum make up the large intestine which is divided up in to four sections: ascending colon and transverse colon (referred to as the proximal colon) and the descending and sigmoid colon (referred to as the distal colon) (Danielsen et al., 2013). • Colorectal cancers derive from benign polyps (adenomas) that go on to become malignant. Adenocarcinomas are the most common histological subtype of colorectal cancer, accounting for more than 90% of cases, arising from the mucosal epithelial cells (Alzahrani et al., 2021). • Colorectal cancer is the 4th most common cancer in the UK. The incidence of colorectal cancer in the UK in 2018 was 69.3 (95% CI 68.9-69.7) per 100,000 population (CRUK, 2021d).		2021d). The estimate lifetime risk of developing colorectal is 1 in 15 (7%) for men and 1 in 18 for women born in the UK after 1960 (Smittenaar et al., 2016).
		Smoking	• Tobacco smoking has been designated as group 1 carcinogens for both colon and rectum cancer by the IARC (IARC, 2019). • Individuals who smoke have a 16% (RR 1.16 [95% CI 1.09-1.24]) to 20% (RR 1.20 [95% CI 1.10-1.30]) statistically significant increased risk of colorectal cancer compared to those who have never smoked (Huxley et al., 2009; Tsoi et al., 2009). Former smokers also had a statistically significantly increased risk of colorectal cancer compared with never smokers (RR 1.18 [95% CI 1.12-1.25]) (Tsoi et al., 2009). • Risk of colorectal cancer is alo increased with duration of smoking: a 20 year increase in smoking duration was associated with a 9.4% increase in risk and a 40 year increase in smoking duration was associated with a 13.5% increase in risk (Liang et al., 2009).
		Obesity (BMI ≥ 30 kg/m^2)	• The IARC working group designated body fatness as a group 1 carcinogen for both colon and rectal cancer (Lauby-Secretan et al., 2016). • Individuals who are obese (BMI ≥ 30 kg/m^2) have a statistically significant increased risk of developing colorectal cancer compared those with BMI< 25 kg/m^2 (RR 1.19 [95% CI 1.11-1.29] (Huxley et al., 2009). • Risk of developing colon cancer is raised by 30% in men and 12% in women, for every 5-unit increase in BMI, respectively (Kyrgiou et al., 2017).
	• Colorectal cancer consists of colon cancer and rectal cancer, considered a single entity due a number of shared features between the colon and the rectum. Colorectal cancers consist primarily of cancers in the colon (72%) (Alzahrani et	Alcohol consumption	• Consumption of alcoholic bevarages is designated as a group 1 carcinogen for both colon and rectal cancer by the IARC (IARC, 2019). • A dose-response relationship between alcohol intake and colorectal cancer has been demonstrated for moderate drinkers (1.5-6 units per day) (RR 1.17 [95% CI 1.11-1.24]) and heavy drinkers (>6 units per day) (RR 1.44 [95% CI 1.25-1.65]) compared with non-drinkers (Bagnardi et al., 2015).

Colorectal cancer	al., 2021). • The colon and rectum make up the large intestine which is divided up in to four sections: ascending colon and transverse colon (referred to as the proximal colon) and the descending and sigmoid colon (referred to as the distal colon) (Danielsen et al., 2013). • Colorectal cancers derive from benign polyps (adenomas) that go on to become malignant. Adenocarcinomas are the most common histological subtype of colorectal cancer, accounting for more than 90% of cases, arising from the mucosal epithelial cells (Alzahrani et al., 2021). • Colorectal cancer is the 4th most common cancer in the UK. The incidence of colorectal cancer in the UK in 2018 was 69.3 (95% CI 68.9-69.7) per 100,000 population (CRUK, 2021d).	Family history and genetic factors	• Risk of developing colorectal cancer is strongly associated with family history of the disease. Individuals with at least one affects first-degree relative had a 2.2-fold statistically significant increased in risk (RR 2.24 [95% CI 2.06-2.43]) compared to those with no relatives affected by the condition. Individuals with two or more first-degree relatived with the disease had a near 4-fold increase in risk (RR 3.97 [95% CI 2.60-6.06]) (Butterworth et al., 2006). • Risk of colon cancer is increased in women under the age of 50 who carry BRCA2 mutations (SIR 3.81 [95% CI 1.77-7.23]) (Phelan et al., 2014).
		Inflammatory bowel disease	• Risk of colorectal cancer is is estimated to be 17% higher (SIR 1.7 [95% CI 1.2-2.2]) in individuals with inflammatory bowel disease compared with the general population (Lutgens et al., 2013). • Risk of colorectal cancer in these patients is further increases with the extent of inflammatory bowel disease (SIR 6.4 [95% CI 2.4-17.5]) and diagnosis before the age of 30 (SIR 7.2 [95% CI 2.9-17.9]) (Lutgens et al., 2013).
	• Melanoma is a potentially aggressive form of skin cancer originating in the melanocytes in the epidermis or arising from nevi (moles) (Leonardi et al., 2018).	Age	• Melanoma occurs more frequently in younger people than most cancers, however there is still an associated with older age with 29% of cases in the UK in 2018 diagnosed in people aged 75 and over (CRUK, 2021g).
		Sex	• The overall incidence of melanoma is slightly higher for men than women, however age-specific incidence vary greatly between the two: incidence is higher for women up to age 55 and higher for men from age 60 onwards

Melanoma	• Melanoma can develop anywhere on the skin but predominantly on the trunk in men and lower limbs among women (Bataille and de Vries, 2008). • Pre-cancerous melanoma is referred to as melanoma in situ. Superficial spreading melanoma is the most common malignant subtype, accounting for 70% of all cases. Other common subtypes include nodular melanoma and acral lentiginous melanoma, • Melanoma is the 5th most common cancer in the UK, accounting for 4% of all cases in 2018. The incidence of melanoma in the UK in 2018 was 26.8 (95% CI 26.6-27.0) per 100,000 population (CRUK, 2021g).		(CRUK, 2021g). This reflects the slight higher lifetime risk of developing melanoma in men (3%) versus women (2%) (Smittenaar et al., 2016).
		Exposure to UVR	• The IARC working group designated solar radiation or UV emitting tanning beds as a group 1 carcinogen for melanoma (El Ghissassi et al., 2009). • Risk of melanoma is significantly higher in individuals exposed to intermittent exposure to high intensity UVR, such as sunbathing or holidays in tropical climates (RR 1.61 [95% CI 1.31-1.99]) (Gandini et al., 2005). • Indoor tanning at any point in life is associated with a statistically significant increase in risk of developing melanoma compared to individuals who have never used indoor tanning equipment (RR 1.15 [95% CI 1.00-1.31]) with a further increase in risk observed in this who are first eposed in their youth (RR 1.75 [95% CI 1.35-2.26]) (IARC, 2007). • Risk of melanoma in those who have had sunburn is increased at any point in life compared with those who have never had a sunburn: childhood sunburn (OR 1.91 [95% CI 1.59-2.30]); adolescence sunburn (OR 1.63 [95% CI 1.42-1.86]); adulthood sunburn (OR 1.44 [95% CI 1.27-1.63]) (Dennis et al., 2008).
		Skin phenotype	• Skin pigmentation is stronly associated with melanoma risk. Individuals with Fitzpatrick skin phototype I (RR 2.27 [95% CI 1.77-2.92]), skin phototype II (RR 1.99 [95% CI 1.62-2.45]) and skin phototype III (RR 1.35 [95% CI 1.12-1.63]) all have a statistically significant increased risk of developing melanoma compared with individuals with Fitzpatrick skin phototype IV (Catherine M. Olsen et al., 2010). • Other features associated with fair skin such as hair colour and eye colour also indicate a statistically significant increased risk of melanoma compared with those with features associated with darker skin. Individuals with blond hair have 2-fold statistically significant increase in risk of melanoma (RR 2.00 [95% CI 1.47-2.73]) compared to individuals with dark hair (Catherine M. Olsen et al., 2010). Similarly, individuals with blue or

Melanoma			blue/grey eye colour has a near 1.6-fold statistically significant increase in risk of melanoma (RR 1.57 [95% CI 1.39-1.78]) compared with individuals with dark eye colour (Catherine M. Olsen et al., 2010).
		Family history and genetic factors	• Melanoma risk is markedly raised in individuals with a familial history of the disease. A 2.2-fold increase in risk has been observed in individuals with either a first-degree or second-degree relative (RR 2.06 [95% CI 1.72-2.45]) compared to those with no familial history of the disease (C. M. Olsen et al., 2010)

Abbreviations: Basal Cell Carcinoma (BCC); Keratinocyte Carcinoma (KC); Squamous Cell Carcinoma (SCC); United Kingdom (UK); International Agency for Research on Cancer (IARC); Body Mass Index (BMI); Relative Risk (RR); 95% Confidence Interval (CI); Odds Ratio (OR); Standardised Incidence Ratio (SIR); Cancer Research UK (CRUK); Ultra Violet Radiation (UVR)

1.4.3 Potential risk of cancer in psoriasis

1.4.3.1 Treatment with phototherapy

The primary environmental risk factor for BCC, SCC and melanoma is exposure to UVR from either natural (sunlight) or artificial (sunbed) sources (Calzavara-Pinton et al., 2015). UVR initiates and promotes carcinogenesis through a number of mechanisms (Nagarajan et al., 2019). UVR exposure induces DNA damage in keratinocyte cells and localized immunosuppression (Narayanan et al., 2010). DNA repair or apoptosis of damaged keratinocytes is impaired by UVR mediated mutations in p53 tumour suppressor genes (Benjamin and Ananthaswamy, 2007). Dysregulation in DNA repair and apoptosis leads to the survival and proliferation of mutated keratinocytes and initiation of KC (Kim and He, 2014). The IARC working group designated solar radiation or UV emitting sunbeds as a group 1 carcinogen for which there is sufficient evidence to conclude that it can cause BCC, SCC and melanoma in humans (El Ghissassi et al., 2009). The estimated proportion of BCC, SCC and melanoma cases attributable to UVR exposure globally was calculated using the population attributable factor (PAF) by Lucas et al (Lucas et al., 2008). The PAF is an epidemiological measure widely used to assess the impact of exposures in a population and is defined as the fraction of all cases of a particular disease (e.g. cancer) in a population attributable to a specific exposure (e.g. UVR) (Mansournia and Altman, 2018). PAF is calculated by subtracting the expected number of cases under no exposure (E) from the observed number of cases (O) in the population and dividing it by the observed number of cases ((E-0)/0) (Mansournia and Altman, 2018).The estimated PAF of skin cancers thought to be attributable to UVR exposure globally ranged from 0.5 to 0.9 for BCC and melanoma and 0.5 to 0.7 for SCC (Lucas et al., 2008).

1.4.3.2 Treatment with non-biologic systemic therapy

Methotrexate

Methotrexate has distinct anti-inflammatory and anti-tumourigenic mechanisms of action establishing it as one of the most widely used drugs in both the treatment of cancers and inflammatory conditions (BNF, 2021). Since the discovery that treatment with aminopterin led to remission in patients with leukaemia in the 1940's, anti-folate anti-metabolites have been a mainstay in chemotherapy of a number of cancers (Dayton et al., 2016). Indeed,

methotrexate was first developed as chemotherapeutic agent a decade before it was introduced in the treatment of psoriasis (Luber and Lee, 2012). Anti-folate anti-metabolites are molecules that resemble nucleotide metabolites and achieve their therapeutic effects by inhibiting the enzyme dihydrofolate reductase (DHFR) (Genestier et al., 2000). DHFR mediates the conversion of DHFR to tetrahydrofolate which plays an important role in the synthesis of pyrimidine and purine nucleotides. (Koźmiński et al., 2020). These pathways are essential in the repair and replication of DNA strands and cell division (Goodsell, 1999). Decreased levels of folate via the inhibition of DHFR by methotrexate leads to a downstream apoptotic effect on cells (Goodsell, 1999). Crucially, this cytotoxic effect is more pronounced in tumour cells due to the greater metabolic demands for folate that come with rapidly proliferating cells (Luengo et al., 2017).

Ciclosporin

Since the discovery of its immunosuppressive properties in the 1970's, ciclosporin has played a prominent role in the care of patients following organ transplantation and in bone marrow transplant recipients with graft versus host reactions (Ghalie et al., 1994; Tedesco and Haragsim, 2012). The immunosuppressive effects of ciclosporin are as a result of its inhibition of T-helper and cytotoxic T-cells implicated in transplant and graft rejection (Russell et al., 1992). Ciclosporin selectively binds to cyclophilin, a family of proteins secreted by T-cells in response to inflammatory stimuli (Nigro et al., 2013). This stimulates cyclophilin to the recruitment of calcineurin, leading to the inhibition of calcineurin-dependent transcriptase factors essential for the transcription of the IL-2 gene (Flores et al., 2019). This leads to the downstream effect of reduced IL-2 secretion by activated T cells and expression of IL-2 receptors by cytotoxic T cells (Flores et al., 2019). Ciclosporin also induces the production of transforming growth factor (TGF)-β, an inhibitor of IL-2 mediated T-cell proliferation, and induces T-cell apoptosis (Hojo et al., 1999).

Ciclosporin's immunosuppressive mechanisms have also been implicated in tumourigenesis. Ciclosporin treatment has been reported to diminish DNA repair in keratinocytes after exposure to UV irradiation in renal transplant patients (Herman et al., 2001). A study of gene expression in human peripheral blood mononuclear cells in the presence and absence of therapeutic levels of ciclosporin observed inhibition of the gene coding for the DNA repair

enzyme, DNA polymerase β (Ahlers et al., 1999). Depressed DNA repair in keratinocytes damaged by UVR can lead to increased risk of DNA mutations and eventual skin carcinogenesis (Thoms et al., 2011). Ciclosporin has also been implicated in the inhibition of apoptosis. Cyclophilin is part of the permeability transition pore (PTP), a complex of proteins that sit between the inner and outer membranes of mitochondria (Halestrap et al., 2002). Ciclosporin binding with cyclophilin in the mitochondria inhibits the PTP from releasing pro-apoptotic molecules (Pritchard et al., 2000). PTP is implicated in the release of pro-apoptotic molecules that trigger the execution phase of apoptosis, (Ravagnan et al., 2002). Inhibition of the release of these molecules from the mitochondria will prevent the destruction of abnormal cells which can go on to develop into tumour cells. TGF-β is a cytokine with both tumour-supressing and tumour-promoting functions within cancer cells depending on the tumour stage (Colak and ten Dijke, 2017). In healthy non-cancerous cells and early stage tumour cells, TGF-β plays an important role in the induction of apoptosis, inhibition of angiogenesis and suppression of the proliferation of cancer cells through cell cycle arrest (Kubiczkova et al., 2012). In late stage tumour cells, mutations of the TGF-β signalling pathway lead to secreted TGF-β promoting cell proliferation, promotion of angiogenesis, invasion of nearby tissue and metastasis (Tian et al., 2011). These individual mechanisms, when considered in isolation, don't fully explain the potential tumourigenic role of ciclosporin. However, they could provide a working model when considers as part of one process: (1) Inhibition of the DNA repair mechanism can lead to DNA mutation; (2) Inhibition of apoptosis impairs the ability of the immune system to eliminate tumour cells; (3) Induction of TGF-β promotes progression of surviving tumour cells (Wong, 2011).

Acitretin

Acitretin, a synthetic retinoid, is unique among the systemic therapies approved for the treatment of psoriasis in that its antipsoriatic effects are not mediated via immunosuppression (Lin et al., 2016). Although it's mechanism of action in psoriasis has not been fully elucidated, acitretin is thought to activate the retinoic acid receptors (α, β and γ) by selective binding to these nuclear receptors (Saurat, 1999). This leads to downstream effect on expression of epidermal growth factor genes translating to a reduction in the proliferation of keratinocytes, migration of neutrophils to the epidermis and reduced CD25 lymphocytes in psoriatic plaques (Bécherel et al., 1994; Gottlieb et al., 1996). Systemic

retinoids, such as acitretin, have also been shown to have anti-tumourigenic effects in a number of cancers (Bushue and Wan, 2010). Retinoic acid, the active metabolite of retinols, play a central role in regulation of cell growth, differentiation and apoptosis (Tang and Gudas, 2011). In tumour cells, they inhibit angiogenesis, induce cells to differentiate and inhibit their proliferation (Lens and Medenica, 2008).

1.4.3.3 Treatment with biologic therapy

Tumour necrosis factor inhibitors

Cytokines targeted by biologic therapies in the treatment of psoriasis play dual roles in tumour development and progression. TNF is a pro-inflammatory cytokine first identified in 1975 and cloned in 1984 and acquired its name after it was observed that high concentrations of locally injected TNF induced necrosis of sarcomas in mice (Carswell et al., 1975; Pennica et al., 1984). TNF was found to achieve its anti-tumourigenic effect by triggering apoptosis of tumour endothelial cells thus playing an important role in the suppression of tumour cell proliferation and the initiation of tumour regression (Daniel and Wilson, 2008; Wang and Lin, 2008). Subsequently, TNF was briefly incorporated in the treatment of cancer; high concentrations of TNF, in combination with the alkylating agent melphalan and interferon gamma, were perfused in the limbs of patients with melanoma and locally advanced soft tissue sarcoma (Eggermont et al., 1996; Fraker et al., 1996).

TNF has also been implicated in tumourigenesis in a number of ways. The potential role of TNF in tumour development was first demonstrated in mouse models, deficient of TNF or its receptors (TNFR1 and TNFR2), such models were associated with resistance to the development of skin and liver cancer (Arnott et al., 2004; Knight et al., 2000; Moore et al., 1999). Serum concentration of TNF has been found to be increased in patients with a number of cancers including breast cancer and prostate cancer and subsequently decreased following chemotherapy (Berberoglu et al., 2004; García-Tuñón et al., 2006; Michalaki et al., 2004). TNF is thought to promote tumour angiogenesis, invasion and metastasis through a number of mechanisms which include the upregulation of nitric oxide leading to DNA mutations, the upregulation of angiogenic factors such as IL-8 and vascular endothelial growth factors and increasing tumour cell invasion by inducing matrix metalloproteases (Hagemann et al., 2005; Jaiswal et al., 2000; Nabors et al., 2003). Thus, blocking TNF could potentially have a role in the treatment of cancer. Treatment with the TNFi therapies

etanercept and infliximab in mice was demonstrated to reduce the growth of pancreatic ductal adenocarcinoma and metastasis to the liver (Egberts et al., 2008). Phase I and II clinical trials evaluating TNFi for refractory renal cell carcinoma, metastic breast cancer and recurrent ovarian cancer reported that treatment with etanercept and infliximab led to partial response and disease stabilization in some patients (Harrison et al., 2007; Madhusudan et al., 2004; Madhusudan et al., 2005).

Interleukin-12 and interleukin-23 inhibitors

IL-12 and IL-23 are pleiotropic cytokines central to the regulation of inflammation, linking the innate and adaptive immune response (Watford et al., 2003). Both are expressed by activated dendritic cells and phagocytes and have conflicting roles in the immune response to tumour initiation, growth and metastases (Colombo and Trinchieri, 2002; Jantschitsch et al., 2012). In the tumour micro-environment IL-12 acts on natural killer cells, T-cells and innate lymphoid cells to induce IFN-y secretion (Cavallo et al., 1997). IFN-y is directly involved in the inhibition of angiogenesis by upregulating adhesion molecules and facilitating leukocyte recruitment to the tumour site (Eisenring et al., 2010; Sorensen et al., 2010). In addition, IL-12 also stimulates the cytotoxic activities of CD4 and CD8 T cells and inhibits the activity of pro-tumourigenic cells such as tumour associated macrophages and myeloid-derived suppressor cells (Buszello, 1995; Steding et al., 2011; Watkins et al., 2007). The IL-23 mediated immune response is postulated to have pro-tumourigenic effects. Although the exact mechanisms are poorly understood, IL-23 is thought counteract the anti-tumourigenic effects of IL-12 activated cytotoxic T cells (Jantschitsch et al., 2012)

Studies in mice lacking the IL-12 specific p35 and the IL-12/23 shared p40 subunits were demonstrated to developed tumours at a higher frequency then mice not deficient of the p35 and p40 subunits (Meeran et al., 2006; Smyth et al., 2000). Furthermore, mice deficient of IL-12 receptor β2 subunit showed enhanced growth of transplanted tumours compared with wild type mice with the IL-12 receptor β2 subunit (Airoldi et al., 2005). A number of genome wide association studies of individuals with genetic polymorphisms in genes encoding IL-12p35 or the IL-12/23 p40 subunits have indicated increases susceptibility for cancers of the oesophagus, bladder, prostate and glioblastoma, respectively (Ebadi et al., 2014; Tao et al., 2012; Winchester et al., 2015; Zhao et al., 2009). Malignancy data for IL-23 from murine models and genome wide association studies in humans are limited. Mice that

had lost IL-23 functioning via deficiencies in the IL-23p19 subunit or IL-23 receptor were resistant to skin cancer development and growth compared to mice with functioning IL-23 (Teng et al., 2010; Teng et al., 2011). Il-23p19 or IL-23 receptor deficiency was also reported to result in decreased tumour development and growth in murine models of colorectal cancer (Grivennikov et al., 2012). Several clinical studies have found increased serum levels of IL-23 in patients with cancer compared with healthy controls (Gangemi et al., 2012; He et al., 2011; Li et al., 2012; Ljujic et al., 2010). Increased levels of Il-23 were associated with poorer survival in breast cancer and pancreatic cancer (Gangemi et al., 2012; He et al., 2011). In patients with liver cancer, increased expression of IL-23 in the tumour microenvironment was also associated with metastasis (Li et al., 2012). Although these individual studies are not designed to study the causal relationship between IL-12 and Il-23 deficiency and cancer, they do indicate that inhibition of IL-12 could confer a potential increased risk while inhibition of Il-23 could confer a decreased risk.

Interleukin-17 inhibitors

IL-17 production and signaling have emerged as a major pathogenic factor in cancer development (Vitiello and Miller, 2019). IL-17 cytokines are also postulated to promote tumour progression through a number of mechanisms (Vitiello and Miller, 2019). IL-17 induces chemokines to recruit myeloid cells to tumour tissue where they augment angiogenesis (Veglia et al., 2018). IL-17 also creates an immunosuppressive tumour microenvironment by inducing IL-6 production from macrophages and tumour cells while also repressing the expression of Th1 activated cytotoxic chemokines (Fisher et al., 2014; He et al., 2010).

In preclinical cancer models, inhibition of IL-17 has been shown to suppress metastasis in breast cancer and improve sensitivity to chemotherapy and radiation in colorectal cancer (Coffelt et al., 2015; Lotti et al., 2013; Wang et al., 2014). In support of these preclinical observations, higher serum levels of IL-17 have been associated with poor prognosis (metastasis or recurrence) in patients with gastric, colorectal, liver and lung cancer (Tseng et al., 2014; Xu et al., 2014; Yamada et al., 2012). Taken together, these finding suggest that IL-17 inhibition could potentially decrease risk of cancer.

1.5 Literature review of psoriasis and risk of cancer

1.5.1 Risk of cancer in patients treated with topical and phototherapy

1.5.1.1 Topical therapies

Topical therapies in the form of either topical corticosteroids or vitamin D_3 analogues are the most widely used treatments in psoriasis. The evidence to date pertaining to cancer risk in patients with psoriasis treated with these topical therapies is scarce; the authors of a recently published systematic review investigating risk of skin cancer in patients with psoriasis or other conditions treated with topical corticosteroids were unable to identify any studies meeting their broad inclusion criteria (Ratib et al., 2018). There has been some discussion of whether or not prolonged treatment with systemic corticosteroids could increases the risk of cancer due to their role in the regulation of metabolism, cell growth and proliferation, apoptosis and immune function (Ostenfeld et al., 2013; Sørensen et al., 2012). However, population based case-control studies of 1.8 million patients in Denmark found no effect on risk of colorectal cancer (Odds Ratio [OR] 0.93 [95% CI 0.85-1.00]) and breast cancer (OR 1.0 [95% CI 0.96-1.10]) compared with general population controls after adjusting for risk factors (Ostenfeld et al., 2013; Sørensen et al., 2012).

1.5.1.2 Phototherapies

Due to the well-established association of UV radiation with the development of skin cancer (described in Section 1.4.3.1), the most widely studied treatments as it pertains to cancer risk are phototherapies. Treatment with PUVA, a mutagenic, carcinogenic and immunosuppressive form of photochemotherapy, has long been associated with dose-dependent increased risk of KC, particularly SCC (Bruynzeel et al., 1991; Lindelöf et al., 1999; McKenna et al., 1996; Stern, 2012). This also included the development of SCC on skin in areas not exposed phototherapy such as the male genitalia (Stern et al., 2002; Stern et al., 1998). Melanoma risk following PUVA exposure is less clear. The US-based PUVA follow-up study demonstrated an increased risk of melanoma after 15 years of follow-up (Relative Risk [RR] 5.40 [95% CI 2.20-11.10]), with patients receiving 200 courses having a greater risk than those treated with less than 200 courses (Incidence Rate Ratio [IRR] 2.90 [95% CI 1.30-6.40]) (Stern, 2001; Stern et al., 1997). Although this increased risk was not demonstrated in other prospective studies, these studies were carried out in European populations where

treatment guidelines are different, enrolled smaller numbers of participants and had shorter follow-up periods than the PUVA follow-up study (Bruynzeel et al., 1991; Hannuksela-Svahn et al., 2000; Lindelöf et al., 1999).

Far fewer studies have examined risk of cancer associated with narrowband UVB therapy than PUVA which was highlighted by a systematic review of studies investigating the risk of skin cancers in patients treated with phototherapies published between 1980 and 2010 identifying only 4 studies in patients treated with UVB (Archier et al., 2012). The limited evidence to date does not support an increased risk of KC or melanoma in patients treated with narrowband UVB (Black and Gavin, 2006; Hearn et al., 2008; Weischer et al., 2004). However, patients who received more than 300 treatment of broadband UVB and previous exposure to PUVA were reported to have had a statistically significant increased risk of developing BCC (IRR 1.45 [95% CI 1.07-1.96]) and SCC (IRR 1.37 [95% CI 1.03-1.83]) (Lim and Stern, 2005).

1.5.2 Risk of cancer in patients treated with non-biologic systemic therapies

1.5.2.1 Methotrexate

The earliest studies of cancer risk in patients with psoriasis treated with systemic therapy in the pre-biologic era found no increased risk of cancer following treatment with methotrexate (Bailin et al., 1975; Nyfors and Jensen, 1983). The PUVA follow-up study found that methotrexate-treated patients had a statistically significant increased risk of developing lymphoma (IRR 4.39 [95% C 1.59-12.06]), however it was not clear to what extent this was driven by previous exposure to PUVA or the disease itself as they were compared to the general population (Stern, 2006). Patients in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) treated with methotrexate were reported to have a statistically significant increased risk of developing BCC (Hazard Ratio [HR] 8.58 [95% CI 3.29-22.4]) when compared with patients treated with non-biologic therapy other than methotrexate (deShazo et al., 2019). However, there was no statistically significant difference in risk of developing SCC between these cohorts (HR 0.91 [95% CI 0.43-1.95]) (deShazo et al., 2019). A recently published Swedish nationwide registry-based nested case-control study of psoriasis patients found no statistically significant difference in risk of developing melanoma (OR 1.0 [95% CI 0.80-1.30]) between methotrexate-treated patients those have never been treated with methotrexate (Polesie et al., 2020).

1.5.2.2 Ciclosporin

The earliest evidence pertaining to the risk of cancer following treatment with ciclosporin was provided by a post-marketing surveillance study monitoring organ transplant recipients for 7 years after surgery demonstrating a two-fold increase in risk of all cancer, mainly attributed to an increase in skin cancers (Cockburn and Krupp, 1989). Organ transplant recipients have been demonstrated to have an 84-fold increased risk of Kaposi's sarcoma, a 65-fold increased risk of SCC, and a 3-fold increased risk of melanoma compared with the general population (Jensen et al., 1999). Kidney transplant recipients receiving a combination of ciclosporin, azathioprine and prednisolone had a 2.8-fold greater risk of SCC than patients receiving just azathioprine and prednisolone (Jensen et al., 1999).

Patients with psoriasis are treated with lower doses of ciclosporin than organ transplant recipients (max dose of up to 4-5mg/kg, twice daily vs 10-15mg/kg daily) with treatment duration limited to a few years which suggests that cancer risk should be negligible (Griffiths et al., 2004). However, there is some evidence that patients with psoriasis treated with ciclosporin have an increased risk of SCC. A prospective cohort study, following 1252 patients with psoriasis for a period of 5 years after initiating treatment with ciclosporin, reported a statistically significant increased risk of developing any cancer (Standardised Incidence Ratio [SIR] 2.10 [95% CI 1.60-2.90]), primarily driven by a 6-fold statistically significant increased risk of KC (SIR 6.20 [95% CI 3.80-9.50]) (Paul et al., 2003). In this same study, treatment with ciclosporin was not associated with a statistically significant increase or decrease in risk for any of the solid or haematological cancers (Paul et al., 2003). The increased risk of SCC seen in patients treated with ciclosporin could be explained by previous exposure to PUVA (Marcil and Stern, 2001; Muellenhoff and Koo, 2012; Paul et al., 2003).

1.5.2.3 Acitretin

Acitretin is a systemic retinoid drug used not only in the treatment of psoriasis but also in the treatment and prevention of a number of different cancer types in organ transplant recipients which could suggest a possible protective role in psoriasis (Cheeley et al., 2013; Huen and Kim, 2015; McKenna and Murphy, 1999). The evidence to date, as synthesised by a systematic review, suggests no association between treatment with acitretin monotherapy or in combination with phototherapy. Furthermore, a 5-year prospective

study of 956 patient evaluating the long-term safety of the oral retinoid etretinate found no evidence of any increased risk or decreased risk of developing cancer compared with patients treated with PUVA (Stern et al., 1995).

1.5.2.4 Fumaric Acid Esters

FAEs are the most widely prescribed therapies for patients requiring systemic therapy in Germany and do not appear to be associated with an increased risk of cancer based on the evidence provided by a systematic review of 19 RCTs and two prospective cohort studies (Smith, 2017). Similarly, a German single-centre retrospective cohort study of 859 patients followed up for a mean period of 3.6 years indicated that treatment with FAEs, prescribed as monotherapy or in combination with either phototherapy or methotrexate, was not associated with an increased risk of cancer (Dickel et al., 2018).

1.5.2.5 Apremilast

Safety data for the novel small molecule immunomodulatory apremilast was limited to a long-term analysis of up 156 weeks for 1184 patients initially enrolled to two phase 3, RCTs (ESTEEM 1 and ESTEEM 2) (Crowley et al., 2017). They reported that the incidence rate for all cancer (excluding KC) was comparable to that reported for patients with psoriasis in the PSOLAR and an analysis of a claims database in the USA (Crowley et al., 2017; Gottlieb et al., 2014; Kimball et al., 2015b).

1.5.3 Risk of cancer in patients treated with biologic therapies

1.5.3.1 Tumour necrosis factor inhibitors

The majority of studies investigating risk of cancer risk in biologic-treated patients were in those treated with TNFi (Table 1.3). A systematic review of 20 RCTs in TNFi-treated patients reported an increased, but not statistically significant, risk of developing cancer (OR 1.48 [95% CI 0.71-3.09]) compared with controls (Dommasch et al., 2011). A long-term integrated analysis of 18 clinical trials of adalimumab for psoriasis found no statistically significant difference in risk of developing all cancer (excluding KC) compared with controls (Standardised Incidence Ratio [SIR] 0.86 [95% CI 0.58-1.23]) (Leonardi et al., 2019). An integrated analysis of 7 short and long-term etanercept trials similarly found no statistically significant increase in risk for all cancer (excluding KC) (SIR 1.15 [95% CI 0.78-1.64] (Pariser et al., 2012). A study of 1,373 infliximab treated patients from three international clinical trials reported a potentially decreased risk of all cancer (excluding KC) (SIR 0.39 [95% CI 0.05-1.42]) but the results was not statistically significant (Menter et al., 2008a).

When considering the total risk of cancer in patients treated with TNFi compared with patients treated with non-biologic systemic therapy, the evidence is limited to three published studies. The OBSERVE-5, observational, surveillance registry study of patients with psoriasis treated with etanercept reported a slight decreases, statistically non-significant, decreased risk of developing all cancer (excluding KC) compared with patients in health insurance databases in the USA treated with either methotrexate or ciclosporin (SIR 0.78 [95% CI 0.59-1.00]) (Kimball et al., 2015a). However, patients in the comparator group were those with any indication so could have included patients with other inflammatory conditions (Kimball et al., 2015a). A nested case-control study of 12,090 patient enrolled in PSOLAR reported that patients treated with TNFi for more than 12 months had a statistically significant increased risk of developing all cancer (excluding KC) (OR 1.53 [95% CI 1.10-2.12]) compared with psoriasis patients treated with conventional systemic therapy (Fiorentino et al., 2017). However, it was not clear from this study if patients in the comparator group were all biologic-naïve, potentially confounding any possible association between biologic therapy and cancer risk (Fiorentino et al., 2017). Similarly, a study of malignancy risk in patients with psoriasis in the Kaiser Permanente Northern California health (KPNC) insurance database demonstrated no statistically significant difference in risk of developing

all cancer (excluding KC) in patients treated with biologics (97% TNFI-treated) compared with non-biologic systemic therapy (adjusted HR [aHR] 0.86 [95% CI 0.66-1.13]) (Asgari et al., 2017).

Long-term safety analysis of adalimumab trials reported a statistically significant increased risk of KC (SIR 1.55 [95% CI 1.10-2.13]) compared with the general population in the USA (Leonardi et al., 2019). The evidence for risk of KC in etanercept-treated is conflicting. The integrated safety analysis of short and long-term etanercept trials reported a statistically significant increased risk of SCC (SIR 4.80 [95% CI 1.31-12.29]) compared with the general population of Minnesota (USA) (Pariser et al., 2012). However, no statistically significant increased risk of SCC (SIR 2.03 [95% CI 0.55-5.20]) or BCC (SIR 0.64 [95% CI 0.21-1.50]) was observed in these patients when compared with the general population of Arizona (Pariser et al., 2012). Both analyses in the Pariser et al study used comparator populations that were not contemporaneous with the biologic cohort. The general population rates were obtained from the 1985-1996 Arizona and 1984-1992 Minnesota cancer registries (Pariser et al., 2012). The incidence of KC in the USA has significantly increases since the 1990s (Rogers et al., 2015). Comparing risk of KC at distinct time points in this likely lead to the inflated risk estimates. The OBSERVE-5 study reported a statistically significant decreased risk of KC for etanercept-treated patients (SIR 0.54 [95% CI 0.42-0.69]) compared with patients with any indication treated with either methotrexate or ciclosporin (Table 1.3) (Kimball et al., 2015a).

Patients with psoriasis treated with TNFi were found to have a statistically significant 6-fold increase in risk of developing KC (aHR 6.0 [95% CI 1.60-22.40]) compared with patients with rheumatoid arthritis (RA) in a prospective cohort study set in the Netherlands (van Lümig et al., 2015). Biologic-treated patients in the KPNC study were found to have an overall statistically significant increased risk of developing KC (aHR 1.42 [95% CI 1.12-1.80]) and SCC (aHR 1.81 [95% CI 1.23-1.67]) compared with patients treated with non-biologic systemic therapy (Asgari et al., 2017). Biologic-treated psoriasis in the KPNC study also had a raised but not statistically significant risk of developing BCC (aHR 1.23 [95% CI 0.91-1.66]) compared with the non-biologic systemic comparator group (Asgari et al., 2017).

A cohort study set in PSOLAR reported an increased but not statistically significant risk of developing BCC (HR 2.09 [0.90-4.85]) and a decreased but not statistically significant risk of developing SCC (HR 0.67 [0.32-1.41]) in biologic-treated psoriasis patients compared with

biologic-naive patients with psoriasis who have not had treatment with methotrexate (deShazo et al., 2019). However, when considering just patients treated with TNFi, the authors reported a statistically significant increased risk of developing BCC (aHR 2.54 [1.08-5.98]) (deShazo et al., 2019).

The evidence to date pertaining to the risk of cancers other than the KCs (BCC, SCC) in TNFi-treated patients is limited to a few studies. A three-fold increased risk of melanoma was reported for patients treated with adalimumab in clinical trials (SIR 3.04 [95% CI 1.11-6.62]) compared with the US general population (Leonardi et al., 2019). However, the KPNC study reported no increased risk of melanoma in biologic-treated patients (aHR 1.57 [95% CI 0.61-4.09]) compared with patients treated with non-biologic systemic therapy (Asgari et al., 2017). The OBSERVE-5 study reported a statistically significant decreased risk of developing lymphoma (SIR 0.26 [95% CI 0.03-0.95]) in patients treated with etanercept compared with patients treated with methotrexate or ciclosporin (Kimball et al., 2015a). However, KPNC cohort study found no statistically significant difference in risk of developing lymphoma between biologic-treated and non-biologic systemic-treated patients (aHR 0.97 [95% CI 0.37-2.51]) (Table 1.3) (Asgari et al., 2017).

1.5.3.2 Other biologic therapies

The evidence for risk of cancer in patients treated with biologic therapies other than TNFi is limited to a handful of studies (Table 1.3). In the PSOLAR study, treatment with ustekinumab was associated with a potential increased but statistically non-significant increased risk of developing BCC (aHR 1.35 [95% CI 0.49-3.67]) (deShazo et al., 2019). When considering SCC risk, ustekinumab-treated patients in the PSOLAR study were demonstrated to have a decreased but statistically non-significant risk of developing SCC (aHR 0.30 [95% CI 0.10-0.90]) (deShazo et al., 2019). In a five-year safety analysis of four clinical trials, treatment with ustekinumab was associated with an elevated but not statistically significant risk of developing breast cancer (SIR 0.62 [95% CI 0.17-1.58]) and prostate cancer (SIR 1.21 [95% CI 0.66-2.04]) (Papp et al., 2013). The same study also indicated decreased risk of developing colorectal cancer (SIR 0.99 [95% CI 0.32-2.31]) and lymphoma (SIR 0.80 [95% CI 0.10-2.91]) for ustekinumab-treated patients, however these results were not statistically significant (Papp et al., 2013).

To date, there is no real world evidence for risk of cancer in patients treated with IL-23 and IL-17 inhibitors. A recently published systematic review and meta-analysis of clinical trials examining adverse events reported for IL-17 and IL-23 inhibitors showed no increased risk of any cancer for these therapies (Loft et al., 2020). Pooled analyses of clinical trials for the IL-17A inhibitors secukinumab and ixekizumab demonstrated comparable incidence rates of all cancer (excluding KC) with etanercept and the general population (Strober et al., 2017; van de Kerkhof et al., 2016). For the IL-23 inhibitor guselkumab, a long-term extension of a phase 3 clinical trial reported no increased risk of all cancer (excluding KC) or KC (Reich et al., 2020).

Table 1.3: Summary of studies assessing the risk of developing cancer in patients with psoriasis treated with biologic therapy

Study	Study type	Biologic therapy	Study population (follow-up)	Reference population	Outcome	Risk estimate (95% CI)
Total cancer (all sites)						
Menter et al., 2008	Analysis of 3 clinical trials	Infliximab	1,373 patients (30-50 weeks)	US general population	All cancer (excluding KC)	SIR 0.39 (0.05-1.42)
Pariser et al., 2012	Integrated analysis of 7 clinical trials	Etanercept	4,410 patients (4,775.1 person years)	US general population	All cancer (excluding KC)	SIR 1.15 (0.78-1.64)
Papp et al., 2013	Safety analysis of four clinical trials	Ustekinumab	3,317 patients (8,998 person years)	US general population	All cancer (excluding KC)	SIR 0.98 (0.74-1.29)
Leonardi et al., 2019	Integrated analysis of 18 clinical trials	Adalimumab	3,727 patients (5,429.9 person years)	US general population	All cancer (excluding KC)	SIR 0.86 (0.58-1.23)
Kimball et al., 2015	Observational, post-marketing safety study	Etanercept	2,510 patients (7-8 years)	US claims database (systemically-treated patients with inflammatory conditions)	All cancer (excluding KC)	SIR 0.78 (0.59-1.00)
Fiorentino et al., 2017	Case-control study nested in a registry-based cohort study	TNFi	12,090 patients, 252 malignancy cases (>12 months)	1,008 systemically-treated matched controls	All cancer (excluding KC)	OR 1.53 (1.10-2.12)
Asgari et al., 2017	Cohort study of a Health insurance Database (KPNC)	Biologics (97% TNFI)	2,285 patients (9,175 person-years)	3,604 systemically-treated patients from same population	All cancer (excluding KC)	HR 0.86 (0.66-1.13)

Study	Study type	Biologic therapy	Study population (follow-up)	Reference population	Outcome	Risk estimate (95% CI)
Solid and haematological cancer						
Papp et al., 2013	Safety analysis of four clinical trials	Ustekinumab	3,317 patients (8,998 person years)	US general population	Breast cancer	SIR 0.62 (0.17-1.58)
Papp et al., 2013	Safety analysis of four clinical trials	Ustekinumab	3,317 patients (8,998 person years)	US general population	Prostate cancer	SIR 1.21 (0.66-2.04)
Papp et al., 2013	Safety analysis of four clinical trials	Ustekinumab	3,317 patients (8,998 person years)	US general population	Colorectal cancer	SIR 0.99 (0.32-2.31)
Papp et al., 2013	Safety analysis of four clinical trials	Ustekinumab	3,317 patients (8,998 person years)	US general population	Lymphoma	SIR 0.80 (0.10-2.91)
Kimball et al., 2015	Observational, post-marketing safety study	Etanercept	2,510 patients (7-8 years)	US claims database (systemically-treated patients with inflammatory conditions)	Lymphoma	SIR 0.26 (0.03-0.95)
Asgari et al., 2017	Cohort study of a health insurance database (KPNC)	Biologics (97% TNFi)	2,285 patients (9,421 person-years)	3,604 systemically- treated patients from same population	Lymphoma	HR 0.97 (0.37-2.51)

Study	Study type	Biologic therapy	Study population (follow-up time)	Reference population	Outcome	Risk estimate (95% CI)
Skin cancer						
Leonardi et al., 2019	Integrated analysis of 18 clinical trials	Adalimumab	3,727 patients (5,429.9 person years)	US general population	All KC	SIR 1.55 (1.10-2.13)
Leonardi et al., 2019	Integrated analysis of 18 clinical trials	Adalimumab	3,727 patients (5,429.9 person years)	US general population	Melanoma	SIR 3.04 (1.11-6.62)
Pariser et al., 2012	Integrated analysis of 7 clinical trials	Etanercept	4,410 patients (4,775.1 person years)	General population of Minnesota (USA)	SCC	SIR 4.80 (1.31-12.29)
Pariser et al., 2012	Integrated analysis of 7 clinical trials	Etanercept	4,410 patients (4,775.1 person years)	General population of Arizona (USA)	SCC	SIR 2.03 (0.55-5.20)
Pariser et al., 2012	Integrated analysis of 7 clinical trials	Etanercept	4,410 patients (4,775.1 person years)	General population of Arizona (USA)	BCC	SIR 0.64 (0.21-1.50)
Kimball et al., 2015	Observational, post-marketing safety study	Etanercept	2,510 patients (7-8 years)	US claims database (systemically-treated patients with inflammatory conditions)	All KC	SIR 0.54 (0.42-0.69)
van Lümig et al., 2015	Cohort study	TNFI	280 patients (Median 4.8 years)	Biologic-treated rheumatoid arthritis patients from the same region	All KC	HR 6.00 (1.60-22.4)
Asgari et al., 2017	Cohort study of a health insurance database (KPNC)	Biologics (97% TNFI)	2,285 patients (9,079 person-years)	3,604 systemically- treated patients from same psoriasis population	All KC	HR 1.42 (1.12-1.80)
Asgari et al., 2017	Cohort study of a health insurance database (KPNC)	Biologics (97% TNFI)	2,285 patients (9,323 person-years)	3,604 systemically- treated patients from same psoriasis population	SCC	HR 1.81 (1.23-2.67)

Asgari et al., 2017	Cohort study of a health insurance database (KPNC)	Biologics (97% TNFI)	2,285 patients (9,211 person-years)	3,604 systemically- treated patients from same psoriasis population	BCC	HR 1.23 (0.91-1.66)
Asgari et al., 2017	Cohort study of a health insurance database (KPNC)	Biologics (97% TNFI)	2,285 patients (9,421 person-years)	3,604 systemically- treated patients from same psoriasis population	Melanoma	HR 1.57 (0.61-4.09)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	Biologics combined	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	BCC	HR 2.09 (0.90-4.85)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	TNFi	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	BCC	HR 2.54 (1.08-5.98)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	Ustekinumab	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	BCC	HR 1.35 (0.49-3.67)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	Biologics combined	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	SCC	HR 0.67 (0.32-1.41)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	TNFi	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	SCC	HR 0.91 (0.43-1.95)
Deshazo et al., 2019	Registry-based cohort study (PSOLAR)	Ustekinumab	7,955 patients	Biologic-naïve patients treated with systemic-therapies other than methotrexate	SCC	HR 0.30 (0.10-0.90)

Abbreviations: Randomised Controlled Trial (RCT); United States of America (USA); Keratinocyte Carcinoma (KC); Standardised Incidence Ratio (SIR); Tumour Necrosis Factor Inhibitors (TNFi); Odds Ratio (OR); Hazard Ratio (HR); Squamous Cell Carcinoma (SCC); Basal Cell Carcinoma (BCC); Kaiser Permanente Northern California (KPNC); Psoriasis Longitudinal Assessment and Registry (PSOLAR).

1.5.4 Overview of systematic reviews and meta-analyses

A possible association between psoriasis and cancer was initially muted in the late 1970s (Alderson and Clarke, 1983; Halprin et al., 1982). The first major study of the risk of cancer in psoriasis patients was a population-based retrospective cohort study conducted in health insurance claims database populations in the USA between 1992 and 1996 (Margolis et al., 2001). Incidence rates of cancer in 16,519 psoriasis patients and in 234,204 psoriasis-free patients with hypertension were compared (Margolis et al., 2001). This study demonstrated that patients with severe psoriasis, defined as those treated with systemic therapy, were significantly more likely to develop cancer than those with hypertension (relative risk [RR] 1.78 [95% CI 1.32 -2.40]). In the following two decades, multiple studies in a number of different populations, have investigated whether or not patients with psoriasis have an increased risk of developing cancer compared with the general population, with conflicting results (Geller et al., 2018).

The results from these individual studies, described in Sections 1.5.1-1.5.3, have been synthesised in three systematic reviews and meta-analyses published between 2013 and 2020 (Table 1.4). The first of these investigated the risk of overall and site-specific cancer in patients with psoriasis compared with the general population and consisted of 37 observational studies (33 cohort studies; 4 case-control studies) published between January 1980 and January 2012 (Pouplard et al., 2013). According to this study, patients with psoriasis had a statistically significant increase in their background risk of developing KC, BCC, SCC, solid cancers (respiratory tract; upper aerodigestive tract; urinary tract; liver) and non-Hodgkin lymphoma (Pouplard et al., 2013).

In 2019, a second systematic review and meta-analysis of 58 observational studies reporting on cancer incidence and cancer mortality was published (Trafford et al., 2019). This comprehensive study updated the previous systematic review and meta-analysis (Pouplard et al., 2013) and stratified the risk of overall and site-specific cancers by disease severity, presenting separate analyses for risk of cancer for patients with severe disease, and level of adjustment for lifestyle factors associated with cancer (obesity; smoking; excessive alcohol consumption). Trafford et al found that patients with psoriasis, with any disease severity, had a statistically significant increased risk for overall cancer (all sites) and for a number of site-specific cancers including BCC, SCC, colorectal cancer, oesophageal cancer, liver cancer

and non-Hodgkin lymphoma. Risk of overall and site-specific cancer was highest in those with severe disease severity, corresponding to patients treated with systemic therapy (Table 1.4) (Trafford et al., 2019).

A third systematic review and meta-analysis was published studying the prevalence, incidence and risk of cancer in adults with psoriasis and PsA. This consisted of 112 cohort studies published up to January 1st 2019 (Vaengebjerg et al., 2020). Unlike the two prior systematic reviews and meta-analyses, Vaengebjerg et al limited their inclusion criteria to studies reporting risk estimates for the following outcomes: all cancer; cancer excluding KC; KC; melanoma; lymphoma (lymphoma overall, Hodgkin lymphoma, non-Hodgkin lymphoma); breast cancer; lung cancer; colorectal cancer and bladder cancer. They reported an increased risk for several cancers including KC, lymphomas, lung cancer and bladder cancer (Vaengebjerg et al., 2020). Despite differences in search strategies and inclusion criteria, these three systematic reviews and meta-analyses provide the most comprehensive and up to date overview of risk of cancer in psoriasis populations. The results from these systematic reviews and meta-analyses are summarised in Section 1.5.1 and Table 1.4.

1.5.5 Results from the systematic reviews and meta-analyses

1.5.5.1 Total cancer (all sites)

Risk estimates for studies considering the risk of all cancer were pooled by the two most recent systematic reviews and meta-analysis (Trafford et al., 2019; Vaengebjerg et al., 2020). In both studies patients with psoriasis of all severities and those with severe disease were reported to have statistically significant increases in risk of developing cancer (overall) compared with the general population with pooled relative risk (pRR) estimates of 1.18 (95% CI 1.06-1.31; 7 studies), 1.22 (95% CI 1.08-1.39; 9 studies) and 1.21 (95% CI 1.11 -1.33; 14 studies), respectively (Table 1.4) (Trafford et al., 2019; Vaengebjerg et al., 2020).

Studies reporting the risk of all cancer excluding KC were pooled in two of the three systematic reviews and meta-analyses (Pouplard et al., 2013; Vaengebjerg et al., 2020). Despite the sizable difference in the number of included studies between the two systematic reviews, pRR estimates demonstrated similar levels of statistically significant increased risks of developing all cancer (excluding KC) in patients with psoriasis with

reported pRR estimates of 1.16 (95% CI 1.07-1.25; 6 studies) and 1.14 (95% CI 1.04-1.25; 15 studies), respectively (Table 1.4) (Pouplard et al., 2013; Vaengebjerg et al., 2020).

1.5.5.2 Solid cancers

Breast cancer

Patients with psoriasis were not demonstrated to have a statistically significant increased risk of breast cancer compared with the general population in the two most recently published systematic reviews and meta-analyses: pRR 1.04 (95% CI 0.98-1.11; 6 studies) and pRR 1.07 (95% CI 0.99-1.15; 13 studies) (Trafford et al., 2019; Vaengeberg et al., 2020). Although Pouplard et al. reported a statistically significant increased risk of breast cancer for patients with psoriasis (pRR 1.15 [95% CI 1.02-1.29; 7 studies]), the increased overall pRR estimate was significantly driven by the inclusion of two studies reporting a positive association, with the remaining 5 studies reported no statistically significant increase in risk (Table 1.4) (Lindelöf et al., 1990; Stern and Lange, 1988).

Lung cancer

The reported pRR estimates of lung cancer for patients with psoriasis varied between the systematic reviews and meta-analyses. Both the Pouplard et al. study (pRR 1.52 [95% CI 1.02-1.29; 6 studies]) and the Vaengebjerg et al. study (pRR 1.26 [95% CI 1.13-1.40; 14 studies] reported an increased risk of lung cancer. However, Trafford et al. reported no increase in risk of lung cancer for patients with psoriasis of all severities (pRR 1.28 [95% CI 0.98-1.68; 6 studies]) or those with severe psoriasis (pRR 1.32 [95% CI 0.94-1.86]; 6 studies) (Table 1.4) (Trafford et al., 2019).

Prostate cancer

Studies reporting pRR estimates for prostate cancer were included in only one of the published systematic reviews and meta-analyses (Trafford et al., 2019). Patients with psoriasis (all severities) (pRR 1.03 [95% CI 0.91-1.17]; 5 studies) and severe psoriasis (pRR 1.01 [95% CI 0.87-1.18]; 3 studies) were reported to have a slightly raised but not statistically significant risk of prostate cancer (Table 1.3) (Trafford et al., 2019).

Colorectal cancer

Studies investigating risk of developing colorectal cancer in patients with psoriasis were included in all three systematic reviews and meta-analysis (Table 1.4). Patients with psoriasis of all severities were reported to have increased, but not statistically significant, risks of developing colorectal cancer in the studies pooled by Pouplard et al. (pRR 1.12 [95% CI 0.95-1.32]; 5 studies) and Vaengebjerg et al. (pRR 1.16 [95% CI 0.99-1.35]; 10 studies). Trafford et al reported a statistically significant increases in risk of colorectal cancer for patients with (pRR 1.34 [95% CI 1.06-1.70]; 3 studies), however, a smaller number of studies were pooled for this outcome.

1.5.5.3 Skin cancers

Keratinocyte carcinomas

Studies reporting risk estimates for KC, BCC and SCC represent that largest group of studies synthesised by the two most recently published systematic reviews and meta-analyses (Table 1.4) (Trafford et al., 2019; Vaengebjerg et al., 2020). Psoriasis patients with any disease severity had a 1.7-fold (pRR 1.71 [95% CI 1.08-2.71; 4 studies]) and a near 2.3-fold and pRR 2.28 (95% CI 1.73-3.01; 17 studies) statistically significant increased risk of developing KC compared with general population comparators (Trafford et al., 2019; Vaengebjerg et al., 2020). When considering just the studies with psoriasis patients with severe disease, Trafford et al reported a near 2.5-fold statistically significant increase compared with the general population to pRR 2.44 (95% CI 1.68-3.56; 7 studies) (Trafford et al., 2019; Vaengeberg et al., 2020).

Risk of developing BCC and SCC were outcomes of interest in only two of the three systematic reviews and meta-analyses (Pouplard et al., 2013; Trafford et al., 2019). Psoriasis patients with any disease severity were reported to have 2-fold statistically significant increased risk of developing BCC (pRR 2.00 [95% CI 1.83-2.20; 7 studies]) compared with the general populations (Pouplard et al., 2013). Although Trafford et al did not see conclude a statistically significant increased risk of developing BCC when pooling patient cohorts with any disease severity (pRR 1.29 [95% CI 0.73-2.26; 3 studies]), the authors did report a near 3.2-fold statistically significant increased risk when only considering patients with severe disease (pRR 3.17 [95% CI 1.32-7.60; 3 studies]) (Trafford et al., 2019).

When considering the outcome risk of SCC, psoriasis patients with any disease severity were reported to have a 2.5-fold (pRR 2.51 [1.32-3.50]; 4 studies) and 5.3-fold (pRR 5.31 [2.63-10.71]; 7 studies) statistically significant increase in risk compared with general population comparators, respectively (Pouplard et al., 2013; Trafford et al., 2019). There is a possible association between SCC risk and disease severity for patients with psoriasis. Trafford et al reports a near 12-fold statistically significant increase when pooling risk estimates from only studies with patients with severe psoriasis (pRR 11.74 [95% CI 1.52-90.66]) (Trafford et al., 2019).

Melanoma

Pooled RR estimates reported by all three of the systematic reviews and meta-analyses suggest a potentially increased, but not statistically significant, risk of developing melanoma for psoriasis patients with any disease severity compared with the general population: 1.07 (95% CI 0.85-1.35; 6 studies), 1.17 (95% CI 0.82-1.66; 6 studies) and 1.13 (95% CI 0.99-1.29); 16 studies), respectively (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020).

1.5.5.4 Haematological cancers

Lymphoma

Patients with psoriasis of all severities were reported to have an increased risk of lymphoma (included Non-Hodgkin lymphoma and Hodgkin lymphoma) by Trafford et al. (pRR 1.40 [95% CI 1.24-1.57]; 4 studies) and Vaengebjerg et al. (pRR 1.56 [95% CI 1.37-1.78]; 15 studies) (Trafford et al., 2019; Vaengebjerg et al., 2020). Trafford et al. also reported a near 3.4-fold statistically significant increase in risk when considering studies with patients cohorts with severe psoriasis (pRR 3.39 [95% CI 1.34-8.62]; 4 studies) (Table 1.4) (Trafford et al., 2019).

The three systematic reviews also reported statistically significant increases in risk of developing non-Hodgkin lymphoma in patients with psoriasis of all disease severities: 1.40 (95% CI 1.06-1.86; 4 studies), 1.28 (95% CI 1.15-1.43; 5 studies) and 1.48 (95% CI 1.30-1.69; 9 studies) (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020). However, Trafford et al. reported an increased but statistically non-significant increase in risk when restricting inclusion to studies of patients with severe psoriasis (pRR 1.64 [95% CI 0.99-2.72]). The systematic review and meta-analysis by Vaengebjerg et al. was the only study

pooling studies with risk estimates for Hodgkin lymphoma in patients with psoriasis reporting a statistically significant increased risk (pRR 1.87 [95% CI 1.40-2.48]; 6 studies) Table 1.4 (Vaengebjerg et al., 2020).

Leukaemia

Studies reporting risk estimates for leukaemia were included in the Pouplard et al and Trafford et al systematic reviews and meta-analyses. Patients with psoriasis of all disease severities were reported to have an increased but not statistically significant risk of developing leukaemia in both studies: pRR 1.84 (95% CI 0.78-4.34; 4 studies) and pRR 1.23 (95% CI 0.85-1.78; 3 studies) (Pouplard et al., 2013; Trafford et al., 2019). Similarly, when restricting inclusion to studies with patients with severe psoriasis, an increased but not statistically significant risk of developing leukaemia compared with the general population (pRR 1.53 [95% CI 0.92-2.55]; 4 studies) (Table 1.4)

Table 1.4: Summary of pooled risk estimates for overall and common site-specific cancers from patients with psoriasis from meta-analyses

Cancer site/type	Pouplard et al 2013	Trafford et al 2019†	Trafford et al 2019‡	Vaengebjerg et al 2020
	pRR (95% CI); [number of pooled studies]			
Total cancer				
All cancer	-	**1.18 (1.06 - 1.31); [7]**	**1.22 (1.08 - 1.39); [9]**	**1.21 (1.11 - 1.33); [14]**
All cancer excluding keratinocyte carcinoma	**1.16 (1.07 - 1.25); [6]**	-	-	**1.14 (1.04 - 1.25); [15]**
Solid cancers				
Breast (female)	**1.15 (1.02 - 1.29); [7]**	1.04 (0.98 - 1.11); [6]	1.14 (0.98 - 1.33); [8]	1.07 (0.99 - 1.15); [13]
Lung	**1.52 (1.35 - 1.71); [6]**	1.28 (0.98 - 1.68); [6]	1.32 (0.94 - 1.86); [6]	**1.26 (1.13 - 1.40); [14]**
Colorectum	1.12 (0.95 - 1.32); [5]	**1.34 (1.06 - 1.70); [3]**	-	1.16 (0.99 - 1.35); [10]
Prostate	-	1.03 (0.91 - 1.17); [5]	1.01 (0.87 - 1.18); [3]	-
Kidney	-	**1.58 (1.11 - 2.24); [3]**	1.21 (0.96 - 1.52); [3]	-
Liver		**1.83 (1.28 - 2.61); [2]**	**1.94 (1.51 - 2.49); [2]**	-
Haematological cancers				
All lymphoma	-	**1.40 (1.24 - 1.57); [4]**	**3.39 (1.34 - 8.62); [4]**	**1.56 (1.37 - 1.78); [15]**
Non-Hodgkin lymphoma	**1.40 (1.06 - 1.86); [4]**	**1.28 (1.15 - 1.43); [5]**	1.64 (0.99 - 2.72); [2]	**1.48 (1.30 - 1.69); [9]**
Hodgkin lymphoma	-	-	-	**1.87 (1.40 - 2.48); [6]**
Leukaemia	1.84 (0.78 - 4.34); [4]	1.23 (0.85 - 1.78); [3]	1.53 (0.92 - 2.55); [4]	-
Skin cancers				
All keratinocyte carcinoma	-	**1.71 (1.08 - 2.71); [4]**	**2.44 (1.68 - 3.56); [7]**	**2.28 (1.73 -3.01); [17]**
Basal cell carcinoma	**2.00 (1.83 - 2.20); [7]**	1.29 (0.73 - 2.26); [3]	**3.17 (1.32 - 7.60); [3]**	-
Squamous cell carcinoma	**5.31 (2.63 - 10.71); [7]**	**2.15 (1.32 - 3.50); [4]**	**11.74 (1.52 - 90.66); [3]**	-
Melanoma	1.07 (0.85 - 1.35); [6]	1.17 (0.82- 1.66); [6]		1.13 (0.99 - 1.29); [16]

Abbreviations: pRR = pooled relative risk; 95% CI = 95% confidence interval

† = psoriasis patients with any disease severity; ‡ = psoriasis patients with severe disease severity only

1.5.6 Summary of the literature review

Based on the evidence provided by the three systematic reviews and meta-analyses, described in Sections 1.5.4 and 1.5.5, there is a consensus that patients with psoriasis have a statistically significant increased risk of developing cancer (all sites) and cancer (excluding KC) compared with the general population (Table 1.4) (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020). Patients with psoriasis were also found to have statistically significant increases in risk of developing a number of site-specific cancers, namely KC, BCC, SCC, lymphoma and non-Hodgkin lymphoma across the three studies (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020). Moreover, pRR estimates reported for a number of other site-specific cancers, although not statistically significant, also indicated potentially increased risk for patients with psoriasis. These included the commonly occurring site-specific cancers (breast, lung colorectal, melanoma) and less common cancers (leukaemia, kidney, liver) (Table 1.4) (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020).

Despite the large number of studies synthesised by the systematic reviews and meta-analyses and the comprehensive study of overall and site-specific cancer risk for psoriasis patients, there are a number of limitations that need to be considered when interpreting their results. Patients with psoriasis have been demonstrated to have an increased prevalence of a number of cancer risk factors compared with the general population (Guenther and Gulliver, 2009). These include smoking, excessive consumption of alcohol and obesity (Armstrong et al., 2012; Armstrong et al., 2014; Brenaut et al., 2013). The IARC working group has found sufficient evidence to class these risk factors as group 1 carcinogens for a wide range of site-specific cancers (IARC, 2019; Lauby-Secretan et al., 2016). Only 7 of the studies synthesised in the three systematic reviews and meta-analyses adjusted for risk factors, other than age and sex (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020). The inclusion of studies not adjusting for risk factors such as smoking, excessive consumption of alcohol and obesity in the meta-analyses could explain the reported increased risk of overall and site-specific cancers for psoriasis patients compared with the general population, rather than the disease itself. An example of how the synthesis of studies adjusting for these risk factors can lead to attenuation of cancer risk was provided by a subgroup analysis by Trafford et al. Meta-analysis of studies adjusting for

only age and sex (level 1 adjustment) reported a 1.25-fold statistically significant increased risk for all cancer (pRR 1.25 [95% CI 1.08-1.45]) compared with just a 1.09-fold increased risk for all cancer when restricting inclusion to studies adjusting for age, sex and one other risk factor (pRR 1.09 [95% CI 0.97-1.22]) (Trafford et al., 2019).

Another limitation, present in two of the three systematic reviews and meta-analysis, is the inclusion of studies with psoriasis populations made up of those with mild disease and those with severe disease severity (Pouplard et al., 2013; Vaengebjerg et al., 2020). Patients with mild disease are typically treated with topical therapies while those with severe disease are treated with phototherapy and systemic therapy (Section 1.3). The potential difference in risk between the two groups is highlighted by Trafford et al who have presented risk of cancer analyses stratified by disease severity (Trafford et al., 2019). Pooled risk estimates for overall cancer and a number of the site-specific cancer were slightly higher for studies including patients with only severe psoriasis than those including those will all disease severities (Trafford et al., 2019). Thus the inclusion of both groups of patients with varying disease severity and treatment history could have possibly masked or attenuated the reported risk of overall and site-specific cancer in the two of the three systematic reviews and meta-analysis (Pouplard et al., 2013; Vaengebjerg et al., 2020).

There are other important limitations that should also be considered when interpreting the results of the three systematic reviews and meta-analyses. There were several sources of heterogeneity between the included studies in each of systematic review that would make comparisons difficult. These include differences in the risk estimates presented (IRR, HR, SIR, and RR), origins of the reference populations (health insurance databases, national population registries), cancer verification (self-reported, cancer registry data), assessment of psoriasis (physician diagnosed, patient reported) and length of follow-up. (Pouplard et al., 2013; Trafford et al., 2019; Vaengebjerg et al., 2020). The relationship between treatment exposure and cancer risk in patients with psoriasis was also not investigated with studies of biologic-treated patients also not included in two of the three systematic reviews and meta-analysis (Pouplard et al., 2013; Trafford et al., 2019).

The evidence provided by the systematic reviews leave the question of whether treatment with specific antipsoriatic therapies, specifically systemic therapies, is associated with an increased risk of cancer unanswered. The evidence to date, as described in Sections 1.5.1-

1.5.3, indicate treatment with topical therapies are not associated with an increased risk of cancer while there is strong evidence associating phototherapy with PUVA as highlighted by the PUVA follow-up studies (Stern, 2012). The evidence to date does not suggest an increased risk of cancer for patients treated with narrowband UVB, however the evidence to date is too limited to conclusively rule out an increased risk of KC. Ciclosporin is associated with an increased risk of overall cancer in organ transplant recipients and seems to confer an increased risk of KC in patients with psoriasis, however most studies have been carried out in patients previously exposed to PUVA (Paul et al., 2003). The evidence for methotrexate is less conclusive with some studies reporting an increased risk of cancer while others did not report an association between methotrexate exposure and cancer. The limited evidence for acitretin, FAEs and apremilast does not support an increased risk of cancer following treatment with these conventional systemic and small molecule immunomodulatory therapies.

Given the long standing interest in risk of KC in psoriasis patients treated with systemic therapy, studies investigating this outcome represent the majority of studies in biologic-treated populations (Table 1.3). The evidence to date suggests an increased risk of KC in biologic-treated patients compared with general populations. However, most of the studies were analyses of RCTs with few compared risk to psoriasis patients treated with other systemic therapies. Despite the widespread use of biologic therapies, studies investigating the long-term risk of solid and haematological cancers, compared with patients treated with non-biologic systemic therapy are absent. The risk of cancer in biologic treated patients was also investigated in a systematic review by Peleva et al in 2017 (Peleva et al., 2018). The authors were able to identify 8 prospective cohort studies published up to August 2016 of which 7 compared risk of cancer to general population comparators and one study to patients with RA. The studies included in this systematic review reported increased risk of KC and SCC with no reported increased risk for other cancer outcomes (all cancer, lymphoma, melanoma, prostate, colorectal and breast) (Peleva et al., 2018).

Meta-analysis was not performed by the authors due to heterogeneity of the included studies. The literature review and the systematic reviews and meta-analyses have highlighted a clear need to clarify the risk of cancer for patients with psoriasis, who have previously been treated with non-biologic systemic therapy, compared with patients treated

with only non-biologic systemic therapy. A systematic review and meta-analysis of studies investigating risk of melanoma in patients with psoriasis and other immune-mediated inflammatory diseases was conducted in 2019 to begin answering this important research question (Section 1.6). This study was published in JAMA dermatology (Esse et al., 2020).

1.6 Risk of melanoma in patients treated with biologic therapy for common inflammatory diseases: systematic review and meta-analysis.

1.6.1 Introduction

Psoriasis along with the immune-mediated inflammatory conditions, inflammatory bowel disease (IBD) and RA are linked by both overlapping genetic susceptibility and several treatment modalities (Beyaert et al., 2013; David et al., 2018). TNF-α, has proved critical in the immune-pathogenesis of these diseases and inhibition of this cytokine has revolutionized treatment outcomes (Beyaert et al., 2013; Kuek et al., 2007). The standard paradigm of care for immune-mediated inflammatory diseases dictates that those requiring systemic therapy are initially treated with conventional systemic therapy such as methotrexate. If such therapies are contraindicated or response is considered inadequate, treatment progresses to biologic therapy. Highly cost-effective biosimilar TNF inhibitors (TNFi) are currently the first line biologic for all 3 of these immune-mediated inflammatory diseases, although other biologic classes are also commonly used (Baumgart and Sandborn, 2012; Greb et al., 2016; Ordás et al., 2012; Smolen et al., 2017).

Melanoma is a highly immunogenic skin cancer and therefore of concern to patients treated with TNFi since melanoma risk increases with suppression of the immune system, and TNF-α plays an important role in the immune surveillance of tumours (Crusz and Balkwill, 2015; Passarelli et al., 2017). To date, systematic reviews specifically examining the risk of melanoma between biologic-treated and biologic-naïve conventional systemic-treated patients have been limited to RA. The most recently published meta-analysis of studies in biologic-treated RA patients found that treatment with TNFi did not significantly increase risk of melanoma compared with conventional systemics (pRR 1.4, 95% CI 0.70-2.60), but the authors concluded that a clinically meaningful risk of melanoma could not be ruled out (Olsen and Green, 2018).

The risk of melanoma in IBD and psoriasis patients treated with biologic therapy compared with conventional systemic-treated patients is even less clear (Annese et al., 2015; Geller et al., 2018). The most recent meta-analysis examining risk of melanoma in IBD patients did not include any study comparing biologic-treated IBD patients with biologic-naïve IBD

patients (Singh et al., 2014). The only systematic review of any cancer in biologic-treated psoriasis patients identified a single study examining risk of melanoma compared with the general population (Peleva et al., 2018).

Melanoma is a potentially aggressive cancer caused primarily by exposure to ultraviolet radiation (UVR) from natural (sunlight) or artificial (tanning bed) sources with skin pigmentation being a key genetic risk factor (Duffy et al., 2010; Leonardi et al., 2018). Recent decades have witnessed a dramatic increase in the incidence of melanoma in many countries including the USA, the UK, Norway and Sweden (Olsen et al., 2019). Despite the implementation of skin cancer prevention programs, melanoma incidence rates are set to continue rising in these populations for the next few decades (Olsen et al., 2019). Therefore, identifying if patients with common immune-mediated inflammatory disorders who are increasingly prescribed immunomodulatory agents are at further increased risk of developing melanoma is important.

All relevant published studies up to the 7th February 2019 were reviewed systematically and meta-analyses were conducted to determine the most precise estimates of melanoma risk in IBD, RA and psoriasis patients treated with biologic therapy compared with those treated with only conventional systemic therapies.

1.6.2 Methods

This systematic review and meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix 1).

1.6.2.1 Search strategy and eligibility criteria

The Embase, MEDLINE and Cochrane CENTRAL databases were searched for eligible studies published between 1st January 1995 and 7th February 2019 (Appendix 2). No geographic or language restrictions were imposed. The database search was supplemented with hand searching of the reference sections of retrieved articles. Cohort studies comparing the risk of melanoma inpatients with IBD, RA and psoriasis were identified. These studies were eligible for inclusion if patients were treated with biologic therapy for a period of at least 12 months and were compared with biologic-naïve patients with similar clinical and disease characteristics treated with conventional systemic therapies alone.

Study eligibility was independently assessed by two reviewers who screened titles and abstracts of studies followed by reading the studies in full. Disagreements about eligibility were resolved by discussion with a third reviewer.

1.6.2.2 Data extraction and quality assessment

The following items were extracted from the included studies: lead author and year of publication; study design; source population and baseline demographics; type/s of biologic therapy; comparator therapy; treatment duration; follow-up period; outcomes; quantitative estimates with 95% CI. Selection, matching and outcome were assessed for included cohort studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies (NOS, 2019) (Appendix 3). Studies were assessed for adjustment for the following risk factors: age; sex; UVR exposure; concomitant/historic exposure to conventional systemic therapy; exposure to phototherapy with PUVA; skin colour (Appendix 4).

1.6.2.3 Data synthesis and analysis

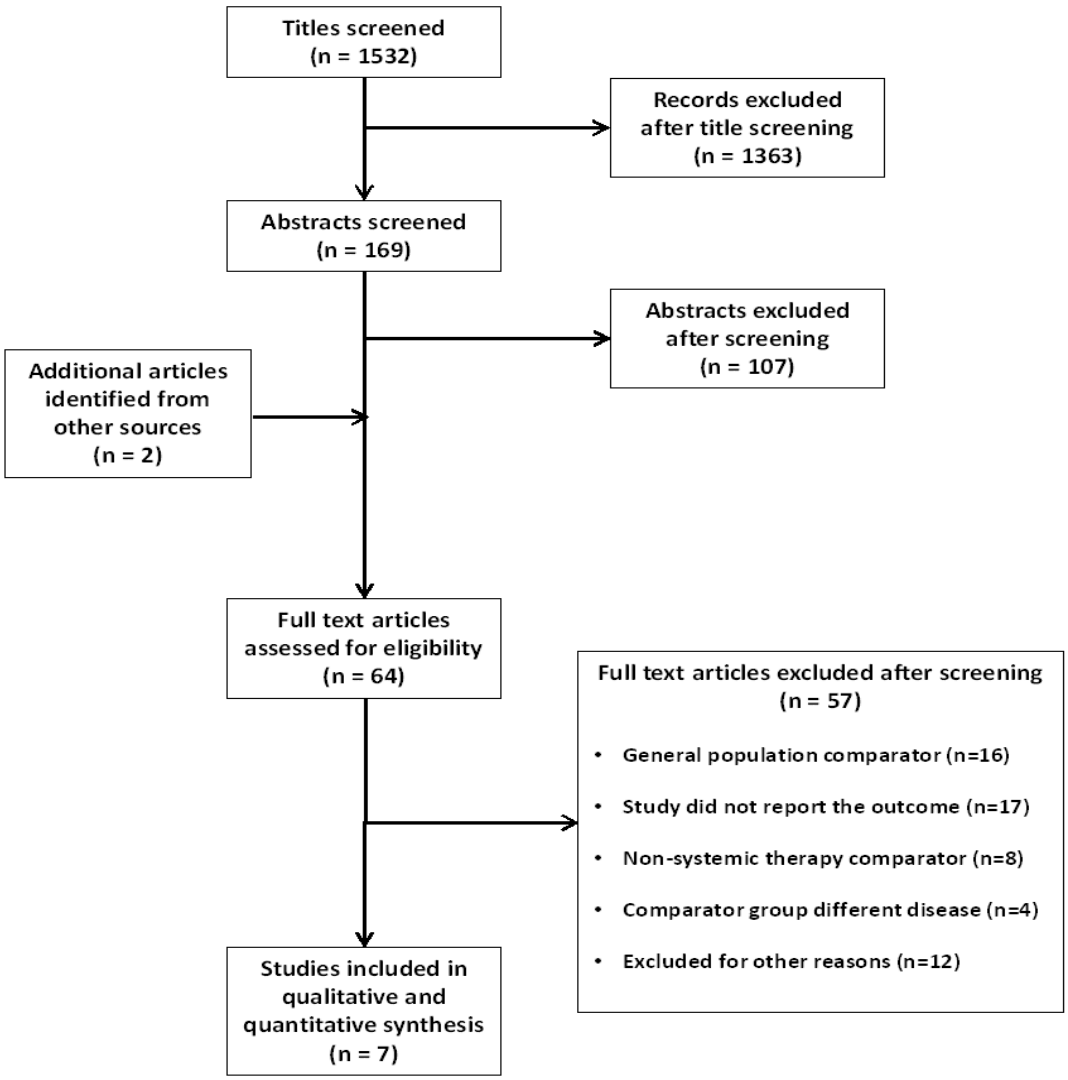
The risk estimates and 95% CIs were calculated for IBD, RA and psoriasis using the generic inverse variance approach. In studies providing multiple relative risk estimates, those adjusted for the greatest number of confounders were adopted. Statistical heterogeneity across the included studies was assessed using the Q-statistic (χ^2), with a significance level of 0.05, and quantified by the I^2 statistic. An I^2 statistic ≥ 50% was considered to represent significant heterogeneity. The random-effects model was adopted in anticipation of clinical heterogeneity. Pre-specified sensitivity analyses were performed by excluding point estimates from the meta-analysis to ensure that overall risk estimates were not markedly affected by individual studies. In response to the large number of TNFi-treated patients identified in the literature search, a post–hoc secondary analysis of melanoma risk in TNFi-treated IBD and RA patients under a fixed-effects model was performed. Factors considered for subgroup analyses were mechanism of biologic therapy, treatment duration and adjustment for risk factors. Publication bias was evaluated through visual inspection of a funnel plot and using Begg's and Egger's tests in which a p-value ≤ 0.05 indicates significant publication bias. All analyses were conducted using STATA, version 14.1 (StataCorp, USA).

1.6.3 Results

1.6.3.1 Search results

A total identified 1532 records after removing duplicates. Following title screening, 1363 records were removed with a further 107 records excluded by abstract screening. The remaining 62 articles along with two additional articles identified by hand-searching were read in full and screened for eligibility. After 57 articles were excluded for ineligibility, 7 studies remained for analysis (Figure 1.6).

Figure 1.6: Systematic review and meta-analysis - flow chart for the search results



1.6.3.2 Characteristics of included studies

The 7 included studies, published between 2007 and 2019, were all cohort studies conducted in the USA (n=3), Denmark (n=2), Sweden (n=1) and Australia (n=1). The majority of studies were set in population-based registries with two studies carried out in health insurance databases. Two studies were conducted in IBD patients (McAuliffe et al., 2015; Nyboe Andersen et al., 2014), 4 in RA patients (Dreyer et al., 2013; Staples et al., 2019; Wadstrom et al., 2017; Wolfe and Michaud, 2007) and 1 study in psoriasis patients (Asgari et al., 2017). In total, there were 34,079 biologic treated patients and 135, 370 biologic-naïve patients treated with conventional systemics. Average patient follow-up duration ranged from 1 to 5.48 years with study periods ranging from 1998 to 2015 (Table 1.5).

All of the included studies consisted of patients treated with TNFi. Five studies included all patients treated with TNFi (Dreyer et al., 2013; McAuliffe et al., 2015; Nyboe Andersen et al., 2014; Staples et al., 2019; Wadstrom et al., 2017) and one study reported individual effect estimates for patients treated with adalimumab, etanercept and infliximab (Wolfe and Michaud, 2007). Asgari et al included all patients treated with biologic therapy (97% treated with TNFi). In addition to TNFi-treated patients, Wadström et al also included patients treated with abatacept (CD-28 inhibitor) and rituximab (CD-20 inhibitor). Adjustment for age and sex was performed in all included studies.

Adjustment for historic or concomitant exposures to immunosuppressive therapies was performed in 1 study (Nyboe Andersen et al., 2014), with adjustment for ethnicity (an indicator of skin colour, a major risk factor for melanoma) also performed in only 1 study (Asgari et al., 2017) (Appendix 4). Exposure to UVR was not reported or adjusted for in any of the included studies.

Table 1.5: Characteristics of the studies included in the systematic-review and meta-analysis

Indication	Study lead author and year (study design)	Population source (study period)	Biologic Cohort			Non-biologic Cohort			Relative Risk (95% CI)	Adjustment for confounders*
			Therapy, N	Treatment duration	Cases	Therapy, N	Treatment duration	Cases		
IBD	Nybou-Andersen 2014 (Cohort Study)	The Danish National Patient Registry (1999-2012)	TNFi, 4,553	Mean - 3.7 years	9	Biologic naïve non-biologic systemic, 51,593	-	176	**RR 1.31 (0.63 - 2.74)**	Disease duration; use of methotrexate, cyclosporine/cyclophosphamide and azathioprine
IBD	McAuliffe 2015 (Cohort Study)	The Health Core Integrated Research Database (2004 - 2011)	TNFi, 3,348	Mean - 1.0 years	1	Biologic naïve non-biologic systemic, 29,472	-		**HR 0.62 (0.08 - 4.75)**	No additional adjustment performed
RA	Dreyer 2013 (Cohort Study)	The Danish Registry for Biologic Therapies in Rheumatology (2000 - 2008)	TNFi, 3,347	Mean - 2.9 years	6	Non-biologic DMARDs **, 3,812	-	3	**HR 1.54 (0.37 - 6.34)**	Calendar time
RA	Staples 2019 (Cohort Study)	The Australian Rheumatology Association Database (2001- 2012)	TNFi, 2,451	10,120 person years	12	Non-biologic DMARDs **, 5,74	2,232 person years	4	**RR 1.18 (0.29 - 4.70)**	Calendar year; smoking status; methotrexate use; prior malignancy.

RA	Wadström 2017 (Cohort Study)	The Swedish Rheumatology Quality of Care Register (2006 - 2015)	TNFi, 10744	Mean - 4.83 years	32	Conventional systemic DMARDs **, 46,315	Mean - 5.9 years	234	**HR 1.43 (0.66 - 3.09)**	Start of treatment year; comorbidities; number of hospitalizations; education; number of hospitalizations; days spent in inpatient care
			Abatacept, 2005	Mean - 3.17 years	7				**HR 0.73 (0.38 - 1.39)**	
			Rituximab, 3545	Mean - 4.23 years	9				**HR 0.84 (0.60 - 1.18)**	
RA	Wolfe 2007 (Cohort Study)	US National Data Bank for Rheumatic Diseases (1998 - 2005)	Infliximab, 790	Mean - 2.9 years	11	Conventional systemic DMARDs **	-	-	**OR 2.60 (1.00 - 6.70)**	Education; smoking history; baseline patient activity scale; baseline prednisone use.
			Etanercept, 754	Mean - 2.7 years	9				**OR 2.40 (1.00 - 5.80)**	
			Adalimumab, 207	Mean - 1.2 years	1				**OR 0.80 (0.10 - 6.60)**	
Psoriasis	Asgari 2017 (Cohort Study)	Kaiser Permanente Northern California health insurance database (1998 -2011)	Biologics, 2285	Mean - 5.86 years	8	Non-biologic systemic therapy, 3604	Mean - 5.23 years	13	**HR 1.57 (0.61 - 4.09)**	Ethnicity; presence of PsA; prior UV light therapy; BMI; cigarette use.

* All studies adjusted for age and sex

** DMARDs = Disease Modifying Anti-Rheumatic drugs

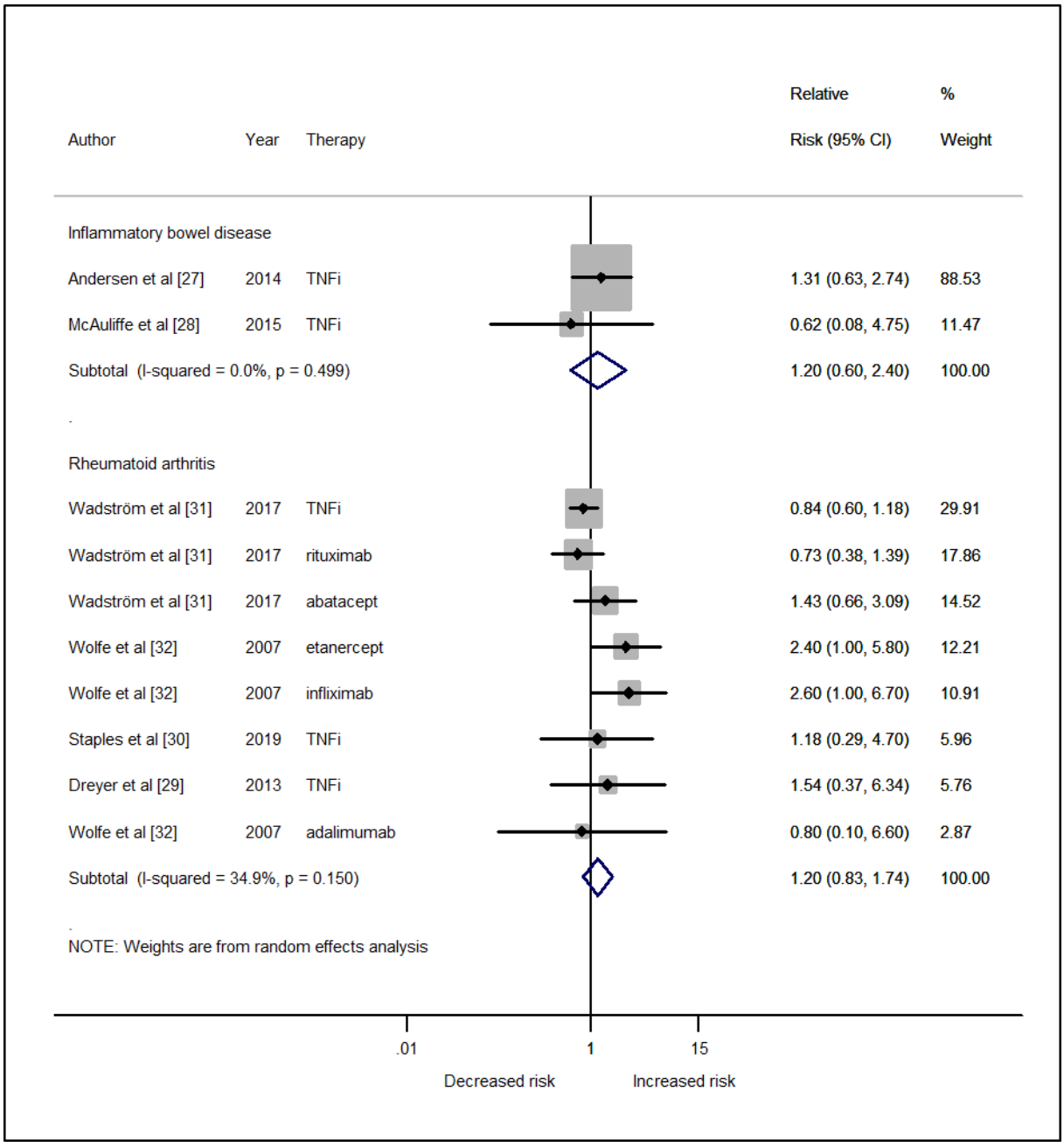
1.6.3.3 Risk of melanoma

The pRR estimates for melanoma in IBD and RA patients treated with biologic therapy compared to conventional systemic therapy were 1.20 (95% CI 0.60-2.40) and 1.20 (95% CI 0.83-1.74) (Figure 1.7). Heterogeneity was non-significant in both the IBD and RA subgroups (I2=0% and I2=34.9%). There was no evidence of publication bias (Begg P=0.87; Egger P=0.16) (Appendix 6). The pRR estimate for RA patients treated with only TNFi compared to conventional systemic therapy was 1.08 (95% CI 0.81 – 1.43) (Appendix 5). The risk of melanoma in the rituximab-treated and the abatacept-treated RA patients relative to their biologic-naïve conventional systemic- treated counterparts were 0.73 (95% CI 0.38 – 1.39) and 1.43 (95% CI 0.66 – 3.09), respectively (Wadstrom et al., 2017). Sensitivity analysis involving the exclusion of individual RA studies produced pRR estimates ranging from 0.91 (95% CI 0.69 – 1.18) with the exclusion of Wolfe et al to 1.95 (95% CI 1.16 – 3.30) with the exclusion of Wadström et al.

1.6.3.4 Quality assessment of the included studies

All of the included studies scores at least 7/9 and were deemed high quality; 5 out of 7 studies scored 7/9 with the 2 remaining studies scoring 8/9 on the Newcastle-Ottawa scale (Appendix 7). All of these studies scored the maximum (4/4) for the selection domain and 2/3 for the outcome domain. The two highest scoring studies scored the maximum 2/2 for the matching domain as they adjusted for both age and-sex and at least concomitant or historic exposure to immunosuppressive therapy or ethnicity.

Figure 1.7: Forest plot of the risk of melanoma in biologic-treated inflammatory bowel disease, rheumatoid arthritis and psoriasis patients compared with conventional systemic therapy



Caption: This forest plot includes a row for each individual study results with the point estimates presented as a diamond with a horizontal line (95% confidence interval). The grey box around each point estimate is proportional to the weight of the study

1.6.4 Discussion

In this systematic review and meta-analysis, an association between biologic exposure and development of melanoma in IBD, RA and psoriasis patients when compared to patients treated with only conventional systemic therapy was not found. This meta-analysis was the first to be performed specifically examining the risk of melanoma in biologic-treated IBD and psoriasis patients relative to their biologic-naïve conventional systemic-treated counterparts. To date, the only other systematic review and meta-analysis examining the risks of melanoma in IBD reported an increased risk of melanoma in IBD patients independent of treatment with TNFi (Singh et al., 2014). However, this finding was based on a sub-group analysis of two studies, neither of which compared TNFi-treated patients with biologic-naïve IBD patients (Long et al., 2012; Peyrin-Biroulet et al., 2012). The absence of a biologic-naïve IBD comparator group consisting of patients treated with systemic therapy in both studies leaves unanswered whether any observed effect is due to the primary disease, treatment with systemic therapy, or both. Our study represents a more robust and clinically relevant analysis of the risk of melanoma in biologic-treated IBD patients than the previous meta-analysis as we restricted our inclusion criteria to studies directly comparing biologic-treated IBD patients to biologic-naïve IBD patients (Singh et al., 2014).

The only published systematic review examining the risk of cancer in biologic-treated psoriasis patients was not able to identify any published study comparing the risk of melanoma relative to biologic-naïve conventional systemics treated patients for inclusion (Peleva et al., 2018). Although it was not possible to perform a meta-analysis for psoriasis, the only published study comparing the risk of melanoma between biologic-treated and biologic-naïve conventional systemics treated psoriasis patients suggests no statistically significant increased risk of melanoma in biologic-treated patients (Asgari et al., 2017).

The analyses in this study also updates and extends the most recently meta-analysis of melanoma risk in biologic-treated RA patients by including more recent reports from the Australian and Swedish biologic registries (Staples et al., 2019; Wadstrom et al., 2017). The results of this systematic review and meta-analysis correspond with those of the previous analyses, suggesting that treatment with biologics does not significantly increase the risk of melanoma in RA patients relative to biologic-naïve patients treated with conventional systemic therapy.

The main strengths of this study included the use of a pre-defined protocol with strict inclusion and exclusion criteria (Appendix 8). The systematic and comprehensive nature of the literature search of multiple databases, guided by a protocol, addressed a focussed and clinically relevant research question with standardised data extraction and quality assessment to minimize errors. The main limitation of this systematic review and meta-analysis was the small number of disease-specific studies examining the risk of melanoma between biologic-treated and conventional systemic-treated patients. Despite the extensive literature search, only 2 IBD studies and 1 psoriasis study were identified as eligible for inclusion. The small number of studies eligible for inclusion meant that the pRR estimates were likely to be disproportionally driven by a single study. In the sensitivity analysis accounting for the effects of singular studies we saw the pRR estimate in the RA group increase from 1.20 (95% CI 0.83 – 1.74) to 1.95 (95% CI 1.16 – 3.30), suggesting a near two-fold statistically significant increased risk of melanoma, with the exclusions of Wadström et al. Any future update of our study through the inclusion of newly published studies could produce significantly different pRR estimates than those reported in this meta-analysis.

Another potential limitation of this study was the inclusion of studies carried out using health insurance databases (Asgari et al., 2017; McAuliffe et al., 2015) . Unlike pharmacovigilance registries, healthcare insurance databases are primarily designed to collect health data for financial reimbursement and not to answer research questions related to treatment safety and effectiveness (Hyman, 2015). These studies had a greater risk of selection bias as patients were derived from databases that do not include uninsured patients or those with other health insurance policies. Health insurance database studies can also be prone to misclassifications of exposure due to treatment status being identified through prescriptions and the healthy user / adherer effect in which patients who comply with treatment for a prolonged time are more likely to be healthy (Shrank et al., 2011).

A major weakness of the studies included in our analysis was the absence of adjustment for established risk factors for melanoma such as UVR exposure and ethnicity. Significant differences in the cumulative exposure to UVR in the form of holiday sun exposure and prevalent tanning bed use or the number of patients from non-white ethnic groups between the biologic-treated and biologic naïve systemics treated cohorts could have led to an under or overestimation of melanoma risk. Phototherapy with PUVA, formerly a common

treatment for psoriasis patients, is associated with an increased risk of melanoma (Archier et al., 2012; Stern, 2001). Although the study by Asgari et al reportedly adjusted for previous phototherapy, it was not clear if treatment with PUVA was included.

Treatment duration period for conventional systemic therapies was poorly reported in the included studies (table 1.7). Adjustment for differences in concomitant and historic treatment with conventional systemic therapies was absent from most of the included studies. Significant differences in duration (and therefore cumulative amount) of these immunosuppressive therapies between the biologic- and conventional systemic-treated patients could have biased our results. Moreover, given the generally long latent period between causal exposure and the development of melanoma, follow-up periods for biologic-treated patients in the included studies may not have been long enough and could have resulted in an underestimation of risk.

Future population-based studies will need to take in to account the rapidly changing landscape of biologic treatment in IBD, RA and psoriasis. The introduction of biologic therapies targeting IL-6, IL-23 and IL-17 has expanded the available treatment options for patients initiating biologic therapy. Future studies should consider the various biologic mechanisms of these therapies, their potential role in the development of melanoma, and how exposure to multiple classes of biologic therapies might impact a patient's risk of melanoma. In order to account for confounding by indication, studies should compare patients treated with TNFi with patients treated with the newer biologics and those treated with more than one type of biologic.

Another development in the treatment of IBD, RA and psoriasis is the introduction of TNFi biosimilars. Provision of biologic therapy varies globally with health economic considerations often dictating access and uptake. Switching patients from reference TNFi to biosimilars for cost-effectiveness has led to significant savings for healthcare providers in the UK with similar savings projected for other European countries. This may lead to greater access for patients requiring these therapies, with possible earlier intervention in IBD and psoriasis patients currently treated with only non-biologic systemics (Aladul et al., 2019; Barker et al., 2019; Jha et al., 2015).

1.6.5 Conclusion

In conclusion, an association between biologic exposure and development of melanoma when compared to conventional systemic treatment was not found. Prospective cohort-studies using an active-comparator new-user study design providing detailed information on treatment history, concomitant therapies, biologic and conventional systemic treatment duration, recreational and treatment-related UV exposure, skin colour and date of melanoma diagnosis are required to help improve certainty. These studies would also need to account for key risk factors and the latency period of melanoma.

1.7 Rationale for this thesis project

The introduction of biologic therapies has revolutionised the treatment of patients with psoriasis requiring systemic therapy, particularly in those who have failed or can no longer tolerate treatment with non-biologic systemics. A recently updated Cochrane network meta-analysis of 140 clinical studies found that both the older biologic therapies (TNFI) and the newly introduced IL-12/23, IL-23 and IL-17 inhibitors were significantly more effective than non-biologic systemic therapies (Sbidian et al., 2020). Real world evidence from a number of pharmacovigilance registries has confirmed that patients with moderate-severe psoriasis have a significantly greater reduction in DLQI than those on non-biologic systemic therapies (Iskandar et al., 2017; Jungo et al., 2016; Norris et al., 2017).

Despite the success of biologic therapy, uncertainty over the long-term risk of serious adverse events could impact uptake and adherence. The decision to initiate or switch from conventional systemic or small molecule immunomodulatory therapy to biologic therapy in the UK is made by clinicians and their patients after discussing the available therapies. This includes considerations of the potential benefits and harms of treatment options (NICE, 2020a). Uncertainty surrounding long-term treatment with biologic therapy might make clinicians less inclined to prescribe these therapies while patients might become non-adherent. Although recently published studies have clarified the real world risk of infections and major adverse cardiovascular events, there remains uncertainty surrounding the long-term risk of cancer in patients treated with biologic therapy compared with patients treated with systemic non-biologic therapy (Rungapiromnan et al., 2019; Yiu et al., 2018b).

The majority of studies investigating risk of cancer in biologic-treated patients were conducted in RCTs (Table 1.3). These studies are considered the ‘gold standard’ in demonstrating the short-term efficacy and safety of novel therapeutics such as biologic therapies due to their experimental design (Hariton and Locascio, 2018). Rigorous inclusion and exclusion criteria, the randomisation process used to allocate patients to treatment and control groups are the main strengths of this study type. These measures ensure that the patients in the treatment and control group(s) are comparable in all the known and unknown demographic and disease characteristics that could potential influence outcomes (Nallamothu et al., 2008). However, due to a number of inherent limitations, RCTs are not

suitable to study risk of adverse events, particularly cancer, in patients with psoriasis treated with biologic therapy. RCTs are funded by pharmaceutical companies to primarily demonstrate the superior efficacy of their products to placebo or other biologic therapies for the purposes of obtaining regulatory approval (Yiu, 2017). Adverse events are usually assessed as secondary outcomes (Péron et al., 2013). Where risk of developing cancer is one of the study outcomes, incidence rates for the biologic-treated patients are compared to those of the general population only (Péron et al., 2013). In UK clinical practice, patients considered for treatment with biologic therapy have had previous treatment with non-biologic systemic therapy. For patients and clinicians considering the potential risk of cancer associated with treatment with biologic therapy relative to continuing with non-biologic systemic therapy, studies with general population comparators are not informative.

There is also the question of the comparability of RCT patients to real-world psoriasis populations. RCTs investigate the safety and efficacy of biologic therapies under ideal conditions (Rothwell, 2005). The stringent inclusion and exclusion criteria for entry to RCTs often exclude patients with chronic co-morbid conditions that are common in the psoriasis population (Torre and Shahriari, 2017). There is evidence from the two largest psoriasis pharmacovigilance registries in Europe demonstrating that a significant proportion of real world patients do not meet eligibility criteria for the phase 3 clinical trials (Garcia-Doval et al., 2012; Mason et al., 2018). In the Spanish biologics registry, 27.8% biologic-treated patients were deemed ineligible after applying the most commonly used exclusion criteria in phase 3 clinical trials (Garcia-Doval et al., 2012). Similarly, the British pharmacovigilance registry reported that 24% of etanercept-treated and 24% of ustekinumab-treated patients would have been ineligible for entry to their respective clinical trials (Mason et al., 2018).

Moreover, biologic-treated patient categorised as ineligible for entry to RCTs, were significantly more likely to experience serious adverse events than biologic-treated patient eligible for these trials. In the Spanish registry study, the rate for serious adverse events for clinical trial ineligible patients treated with biologic therapy was 41.6 events per 1000 person-years of follow-up (95% CI 28.1-61.6) compared with 16.5 events per 1000 person-years in their biologic-treated counterparts (95% CI 11.2-24.2) (Garcia-Doval et al., 2012). In the British pharmacovigilance registry study, patients categorised as ineligible treated with biologic therapy (etanercept: IRR 1.91 [95% CI 1.40-2.60]; ustekinumab: IRR 2.81 [95% CI

2.12-3.72]; adalimumab: IRR 2.00 [95% CI 1.55-2.59]) were also significantly more likely to have a serious adverse event in the first 12 months than their counterparts treated with the same therapy (Mason et al., 2018). Given the limited duration of RCTs (6-12 months), short placebo/comparators control periods and small sample sizes, these studies are not long enough and adequately powered to investigate rare adverse events such as cancer that occur long after first exposure to therapy. (Singh and Loke, 2012). Furthermore, systematic reviews of RCTs across dermatology and other medical specialties have found the collection, reporting and analysis of adverse events to be unreliable (Lineberry et al., 2016).

Many of these limitations can be overcome by conducting observational studies of patients in routinely collected healthcare datasets or pharmacovigilance registries. Prospective cohort studies involve the longitudinal follow-up of large groups of real-world patients including those excluded from clinical trials (Barrett and Noble, 2019). Patients with similar demographic and disease characteristics can be followed up in treatment-specific cohorts and differences in baseline characteristics that function as cancer risk factors (e.g. smoking) can be adjusted for. Prominent examples of the use of observational studies of patients in routinely collected healthcare data and registries are prospective cohort studies conducted in biologic-treated RA populations (Nikiphorou et al., 2017). These studies provide an exemplar for psoriasis studies due to the shared treatment modalities. To date, studies conducted in the Scandinavian (Denmark; Sweden) and British RA registries, have been able to clarify the risk of the incidence and recurrence of a number of site-specific cancers in TNFi-treated patients compared with non-biologic systemic therapy (Hellgren et al., 2017; Louise K. Mercer et al., 2012; Mercer et al., 2015; Raaschou et al., 2015). Although the results from these studies have been reassuring, their findings cannot be directly translated to psoriasis populations due underlying differences between the diseases impacting cancer risk.

The literature review presented in Section 1.5 and the systematic review and meta-analysis in Section 1.6 have highlighted the absence of studies in psoriasis populations investigating the risk of cancer in biologic-treated patients compared with patients treated with only non-biologic systemic therapy. Thus, in order to answer this important research question there is a need for a large, prospective observational cohort study adjusting for risk factors.

2 Aims and objectives

2.1 Aim

The aim of this PhD was to determine the risk of cancer in patients with chronic-plaque psoriasis treated with biologic therapy, who have a previous history of treatment with non-biologic systemic therapy, compared with patients treated with only non-biologic systemic therapy registered to the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR).

2.2 Objectives

I. Compare baseline characteristics between biologic-treated and non-biologic systemically treated psoriasis patients and describe important differences as it relates to risk of cancer.

II. Determine the risk of all cancer, excluding KC, in biologic-treated psoriasis patients compared with non-biologic systemically treated patients.

III. Determine the risk of cancers of infectious origin in in biologic-treated psoriasis patients compared with non-biologic systemically treated patients.

IV. Determine the risk of developing common site-specific cancer (lung, breast, prostate, colorectal, melanoma) in in biologic-treated psoriasis patients compared with non-biologic systemically treated patients.

V. Determine the risk of KC (BCC, SCC) in in biologic-treated psoriasis patients compared with non-biologic systemically treated patients.

VI. Determine the extent to which any observed difference in any of the study outcomes between biologic-treated and non-biologic systemically treated patients are influenced by the following factors: age; Fitzpatrick skin type; mechanism of the biologic therapy and number of biologic therapies received; presence of PsA; obesity.

3 Methodology

3.1 Outline

In this chapter, the methods used to address the thesis aim and objectives are detailed. This chapter includes a brief overview of BADBIR, from which the study data was obtained. This is followed by a more detailed description of the risk of cancer study design, study population and inclusion criteria, exposures, outcomes and confounders. Finally, the data management and statistical analysis methods used to prepare and analyse the study data are presented.

3.2 Aims

- To describe the methodology of BADBIR including patient recruitment to the registry, data collection at baseline and follow-up including adverse events.
- To describe and provide reasoning for the study design of the risk of cancer study which includes selection of the study populations, the exposures of interest and the study outcomes.
- To describe and provide reasoning for the data management and data cleansing process performed to prepare the dataset for the analysis.
- To describe and provide reasoning for the statistical analysis methods used to analyse the data

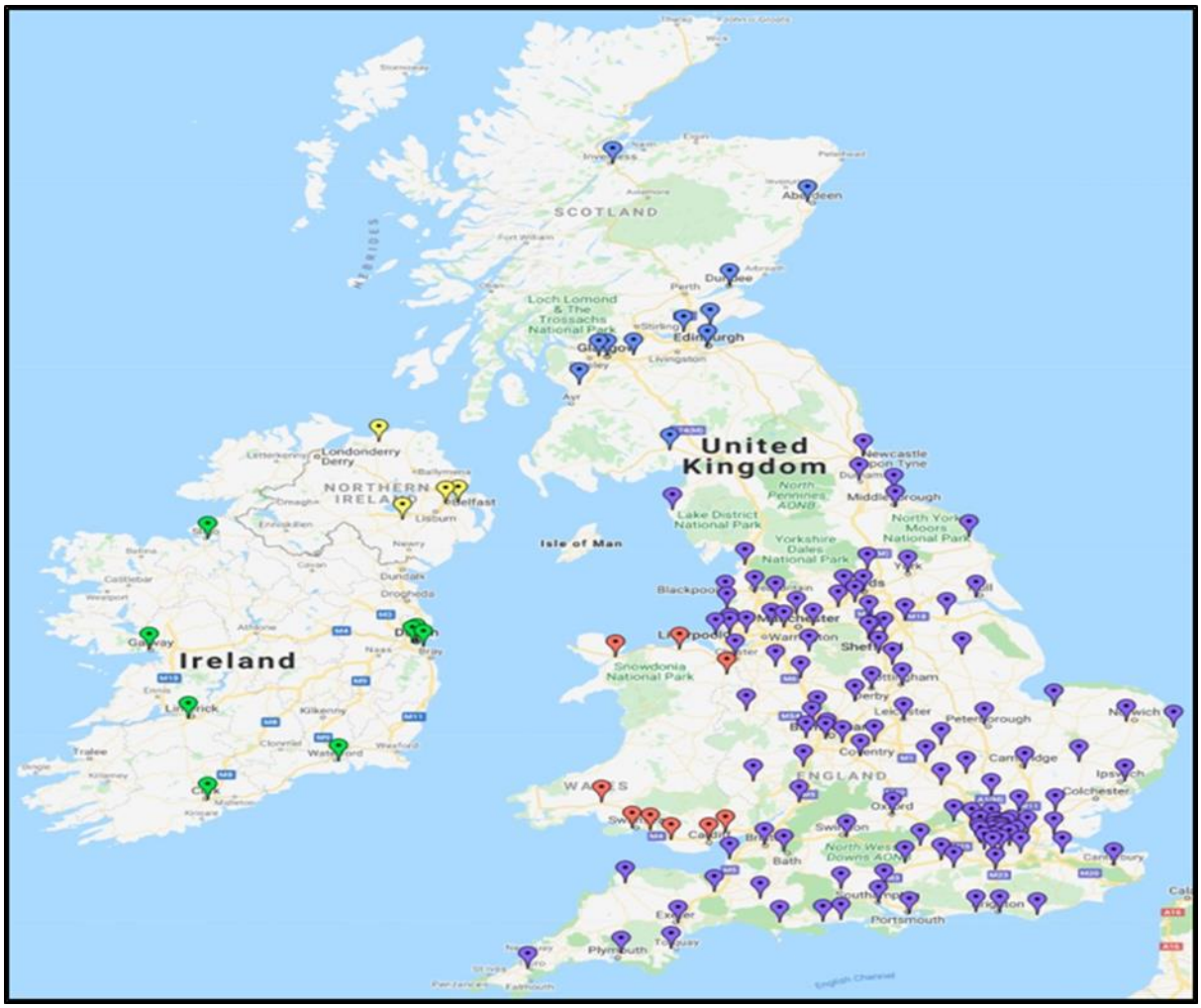
3.3 The British Association of Dermatologists Biologics and Immunomodulators Register

Data were obtained from BADBIR. Established by the BAD and The University of Manchester in September 2007, the primary purpose of BADBIR is to determine the long-term safety of biologic therapy in the treatment of psoriasis (BADBIR, 2020a).

3.3.1 Study Design

BADBIR is a web-based, prospective pharmacovigilance registry of patients with moderate-severe psoriasis in the UK and the Republic of Ireland (ROI) (BADBIR, 2020a). BADBIR prospectively studies three cohorts consisting of patients treated in routine clinical practice, in one of participating dermatology centers, with either biologic therapy, small molecule immunomodulatory therapy or conventional systemic therapy, respectively (BADBIR, 2020a). As of February 2022, there are a total of 168 participating dermatology centres across the UK and ROI. The majority of the participating dermatology centres are located in England (n=130), with the remaining 36 centres located in Scotland (n=13), ROI (n=12), Wales (n=9) and Northern Ireland (n=4) (Figure 3.1).

Figure 3.1: Locations of dermatology centres recruiting to BADBIR in the United Kingdom and the Republic of Ireland (February 2022)



3.3.2 Recruitment

Patients diagnosed with moderate-severe psoriasis attending dermatology centres in the UK and the ROI were invited to participate in BADBIR if they were initiating (or switching between) biologic, small molecule immunomodulatory or conventional systemic therapies studies in BADBIR in the 6 months prior to the date of consent (Table 3.1). Although there were no specific eligibility criteria related to disease severity for patients initiating or switching to treatment with a biologic or small molecule immunomodulatory therapy in BADBIR, clinical guidelines from NICE and the BAD recommend these treatment for patients with disease severity of PASI≥10 and DLQI>10. Patients initiating treatment with conventional systemic therapy were also required to meet the disease severity criteria of PASI≥10 and DLQI>10 to ensure that the cohorts were comparable. Patients meeting all of these eligibility criteria were provide with an information sheet in clinic detailing the study and a consent form, or assent form if under the age of 16, to register to BADBIR (Appendices 9 and 10).

Table 3.1: BADBIR study entry criteria for patients recruited to the biologic, small molecule and conventional systemic cohorts

CRITERIA	BIOLOGIC COHORT	SMALL MOLECULE COHORT	CONVENTIONAL COHORT
CONSENT	Willing to give informed consent (or assent if under the age of 16) for long term follow-up and access to all medical records		
THERAPY	Initiating or switching to a biologic therapy (including biosimilars) within the previous 6 months	Initiating or switching to a small molecule immunomodulatory therapy within the previous 6 month	Initiating or switching to a conventional systemic therapy within the previous 6 months
	Infliximab; adalimumab, etanercept; certolizumab; ustekinumab; guselkumab; secukinumab; ixekizumab; brodalumab; efalizumab	Apremilast; dimethyl fumarate	Methotrexate; ciclosporin; acitretin; FAEs; oral PUVA; hydroxycarbamide
DISEASE SEVERITY	Not specified by BADBIR but stipulated by NICE and the BAD: PASI≥10 and DLQI>10	Not specified by BADBIR but stipulated by NICE and the BAD: PASI≥10 and DLQI>10	PASI≥10 and DLQI>10 (unless switching between conventional systemic therapy)
BIOLOGIC EXPOSURE STATUS	Not applicable	Never exposed to a biologic therapy	Never exposed to a biologic or small molecule immunomodulatory therapy

Abbreviations: Fumeric Acid Esters (FAEs); Psoralen plus Ultraviolet A (PUVA); British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR); National Institute for Health and Care Excellence (NICE); British Association of Dermatologists (BAD); Psoriasis Area and Severity Index (PASI); Dermatology Life Quality Index (DLQI).

The contents of this table were obtained from the BADBIR protocol version 19 (BADBIR, 2020a).

3.3.3 Data collection

Data collection occurs when patients attend routine clinic appointments with questionnaires provided bi-annually in the first three years and annually thereafter (Figure 3.2). Data collection is performed by trained healthcare professionals (e.g. dermatology-specialist or research nurses) using questionnaires completed by clinicians and by patients at baseline and follow-up. Data from the questionnaires are entered in to the BADBIR online database. Data items pertinent to the risk of cancer study are described in brief below and in more detail in Section 3.5.1.

The patient baseline questionnaire collected data on patient demographics, lifestyle factors and UV exposure (occupational and routine) (Appendix 11). The clinical baseline questionnaire included data on psoriasis phenotypes and disease severity, registration therapy and previous therapy details, presence of comorbidities, skin type and skin lesions and anthropometric data (Appendix 12). The clinical follow-up questionnaire was used to record changes to patient treatment and the occurrence of adverse events or serious adverse events for each follow-up appointment until the end of follow-up (Appendix 13). The patient follow-up questionnaire was completed during 6-monthly follow-up appointments during the first three years to identify any new medical problems and lifestyle changes the patient experienced which included changed to cigarette smoking, alcohol drinking status and units of alcohol consumed per week. However, the data collected in this questionnaire was not of interest as only patient lifestyle factors collected at baseline were considered in this thesis.

3.3.4 Adverse events

An adverse event is defined as "*Any untoward medical occurrence in a patient being administered a pharmaceutical product, which does not necessarily need to have a causal relationship with the product.*" (BADBIR, 2020b). In turn, an adverse event is considered a serious adverse event if it meets the following criteria: resulted in death; immediately life threatening; resulted in significant loss of function or disability; resulted in overnight hospital admissions or prolongation of existing hospitalisation; resulted in the patient receiving treatment with IV antibiotics; was a congenital malformation or birth defect (BADBIR, 2020b). In addition, adverse events that may not fit in one these categories but were deemed medically important by BADBIR (e.g. cancer and pregnancy) were also

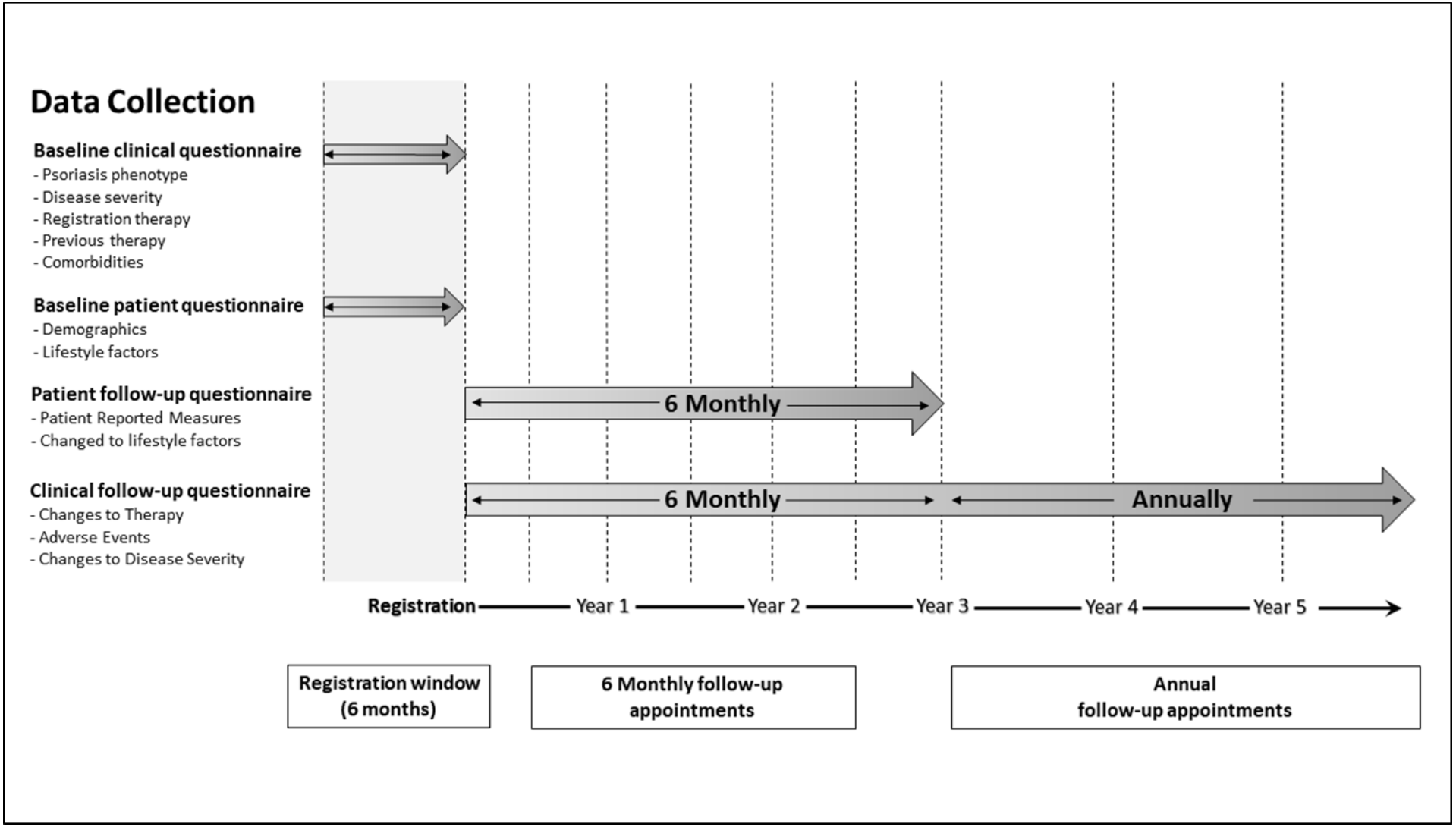
considered serious adverse events (BADBIR, 2020b). Serious adverse event reported for patients registered to BADBIR were reviewed and coded by the pharmacovigilance team using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA hierarchy consists of 5 levels, increasing in specificity, with the following four levels of the hierarchy codes used to categorise an event: system organ class (SOC); higher level group term (HLGT); higher level term (HLT); preferred term (PT) (Brown, 2006).

A number of serious adverse events were considered 'events of special interest'. For these events, additional data was collected through standardised event of special interest (ESI) forms from the participating dermatology centres. The following ESI forms were relevant to this thesis: malignancy (not including skin); lymphoproliferative disease; melanoma or skin cancer including Bowen's disease (Appendices 14-16). Key data collected in these ESI forms were diagnosis (including site) and histopathological classification. In addition to collection information for adverse events directly from the participating dermatology centres, BADBIR also receives information related to hospital admissions, malignancy and mortality through linkage with national healthcare data providers in the UK and the ROI (BADBIR, 2020a). Access to linkage data is restricted to individuals employed by BADBIR so all adverse events studied in this thesis project were those confirmed by the dermatology centres.

3.3.5 BADBIR ethical approval

BADBIR gained multi-center research ethics committee approval in March 2007 (NHS Research Ethics Committee North West England, reference 07/MRE08/9) with local research ethics obtained from participating dermatology centers (Appendix 17). A data sharing agreement was entered in to with the BAD to access BADBIR data.

Figure 3.2: BADBIR study design



3.4 Risk of cancer study

3.4.1 Study population

All patients registered to BABDIR from inception until 1st April, 2019 (data cut-off) with the following criteria were eligible for inclusion to the risk of cancer study: attended at least one follow-up appointment; diagnosed with chronic plaque psoriasis; biologic-naïve at baseline; no personal history of cancer. Patients with no follow-up data, either because of loss to follow-up after baseline or the first follow-up occurred after the cut-off date, were excluded from this study because adverse events are only reported to BADBIR at follow-up. The study population was limited to patients diagnosed with chronic plaque psoriasis as it is the most common presentation of psoriasis with biologic therapy almost exclusively approved for treatment of patients with this phenotype (Smith et al., 2020). As the outcome of interest in the risk of cancer study was the risk of developing first cancer after initiating biologic therapy, patients with a personal history of cancer, including prevalent cancers identified at baseline, were also excluded from this risk of cancer study. For the study of risk of developing the sex-specific cancers (breast; prostate), the study populations were further restricted. In the risk of breast cancer analysis the population consisted of only female patients. For the risk of prostate cancer study, the population was restricted to male patients only.

The same general inclusion and exclusion criteria described above were also used for the risk of KC (BCC, SCC) study populations with the following exceptions: individuals belonging to non-White ethnic groups and those with Fitzpatrick skin type V or VI were excluded. The Fitzpatrick scale, developed in 1975, is a semi-quantitative scale classifying skin color by complexion, levels of melanin and inflammatory response to UV radiation (Fitzpatrick, 1975). Skin type for patients in BADBIR was assessed along the Fitzpatrick scale, ranging from skin type I to skin type VI. Individuals with Fitzpatrick skin type I to III are considered to have ‘fair skin’. The reason why individuals from non-White ethnic groups or those with Fitzpatrick skin type V/VI were excluded as the risk of developing these cancers is negligible for these population (Whiteman et al., 2016).

3.4.2 Exposures

The study population for this risk of cancer studies were grouped in to the following two cohorts based on exposure during follow-up: the biologic cohort and the non-biologic systemic cohort. The biologic cohort consisted of patients registered to the biologic cohort in BADBIR, who have previously been treated with non-biologic systemic therapy, initiating treatment with any of the biologics and biosimilars studied in BADBIR during the study period. A full list of the biologic therapies patients in the biologic cohort were exposed to can be found in Table 3.2.

The non-biologic systemic cohort was the comparator cohort in the risk of cancer study and consisted of all patients who were registered to either the conventional systemic cohort or the non-biologic small molecule cohort in BADBIR. These patients were those who remained biologic-naïve during follow-up and were treated with any of the conventional systemic or small molecule immunomodulatory therapies studied in BADBIR. This included patients switching from treatment with conventional systemic to small molecule immunomodulatory therapy during follow-up. The conventional systemic therapies patients in the non-biologic systemic cohort were exposed to: methotrexate; ciclosporin; acitretin; FAEs; oral PUVA; hydroxycarbamide. The small molecule immunomodulatory therapies patients were exposed to were apremilast (tradename: Otezla) and dimethyl fumarate (tradename: Skilarence).

Table 3.2: Biologic therapies studied in BADBIR during the risk of cancer study period

Biologic class	Drug name	Tradename	Recruitment start
Tumour necrosis factor inhibitors	infliximab	Remicade	01/09/2007
	infliximab (biosimilar)	Erelzi	01/08/2017
	adalimumab	Humira	01/09/2007
	adalimumab (biosimilar)	Hyrimoz	01/08/2018
	adalimumab (biosimilar)	Amgevita	01/01/2019
	etanercept	Enbrel	01/09/2007
	etanercept (biosimilar)	Benepali	01/08/2016
	certolizumab pegol	Cimzia	01/08/2018
Interleukin-12/23 inhibitor	ustekinumab	Stelara	01/07/2009
Interleukin-23 inhibitors	guselkumab	Tremfya	01/08/2018
Interleukin-17A inhibitors	secukinumab	Cosentyx	01/08/2015
	ixekizumab	Taltz	01/08/2016
Interleukin-17 Receptor A inhibitor	brodalumab	Kyntheum	01/08/2018
CD-11A inhibitor	efalizumab*	Raptiva	01/09/2007

* Efalizumab was withdrawn from market in 2009 (Kuehn, 2009).

3.4.3 Study outcomes

The primary outcome measure in this risk of cancer study was incident cancer, defined as the occurrence of the first malignant neoplasm reported for participants during follow-up. Excluded from this outcome were neoplasms described as benign, unspecified, stage 0, carcinoma in situ or metastases. The methodology used to identify patients with the primary outcome measure is described in Section 3.5.3 and summarised in Table 3.5.

The primary outcome measure was divided up in to 5 different study outcomes:

1. All cancer (excluded KC)
2. Cancers of infectious origin
3. Common site-specific cancers (lung; breast; prostate; colorectal; melanoma)
4. BCC
5. SCC

Risk of developing these outcomes for patients in the biologic and non-biologic systemic cohorts were studied in two separate risk of cancer studies. The first three outcomes were part of the risk of all cancer study (Chapter 4). Risk of developing BCC and SCC were the outcomes studied in the risk of KC study (Chapter 5). These outcomes were studied in the two different risk of cancer studies due to differences in the selection of the respective study populations, described in Section 3.4.1.

3.4.3.1 Risk of all cancer study outcomes

The outcome all cancer (excluding KC) comprised any incident haematological or solid cancer, including melanoma, reported for patients during the study period. The outcome cancers of infectious origin was defined as any cancer associated with any of the following infectious agents identified as group 1 carcinogens by the IARC: Epstein-Barr virus (EBV); Human papillomavirus (HPV); Human herpesvirus type-8 (HHV-8); Human T-cell lymphotropic virus type 1 (HTLV); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Helicobacter pylori (de Martel et al., 2020). Cancers associated with the infectious agents *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis* were not included in this outcome as these pathogens are not endemic in the UK and the ROI (Thun et al., 2018).

This outcome was of interest in this thesis project due to the finding that incidence of infection-related cancers are increased in immunocompromised populations (Schulz, 2009). A comprehensive systematic review and meta-analysis studied the incidence of cancer in population-based cohort studies comprising 444,172 individuals with HIV/AIDS and 31,977 organ transplant recipients (Grulich et al., 2007). The authors found that despite the inherit differences between these two populations, cancers related to EBV, HPV, HHV-8, HBV/C and HPV were increased in both populations (Grulich et al., 2007). They concluded that it was immunodeficiency rather than other risk factors that drove the increased in incidence of these infection-related cancers (Grulich et al., 2007). In order to clarify if differences in the immunosuppressive mechanisms between biologic therapy and non-biologic systemic therapy could contribute to increased risk of developing these infection-related cancer, cancers of infectious origin was selected as a study outcome.

Table 3.3: Cancers of infectious origin studies in this thesis

Infectious agent	Cancer type/site
Epstein-Barr virus	Hodgkin lymphoma; Non-Hodgkin lymphoma; Nasopharynx
Human papilloma virus	Oropharynx; Oral cavity; Larynx; Cervix; Vagina; Vulva; Penis; Anus;
Human herpes virus 8	Kaposi's sarcoma
Hepatitis B/C virus	Liver
Human T-cell lymphotropic virus	Leukaemia
Helicobacter pylori	Stomach

The most common site-specific cancers comprised breast cancer (female), prostate cancer, lung cancer, colorectal cancer and melanoma. Combined, these five cancers comprised over half of all cancer diagnosed in the UK in 2018 (CRUK, 2021c). The evidence to date pertaining risk of developing these cancers in biologic-treated patients with psoriasis compared with non-biologic systemic-treated patients is limited to one study investigating risk of melanoma (Asgari et al., 2017). These outcomes were studied to discern the risk of developing these commonly occurring cancers in biologic-treated psoriasis patients compared with patients treated with non-biologic systemic therapy only.

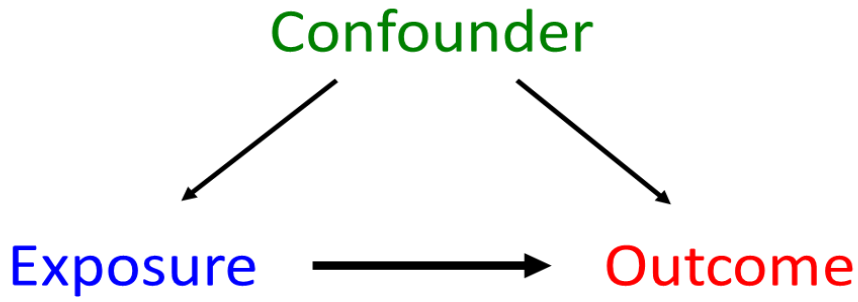
3.4.3.2 Risk of keratinocyte carcinomas study outcomes

The risk of developing of BCC and SCC were of interest in this thesis due to both the frequency of these skin cancers in the general population and their association with phototherapy and systemic therapy (Sections 1.5.2 and 1.5.3). BCC and SCC, are the most commonly occurring cancers in predominantly White populations, including the UK, with incidence rates on the rise for the past 30 years (Olsen et al., 2019). Risk of developing BCC and SCC were identified as being increased in psoriasis patients treated with PUVA with a potential increase in risk also associated with narrowband UVB phototherapy and ciclosporin. The evidence to date as it pertains to risk of BCC and SCC in biologic-treated patients compared with non-biologic systemic therapy is limited with conflicting results (Section 1.5.3). Furthermore, these studies were carried out primarily in North-American populations raising the question of generalisability of these results to the UK population. (Asgari et al., 2017; deShazo et al., 2019). In order to clarify the risk of developing BCC and SCC for patients in the UK treated with biologic therapy compared with non-biologic systemic therapy, these outcomes were investigated in this thesis.

3.4.4 Confounders

Confounding is the distortion of the association between an exposure and an outcome by a third factor, referred to as a confounder (Howards, 2018). If not mitigated for, confounding can lead to an over-or-underestimation of any possible association between the exposure and the outcome of interest (Howards, 2018). The most commonly used criteria used to define a confounder are: it must be associated with both the exposure and the outcome; it must be unequally distributed between the exposure groups; it must not be part of the causal pathway (Figure 3.3) (Jager et al., 2008). Potential confounders in this risk of cancer studies were identified *a priori* for each of the risk of cancer study outcomes from the literature and expert advice from the PhD supervisors (Table 2.1). The relationship between the exposure, the outcomes and potential confounders and mediators (factors that lay between the exposure and the outcome) were investigated using directed acyclic graphs (DAGs) (Appendices 39 and 40).

Figure 3.3: Conventional confounder model

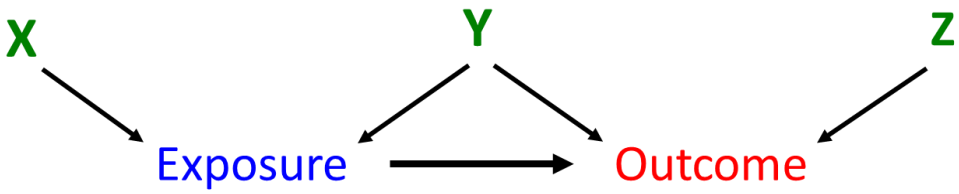


The DAGs for the outcomes risk of all cancer (excluding KC) and KC (BCC/SCC) indicate that a number of the potential confounders might possibly be mediators (Appendices 39 and 40). There is evidence that high BMI is a risk factor for both development of cancer and the initiation or worsening of psoriasis (Jensen and Skov, 2016; Lauby-Secretan et al., 2016). Similarly, smoking and excessive consumption of alcohol have also been associated with cancer and development of psoriasis (Naldi et al., 2005; Qureshi et al., 2010; Rumgay et al., 2021). This would confirm the status of the factors as confounders. Conversely, evidence provided by systematic-reviews and meta-analysis indicate that the incidence and prevalence of obesity, prevalence of smoking and prevalence of consumption of alcohol was

higher in psoriasis populations than the general population (Armstrong et al., 2012; Armstrong et al., 2014; Brenaut et al., 2013).

However, for the analyses in this thesis, factors for which there is evidence of an association with the outcome but not necessarily the exposure were also considered as potential confounders and adjusted for. This includes factors that are potential mediators (Appendices 39 and 40). Propensity score methods were the primary method used to adjust for confounding in this thesis project (Section 3.6.3.3). The optimum confounder selection strategy for propensity score models was evaluated by Brookhart et al using simulation studies in which the effect of including variables associated with just the exposure or just the outcome were considered (Brookhart et al., 2006). The results from these simulation studies demonstrated that propensity score models should include both the confounders and the variables associated with only the outcome (Brookhart et al., 2006). The inclusion of the variables associated with only the outcome were found to increase the precision of the estimated exposure effect without increasing bias (Brookhart et al., 2006). However, variables unrelated to the outcome and strongly related to the exposure were found to decrease the precision of the estimated exposure effect without decreasing bias (Brookhart et al., 2006). Thus, variables unrelated to the outcome were not considered for inclusion (Figure 3.4).

Figure 3.4: Variable selection for propensity score adjusted model



Variable	Association	Bias	Variance	Included?
X	Only the exposure	Not decreased	↑	No
Y	Both the exposure and outcome			Yes
Z	Only the outcome	Not increased	↓	Yes

Figure 3.4 has been adapted from Brookhart et al., 2006, *Variable selection for propensity score models.*

The statistical methods used to test each potential confounder for inclusion to the analysis models for each of the study outcomes is discussed in Section 3.6.3. Potential confounder tested for inclusion for each of the study outcomes in the analyses can be found in Appendix 18.

3.4.5 Study design

3.4.5.1 Incident-user, active-comparator design

To investigate the risk of cancer using a prospective, observational cohort study, an incident-user and an active-comparator design was implemented. Incident user study designs include a cohort of patients for whom follow-up began at the point of initiating the therapy of interest (biologic therapies in this study), in contrast to studies with prevalent user designs where patients received the treatment of interest before entering the study (Johnson et al., 2013). The incident user design has a number of advantages over the prevalent user design for this risk of cancer study. Firstly, it enables the study of cumulative risk of biologic therapy as the treatment duration before the occurrence of the adverse event of interest can be defined (Johnson et al., 2013). Secondly, unlike the prevalent user design, the incident user design enables the collection of pre-treatment (baseline) patient characteristics for all patients entering the study which enables adjustment for potential confounders (i.e. body mass index [BMI]) (Johnson et al., 2013). Active comparators are patients with the same indication (moderate-severe psoriasis) treated with another therapy currently used in clinical practice such as small molecule immunomodulatory and conventional systemic therapy in this study (Yoshida et al., 2015). The active comparator design allows for the inclusion of patients with similar disease characteristics in the comparator cohort enabling a more accurate comparison of drug effect between the cohorts and also reduces unmeasured confounding (Yoshida et al., 2015).

3.4.5.2 Patient follow-up, censoring and time at risk

Patient follow-up began from the date of first initiating registration therapy and lasted until the occurrence of the outcome, date of death or the last date of entry (last date any information was entered in the patient database records). Patients in the non-biologic systemic cohort initiating treatment with biologic therapy at any point during the study were also censored on the date of first initiating biologic therapy, henceforth referred to as

the ‘switch date’. For these participants, follow-up in the non-biologic systemic cohort ended and a new baseline registration was created. Follow-up in the biologic cohort began on switch date and ended at the date of censoring. Patients switching from the non-biologic to biologic cohort contributed follow-up time to both the biologic and non-biologic cohort. Patients who developed the outcome before the switch date were censored and their biologic registration was excluded from this study.

In order to account for the potential long-term risk of developing incident cancer following treatment with biologic or non-biologic systemic therapies, patients were considered at-risk from the date of initiating treatment until the end of follow-up, defined as the first of: developing the outcome; end of follow-up; or patient death. The incidence of cancer at any point during follow-up in the biologic cohort was attributed to biologic exposure or non-biologic system exposure for those in the non-biologic cohort. An ‘ever-exposed’ model (where patients were considered at risk from the point of initiating treatment) was used to attribute risk to exposure to a specific biologic therapy. In the instance where patients were exposed to more than one biologic therapy during follow-up the following approach was taken:

1. Risk was attributed to biologic mechanism (e.g. blocking of tumour necrosis factor (TNF)-α) if the patient was only exposed to biologics with the same mechanism of action (e.g. TNF-inhibitors)
2. Risk was attributed to exposure to multiple biologic mechanisms where patients were treated with more than one class of biologic therapy.

3.5 Data management

A data request form was completed to obtain a minimised dataset comprising only the items required for the risk of cancer study. An anonymised data cut was provided with the requested data items. The data cut was imported in to STATA statistical software, version 14.1 (StataCorp), where data was managed. The data cleansing process undertaking to prepare the dataset for analysis is described in Section 3.5.2. The data items relevant to the risk of cancer study and the corresponding variables in the dataset are described below.

3.5.1 Data items

3.5.1.1 Patient demographics

Demographic data for patients registered to BADBIR pertinent to study included sex (male; female), date of birth (used to calculate age at registration) and ethnic group with the following options: White; Indian; Pakistani; Bangladeshi; Chinese; Black-African; Black-Caribbean; Black-British; Black-other. Those belonging to ethnic groups that fall outside of the categories were able to select 'other' and write in their ethnicity in a separate box.

3.5.1.2 Psoriasis phenotype and disease severity

Baseline psoriasis details included: psoriasis phenotype, such as chronic plaque psoriasis; year of psoriasis diagnosis (used to calculate disease duration); family history (first/second degree relative) of psoriasis. Disease severity recorded at baseline consisted of the PASI score (0-72), PGA clear; almost clear; mild; moderate; moderate to severe; severe) and the presence of PsA ("*rheumatologist diagnosed?"* year of diagnosis). Presence of PsA could also have also been determined for some patients if recorded as a comorbidity under the category 'other'.

3.5.1.3 Lifestyle factors and anthropometrics

Lifestyle factors included smoking and alcohol statuses. Smoking status at baseline was determined for using responses to the questions "Have you even smoked more than one cigarette a day?" and "Do you currently smoke more than one cigarette?" Patients answering yes to either question were categorised as smokers and were asked to enter the average number of cigarettes ever or currently smoked per day. Alcohol status at baseline was identified using responses to the question "Do you drink alcohol?" For those who

responded they do currently drink alcohol, the average number of units consumed per week was recorded. Anthropometric data included: height (centimetres) and weight (kilograms).

3.5.1.4 Skin type and lesions

Patient skin type was assessed along the Fitzpatrick scale, ranging from skin type 1 to skin type 6, and scored with the propensity of skin to tan and burn, which also varies by skin type (Table 3.4). Where patients were also reported to have pre-cancerous and/or cancerous lesions, clinicians were asked to identify these lesion(s) from a list which included BCC, SCC and melanoma. Other details captured for lesions were the number of lesions and the body part where lesions developed.

Table 3.4: Fitzpatrick skin type definitions and descriptions

Fitzpatrick skin type	Constitutive skin color	Sunburn and tanning history	
		General definition	BADBIR definition
1	Ivory white	Burns easily, never tans	Burns easily, never tans
2	White	Burns easily, tans minimally with difficulty	Burns easily, tans minimally
3	White	Burns moderately, tans moderately and uniformly	Burns moderately, tans gradually
4	Beige-olive, lightly tanned	Burns minimally, tans moderately and easily	Burns minimally, tans well
5	Moderate brown or tanned	Rarely burns, tans profusely	Rarely burns, tans profusely
6	Dark brown or black	Never burns, tans profusely	Never burns, tans profusely

This table was adapted from the table in Astner and Anderson, 2004 (Astner and Anderson, 2004).

3.5.1.5 Ultraviolet exposure

Patients were asked about occupational, recreational, and environmental UV exposure with the questions “Do you have an occupation or hobby which is mainly outdoors?” and “Have you ever lived in a tropical/subtropical (hot/sunny climate) country?”

3.5.1.6 Registration therapy

Registration therapies are therapies commenced by patients at registration. Data items for registration therapy included therapy type (biologic; small molecule immunomodulatory; conventional systemic), whether this was their first exposure (if starting on a biologic therapy), drug name, commencement date, dose, dose unit and frequency. Where patients were reported to have had any changes to their registration therapy, clinicians were instructed to specify all changes including dose and dose unit, frequency and information for the final dose dates and stop reasons. If patients have had any UV therapy (narrowband UVB; PUVA) since their last follow-up, clinicians were also expected to include the following details: UV therapy type; number of courses; number of therapies and cumulative dose (joules per square centimeter [J/cm^2]).

3.5.1.7 Previous therapy

For patients who have had previous treatment (before registration) with any systemic therapy, the following details were included: drug name; start date; stop date. Similarly for patients who received previous treatment with UV therapy the following details were included in the data cut: UV therapy type (Narrowband UVB; PUVA); number of courses; number of therapies; cumulative dose (J/cm^2).

3.5.1.8 Comorbidities

Comorbidities in this study were conditions diagnosed before enrolment to BADBIR. Clinicians were asked to confirm if patients ever had any of the following conditions along with year of onset: hypertension; cardiovascular disease; diabetes; autoimmune disorders; thrombosis; liver disease; kidney disease; peptic ulcer; demyelination; epilepsy; psychiatric; IBD; non-skin cancer (including type/site). For comorbidities that were not listed, clinicians could include details and year of onset using 'other' e.g. skin cancer.

3.5.1.9 Adverse events

Where patients were reported to have had an adverse event since their last visit, clinicians were asked to include some of the following details if they believed that the events was related to biologic drug used to the treat their psoriasis; a description of the adverse event (symptoms, diagnosis, treatment); start and stop dates; if the event was a serious adverse event; outcome of the event.

3.5.2 Data cleansing

3.5.2.1 Patient demographics and disease status

Patient age at registration was not captured in the dataset so a variable ('agestart') needed to be generated. Age at registration was obtained by calculating the number of days between patient date of birth and date of registration and then dividing that number by 365.25 to get the number of years between the two dates. In order to identify the number of years patients had psoriasis at baseline, a disease duration variable was generated. Disease duration was calculated as the number of years between the year of onset (captured by the 'yearofonset' variable) and the year of baseline registration to BADBIR.

Multiple PASI measurements are taken for patients during the baseline registration window and throughout follow-up. In order to capture true disease severity at baseline, the PASI score recorded in the 6 month period prior to the registration therapy start date was used as the baseline PASI score. A binary variable for ethnicity was generated to group patients in to one of 'White' or 'Non-White' using the data in the 'ethnicityid' variable capturing ethnicity data described in Section 3.5.1.1

3.5.2.2 Lifestyle factors and anthropometrics

Body Mass Index

Patient height and weight, collected clinically at baseline, were used to generate the Body Mass Index (BMI) score variable. The formula used to generate this score: *BMI = weight (kilograms) / (height (metres)*^{2} (Goacher et al., 2012). In order to facilitate calculating the BMI score a second 'height' variable converting height in centimetres to height in metres^2 was generated. Missing data for the BMI variable were the result of missing data for the variables capturing height and/or weight. The BMI variable was coded '.' to reflect this. BMI scores greater than 75 were considered outliers, due to extreme values recorded for height or weight, and were recoded as missing ('.').

Smoking

A smoking status at baseline variable ('smoking') was generated to consolidate entries for the data items 'eversmoked' and 'currentlysmoke' capturing historic and current smoking status (at baseline), respectively (Section 3.5.1.3). For patients indicating to not have ever

smoked more than one cigarette, the smoking status variable was set to ’0’ for ‘never smoked’. Where patients indicated to have previously smoked, but answered ‘No’ to the question ‘Do you currently smoke more than one cigarette?’, the smoking status variable was set to ‘1’ for ‘previous smoker’. For patients who indicated to have been actively smoking at baseline, the smoking variable was set to ‘2’ for ‘current smoker’. Where there was missing data for both data items, the variable was coded as missing (‘.’).

For cigarette smoking at baseline, a ‘numberofcigsperday’ variable was generated to consolidate entries for the following data items capturing historic and current (at baseline) reported number of cigarettes smoked per day: ‘eversmokednumbercigsperday’ and ‘currentlysmokenumbercigsperday’ (Section 3.5.1.3). Where patients reported number of cigarettes per day for both the data item ‘eversmokednumbercigsperday’ and ‘currentlysmokenumbercigsperday’, the latter was recorded as the number of cigarettes smoked per day at baseline. Where there was missing data for both, the variable was coded as missing (‘.’).

Consumption of alcohol

Alcohol drinking status (yes; no) at baseline was captured in the dataset using the variable ‘drinkalcohol’. The drinkalcohol variable was set to ‘1’ if patients confirmed that they currently drank alcohol and set to ‘0’ if patients did not drink alcohol at baseline with missing responses coded ‘.’. The average units of alcohol consumed per week at baseline was captured using the ‘drnkunitsavg’ variable. Patients who did not provide a response to the alcohol drinking status question but who did provide a value for the average units of alcohol consumed per week were still considered as drinking alcohol at baseline. For these patients, the ‘drinkalcohol’ variable was set to ‘1’.

3.5.2.3 Drug therapies and exposure status

Previous systemic therapies, defined in this study as systemic therapies prescribed to patients up to 6 months before registering to BADBIR, were identified using their drug id number and treatment start date. In order to accurately capture previous exposure to systemic therapy for each patient, binary variables were created for each systemic drug. These variables were set to ‘0’ (not exposed) or ‘1’ (exposed) to denote exposure status. For example, if a patient registering to BADBIR, previously received methotrexate (drug id=16)

but did not receive secukinumab (drug id =41) during follow-up, the 'tot_prev16' variable would be set to '1' and the 'tot_prev14' would be set to '0'.

These variables were also used to identify patients who were biologic-naïve or biologic-experienced at baseline. A new binary variable for previous biologic exposure at baseline, labelled 'bionaive', was generated coded '0' if patients were treated with biologic therapy before registering to BADBIR. In turn, the variable was coded '1' if patients did not have any previous treatment with biologic therapy before registering to BADBIR. A similar approach was taken to capture exposure to non-biologic systemic therapies during follow-up. For each systemic drug, a binary variable was generated and set to '1' or '0' depending on whether or not a patient received treatment with that specific drug. These variables were also used to quantify the number of patients treated with each systemic drug for each cohort.

Differences in cancer risk between the biologic mechanisms of biologic therapies was also of interest in this study so a variable ('biomech') was generated capturing this information. This variables was set to '1' if patients were treated with only TNFi during follow-up, '2' if treated with only ustekinumab. For patients who were treated with biologic therapies with different biologic mechanism during follow-up, e.g. treated with TNFi first and then with ustekinumab, IL-17 or IL-23, the variable was set to '3' for mixed exposure. Patients treated with the IL-17 or IL-23 inhibitors were coded '4' for 'other'.

Cumulative exposure to biologics, in terms of the number of different biologic therapies patients were treated with during follow-up, was also captured. The 'bio_exp' variable was generated, counting each unique biologic therapy a patient was treated. For example, if a patients was treated with only one biologic therapy during follow-up, the 'bio_exp' variable would count this as one exposure (variable coded '1'). In turn, if the patients were treated with two different biologic therapies during follow, the variable would count it as two exposures (variable coded '2').

3.5.2.4 Previous exposure to phototherapy

Although previous treatment details with phototherapy was captured for patients at baseline, some preparatory steps were needed to be taken before this data could be used in the analyses. Previous exposure to narrowband UVB and PUVA were identified at baseline

using the 'uvtherapytypeid' field. For each phototherapy type, an exposure variable was generated ('UVB_narrow; 'UVA'). Previous exposure to these phototherapies was quantified using the number of courses patients received for narrowband UVB ('UVBnarrowcourse') and PUVA ('UVAcourse'), respectively. Where patients were reported to have had multiple courses of phototherapy, these where combined to generate the total number of courses.

3.5.3 Identifying patients with previous, prevalent or incident cancer

Personal history of cancer was reported for patients in this study as either a comorbidity (Section 3.5.1.8) or as previous cancerous lesions (Section 3.5.1.4) in the clinical baseline questionnaire (appendix 12). Prevalent or incident cancers were reported for patients in this study as adverse events during follow-up in the clinical follow-up questionnaire (Appendix 13). Further details for cancers reported to BADBIR were requested from the dermatology centres were collected via the ESI forms (Appendices 14-16). Data from these sources were consolidated in to a set of variables used to identify patients with a previous history of cancer, prevalent cancer or incident cancer. The criteria used to identify these patients are summarised in Table 3.6. The MedDRA codes corresponding to the MedDRA terms used to identify the cancers that were included and excluded in the study outcomes can be found in Tables 3.7 and 3.8.

3.5.3.1 Identifying patients with a previous history of cancer

Firstly, all comorbidities reported as 'non-Skin cancers' were examined. A cancer comorbidity variable ('ComorbidCancer') was generated. The variable was initially set to '1' for all comorbidities that came under the MedDRA SOC "*Neoplasms benign, malignant and unspecified (incl cysts and polyps)*". Comorbidities coded under this MedDRA SOC but were 'benign neoplasms', 'carcinoma in situ', 'stage 0' or of 'unspecified malignancy' were then identified using the MedDRA codes corresponding the MedDRA terms in Table 3.8. For these comorbidities, the 'ComorbidCancer' variable was set to '0' as patients with these events were not considered to have a previous history of cancer.

A second variable was generated for just KC ('ComorbidKC'). These were identified using the MedDRA codes corresponding the MedDRA PTs 'basal cell carcinoma' and 'squamous cell carcinoma'. The variable was set to '1' for patients with SCC or BCC as a comorbidity and set to '0' if this was not the case. Secondly, variables were generated for patients reported to

have had a previous history of skin cancer lesions at baseline. These variables were labelled 'Melanoma', 'BCC' and 'SCC' and were set to '1' if patients were reported to have had a history of developing those specific cancerous lesions.

To consolidate the cancer history information from both these sources, two more variables were generated for history of any cancer (excluding KC) ('CancerHx') and history of KC ('KCHx'). The 'CancerHx' variable was set to '1' if patients had cancer reported as a comorbidity ('ComorbidCancer') or a melanoma skin cancer lesions ('Melanoma'). Similarly, for patients with previous KC, the 'KCHX' variable was set to '1' if reported as a comorbidity ('ComorbidKC') or skin cancer lesions ('BCC', 'SCC').

3.5.3.2 Identifying patients with incident or prevalent cancer

Incident and prevalent cancers were malignant neoplasms reported as adverse events for patients at follow-up in the clinical follow-up questionnaire with further information requested from the dermatology centres for cancer via the ESI forms. Incident cancers were identified using MedDRA corresponding to the MedDRA terms in Table 3.7.

A 'Cancer' variable identifying adverse events reported as cancer was generated. The variable was set to '1' if an adverse event was coded to the MedDRA SOC ''*Neoplasms benign, malignant and unspecified (incl cysts and polyps)*" and '0' for all other adverse events. Adverse events coded to the MedDRA HLT and PT terms for 'benign neoplasm', 'carcinoma in situ', 'stage 0' or of 'unspecified malignancy' were identified using MedDRA codes corresponding to the MedDRA terms in Table 3.7. For these adverse events, the 'Cancer' variable was set to '0'. For each individual cancer type (e.g. Breast; BCC; SCC), a variable was generated. These variables were set to '1' if the adverse event MedDRA code matched the corresponding MedDRA HLT term for that particular cancer.

For each adverse event, diagnosis and histopathology entries from the ESI forms were reviewed by the author and a medical professional (Professor Richard Warren). Where information in the ESI form contradicted the MedDRA coding, the variables were recoded to match the information from the ESI form. For example, an adverse event reported for a patient in the dataset was coded to MedDRA under the HLT "Urinary tract neoplasms unspecified malignancy NEC" and PT "ureteral neoplasm". This was initially identified as a neoplasm of 'unspecific malignancy' based on the MedDRA codes and the 'Cancer' variable

was set to '0'. However, the diagnosis and histopathology information from the ESI form identified the correct cancer type, grade and stage. Thus, the 'Cancer' and the 'urinary tract' variables were both set to '1' to reflect the correct diagnosis for this patient.

Prevalent cancers were defined in this study as adverse events, identified as malignant neoplasms, reported for patients after registering to BADBIR but were diagnosed before initiating their registration therapy. To account for the possibility that prevalent cancers were mistakenly identified as incidence cancers, the date the adverse event was reported to have started ('start date') was reviewed. If the start date was before or on the same day patients initiated their registration therapy, the event was considered a prevalent cancer. In turn, any adverse event with a start date after the registration date was considered an incident cancer. A 'PrevCancer' variable was generated identifying patients with a prevalent cancer and thus excluded from the analyses. In this dataset, only one patient with a prevalent cancer (SCC) was identified.

Table 3.5: Criteria used to identify patients with previous and incident cancer

	Previous cancer	**Incident cancer**
Criteria for previous/incident cancer	• Cancer reported as a comorbidity at baseline • Previous skin cancer lesion reported at baseline	• Cancer reported as an adverse event during follow-up, after initiating registration therapy
Criteria for non-malignant neoplasm/prevalent cancer	• Comorbidities identified as: benign neoplasms; carcinoma in situ; 'stage 0'; of unspecified malignancy • Benign skin lesions: Actinic keratosis; Bowen's disease; Keratoancathoma; Melanoma in situ	• Adverse events identified as: benign neoplasms; carcinoma in situ; 'stage 0'; of unspecified malignancy; metastases • Adverse events identified as being prevalent cancers (diagnosed before the initiation of registration therapy)
Verification method	• Examination of the MedDRA codes and comorbidity description • Examination of the skin cancer lesion description	• Examination of the MedDRA codes, adverse event start dates and description • Examination of the diagnosis and histopathology information from the ESI forms

Abbreviations: Medical Dictionary for Regulatory Activities (MedDRA); Events of Special Interest (ESI).

Table 3.6: MedDRA terms used to identify malignant neoplasms included in the study outcomes

MedDRA HLGT	MedDRA HLT	MedDRA PT
Breast neoplasms malignant and unspecified (incl nipple)	Breast and nipple neoplasms malignant	Breast cancer; oestrogen receptor positive breast cancer; invasive ductal breast carcinoma; mucinous breast carcinoma
Endocrine neoplasms malignant and unspecified	Carcinoid tumours	Carcinoid tumour of the appendix
	Endocrine neoplasms malignant and unspecified NEC	Neuroendocrine carcinoma
	Thyroid neoplasms malignant	Thyroid cancer
	Islet cell neoplasms and Apudoma NEC	Pancreatic neuroendocrine tumour
Gastrointestinal neoplasms malignant and unspecified	Anal canal neoplasms malignant	Anal squamous cell carcinoma
	Colorectal neoplasms malignant	Adenocarcinoma of colon; colon cancer; rectal adenocarcinoma; rectal cancer; rectosigmoid cancer
	Gastric neoplasms malignant	Adenocarcinoma gastric; gastric cancer
	Gastrointestinal neoplasms malignant NEC	Gastrointestinal carcinoma; malignant peritoneal neoplasm
	Lip and oral cavity neoplasms malignant	Squamous cell carcinoma of the oral cavity; squamous cell carcinoma of the tongue; tongue neoplasm malignant stage unspecified; lip and/or oral cavity cancer
	Oesophageal neoplasms malignant	Oesophageal carcinoma; oesophageal squamous cell carcinoma
	Pancreatic neoplasms malignant (excl islet cell and carcinoid)	Pancreatic carcinoma
	Small intestinal neoplasms malignant	Small intestine carcinoma ;small intestine adenocarcinoma
Haematopoietic neoplasms (excl leukaemias and lymphomas)	Myeloproliferative disorders (excl leukaemias)	Polycythaemia vera
	Lymphoproliferative disorders NEC (excl leukaemias and lymphomas)	Lymphoproliferative disorder

Hepatobiliary neoplasms malignant and unspecified	Bile duct neoplasms malignant	Cholangiocarcinoma; biliary cancer
	Gallbladder neoplasms malignant	Gallbladder cancer
	Hepatic cancer	Hepatocellular carcinoma
Leukaemias	Leukaemias acute myeloid	Acute myeloid leukaemia
	Leukaemias chronic lymphocytic	Chronic lymphocytic leukaemia
	Leukaemias NEC	Leukaemia
	Myelodysplastic syndromes	Myelodysplastic syndrome; refractory anaemia with ringed sideroblasts
Lymphomas Hodgkin disease	Hodgkin`s disease lymphocyte predominance type	Hodgkin's disease lymphocyte predominance type
	Hodgkin's disease NEC	Hodgkin's disease
	Hodgkin's disease mixed cellularity type	Hodgkin's disease mixed cellularity
Lymphomas non-Hodgkin B-cell	B-cell lymphomas NEC	B-cell lymphoma
	Follicle centre lymphomas, follicular grade I, II, III	Follicle centre lymphoma
	Mantle cell lymphomas	Mantle cell lymphoma
	Extranodal marginal zone B-cell lymphomas (low grade B-cell)	Extranodal marginal zone b-cell lymphoma (malt type)
Lymphomas non-Hodgkin T-cell	Anaplastic large cell lymphomas T- and null-cell types	Anaplastic large cell lymphoma t- and null-cell types
	Mycoses fungoides	Mycosis fungoides
	Anaplastic large cell lymphomas T- and null-cell types	T-cell lymphoma
Lymphomas non-Hodgkin unspecified histology	Non-Hodgkin's lymphomas NEC	Non-Hodgkins lymphoma
Mesotheliomas	Mesotheliomas malignant and unspecified	Mesothelioma; pleural mesothelioma malignant; epithelioid mesothelioma
Nervous system neoplasms malignant and unspecified	Central nervous system neoplasms malignant NEC	Brain neoplasm malignant
	Glial tumours malignant	Glioblastoma multiforme
Plasma cell neoplasms	Plasma cell myelomas	Plasma cell myeloma

Renal and urinary tract neoplasms malignant and unspecified	Bladder neoplasms malignant	Bladder cancer; bladder transitional cell carcinoma
	Renal neoplasms malignant	Renal cancer
	Urinary tract neoplasms malignant NEC	Transitional cell carcinoma
	Renal pelvis and ureter neoplasms malignant	Ureteric cancer
	Renal neoplasms malignant	Renal cell carcinoma; clear cell renal cell carcinoma
Reproductive neoplasms female malignant and unspecified	Cervix neoplasms malignant	Cervix carcinoma
	Endometrial neoplasms malignant	Endometrial adenocarcinoma; endometrial cancer
	Ovarian neoplasms malignant (excl germ cell)	Ovarian cancer
	Cervix neoplasms malignant	Squamous cell carcinoma of the cervix
	Vulval neoplasms malignant	Vulval cancer
Reproductive neoplasms male malignant and unspecified	Prostatic neoplasms malignant	Prostate cancer
	Testicular neoplasms malignant	Seminoma; testis cancer
	Penile neoplasms malignant	Penile squamous cell carcinoma
Skeletal neoplasms malignant and unspecified	Bone sarcomas	Ewing's sarcoma
	Bone neoplasms malignant (excl sarcomas)	Bone cancer
Respiratory and mediastinal neoplasms malignant and unspecified	Non-small cell neoplasms malignant of the respiratory tract cell type specified	Adenosquamous cell lung cancer; lung adenocarcinoma; non-small cell lung cancer; squamous cell carcinoma of lung; non-small cell lung cancer
	Oropharyngeal, nasopharyngeal and tonsillar neoplasms malignant and unspecified	Oropharyngeal cancer; oropharyngeal squamous cell carcinoma; nasopharyngeal cancer
	Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	Lung neoplasm malignant
	Respiratory tract small cell carcinomas	Small cell lung cancer

Skin neoplasms malignant and unspecified	Skin melanomas (excl ocular)	Malignant melanoma
	Skin neoplasms malignant and unspecified (excl melanoma)	Basal cell carcinoma; squamous cell carcinoma of skin
Soft tissue neoplasms malignant and unspecified	Soft tissue sarcomas histology unspecified	Synovial sarcoma
	Fibrosarcomas malignant	Dermatofibrosarcoma protuberans

Abbreviations: Medical Dictionary for Regulatory Activities (MedDRA); Higher Level Group Term (HLGT); Higher Level Term (HLT); Preferred Term (PT)

Table 3.7: MedDRA terms used to identify non-malignant neoplasms excluded from the study outcomes

Exclusion reason	MedDRA HLT	MedDRA PT
Benign neoplasms	Breast and nipple neoplasms benign	Fibroadenoma of breast
	Cardiovascular neoplasms benign	Haemangioma
	Cervix neoplasms benign	Cervical polyp
	Endocrine neoplasms benign NEC	Parathyroid tumour benign; pituitary tumour benign
	Gastrointestinal neoplasms benign NEC	Intestinal polyp; gastrointestinal tract adenoma; intraductal papillary mucinous neoplasm
	Lower gastrointestinal neoplasms benign	Anal polyp; colon adenoma; large intestine polyp; benign anorectal neoplasm
	Lip and oral cavity neoplasms benign	Benign salivary gland neoplasm
	Neoplasms benign site unspecified NEC	Adenoma benign; cyst; fibroma; papilloma; oncocytoma; polyp
	Nervous system neoplasms benign NEC	Haemangioblastoma
	Ovarian neoplasms benign	Ovarian cyst
	Prostatic neoplasms benign	Prostatic adenoma
	Renal neoplasms benign	Renal cyst; renal oncocytoma
	Reproductive neoplasms male benign NEC	Testicular cyst
	Soft tissue neoplasms benign NEC	Lipoma; synovial cyst; angiomyolipoma
	Thyroid neoplasms benign	Thyroid adenoma
	Uterine neoplasms benign	Uterine leiomyoma; uterine cyst
	Vulval neoplasms benign	Vulva cyst
Malignancy status unspecified	Breast neoplasms unspecified malignancy	Breast neoplasm
	Gastrointestinal neoplasms malignancy unspecified NEC	Gastrointestinal stromal tumour; neoplasm of appendix
	Colorectal and anal neoplasms malignancy unspecified	Anal neoplasm
	Hepatobiliary neoplasms malignancy unspecified	Hepatic neoplasm
	Urinary tract neoplasms unspecified malignancy NEC	Bladder neoplasm; renal neoplasm
	Reproductive neoplasms male unspecified malignancy	Penile neoplasm
	Laryngeal neoplasms malignancy unspecified	Laryngeal neoplasm
	Respiratory tract and pleural neoplasms malignancy unspecified NEC	Lung neoplasm

Stage 0 and Carcinoma in situ	Vulval neoplasms malignant	Vulval cancer stage 0
	Cervix neoplasms malignant	Cervix carcinoma stage 0
	Skin melanomas (excl ocular)	malignant melanoma in situ
	Skin neoplasms malignant and unspecified (excl melanoma)	Bowen's disease
Metastases	Metastases	Metastases to specified sites; metastases to bone; metastases to kidney; metastases to liver; metastases to lung; metastases to lymph nodes; metastases to ovary; metastases to spine

Abbreviations: Medical Dictionary for Regulatory Activities (MedDRA); Higher Level Term (HLGT); Preferred Term (PT)

3.5.4 Handling outliers values

The possibility of outlier values entered for the data items in clinician and patient completed questionnaires were needed to be accounted. This could have arisen due to response error and response burden or simple data entry errors. Response error referrers to interpreting questions on the questionnaire differently from how the researchers intended. Response burden could arise from the amount of perceived effort it takes to complete the questionnaires (Mes et al., 2019). Erroneous data entry errors, even in electronic data collection, is not uncommon (Ley et al., 2019).

The method used to treat outlier values was trimming (Kwak and Kim, 2017). Outlier values in this study were defined as any value greater than the upper fence value (99^{th} percentile) for a respective variable. Values greater than the 99^{th} percentile value were considered a likely product of response or data entry error and recoded as missing ('.'). For example, values entered by patients for the data item capturing average units of alcohol consumed per week ranged between 1 and 400 units. The 99^{th} percentile value was 70 units, meaning that 99% of the data captured for this data item were between 1 and 70 units. Values greater than 70 were censored and recoded as missing. Other variables with outlier values, subjected to trimming, were the continuous variables capturing number of cigarettes smoked per day ('numberofcigsperday'), narrowband UVB courses ('UVBnarrowcourse') and PUVA courses ('UVAcourse').

3.5.5 Handling missing data

3.5.5.1 Types of missing Data

Missing data, observations that were meant to be collected but were unavailable, is common in studies conducted using observational, routinely collected healthcare data. Reasons for missing data are classified as follows: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Sterne et al., 2009). Where data is considered MCAR, the likelihood of a data item to be missing is completely random. There are no systemic differences between patients with the missing value and those with the observed value. For example, missing data for smoking status could be due to specific dermatological centers not proving patients with patient baseline questionnaires. Data is considered MAR if any systemic difference between patients with the missing value and

those with the observed value can be explained by differences in the observed data. Patient with missing information for smoking status could be younger than those who do have information for smoking status as younger people might be less like to report smoking behaviors due to the social stigma attached to it (Castaldelli-Maia et al., 2016). Data is considered MNAR if, even after taking in to account differences in the observed data, systemic differences remain between the missing values and the observed values. Missing data in this thesis project was considered to be MAR.

3.5.5.2 Multiple imputation

Multiple imputation (MI) was the statistical approach taken in this thesis to deal with missing data (Sterne et al., 2009). There are a number of advantaged to using MI. Firstly, it takes in to account the uncertainty of predicting missing data by creating several datasets with different imputed values for the missing data, sampled from their predictive distribution based on the observed data, and combining the results obtained from each dataset in to a final imputation value for the missing data (Sterne et al., 2009). This results in unbiased estimates, providing more validity than adhoc approaches to accounting for missing data (McCleary, 2002). Secondly, MI uses all the available data which preserves the sample size and statistical power (Sterne et al., 2009). Other strategies, such as complete case analyses and last observation carried forward or simple mean imputation can lead to loss of power and the introduction of bias (Joseph et al., 2004; Sterne et al., 2009).

MI using chained equations of 20 cycles was used to replace missing baseline data. The variables in the imputation model informed the distribution of the values imputed for each missing variable. Each imputation model included both the variables with missing baseline data as well as all the other variables in the model, namely the exposure variable ('cohort'), the outcome variable and the other confounders (e.g. age and sex). MI was performed in STATA version 14.1 (StataCorp, USA) using the guide written by Professor Mark Lunt from the University of Manchester (Lunt, 2013).

3.6 Statistical analysis plan

3.6.1 Baseline characteristics

Baseline characteristics for patients in each cohort were described using descriptive statistics. Median values and the upper and lower quartiles were calculated for the continuous variable (age; disease duration; baseline PASI; BMI score; number of cigarettes smoked per day; units of alcohol consumed per week; number of narrowband UVB courses; number of PUVA courses). The frequencies and percentages for missing values, and for sub-categories for binary (sex; ethnicity; PsA status; alcohol consumption status; treatment with systemic therapies; treatment with phototherapy; environmental UV exposure) and categorical variables (BMI category; smoking status; skin type), were calculated.

Baseline characteristics between the biologic and non-biologic cohorts were compared using parametric and non-parametric statistical tests. The assumption underlying parametric tests is that the population from which data are sampled is normally distributed (Guetterman, 2019). Non-parametric tests are "distribution-free" and, as such, can be used for non-normally distributed variables. The distribution of baseline continuous variables was assessed graphically using histograms (Guetterman, 2019). The distribution of baseline continuous variables was assessed graphically using histograms.

Two-sample t-tests were used for normally-distributed continuous variables and Wilcoxon rank-sum for non-normally distributed variables. The two-sample t-test (also known as the independent samples t-test) is a method used to test whether the unknown population means of two groups are equal or not (Cressie and Whitford, 1986). The Mann-Whitney U test (known as Wilcoxon rank sum test in Stata) is used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed (Whitley and Ball, 2002). Binary variables where compared using the chi-squared test (x^2). The chi-squared test is used to compare the distribution of a categorical variable in a sample with the distribution of a categorical variable in another sample; for each observed number in the table an expected number is presented which is the null hypothesis, namely that the numbers in each cell are proportional to the number in the other cell (Campbell and Swinscow, 2011). The Kruskal-Wallis test, used to compare ordinal and non-normal variables for more than two groups, was used to determine if there

were statistically significant differences between the medians of the categorical variables (Campbell and Swinscow, 2011).

3.6.2 Calculating incidence and risk of cancer

Incidence rates per 1,000 person years of follow-up along with 95% CI were calculated for patients in both cohorts by dividing the number of events observed during follow-up by the total number of patients-years of follow-up for each cohort. Survival analysis, also known as time-to-event analysis, using Cox-proportional hazards regression (hereafter referred to as to as 'Cox-regression') was performed to compare the risk of the cancer outcomes between the biologic cohort and the non-biologic systemic cohort. The Cox-regression model is based on the proportional hazards assumption; the ratio of the hazards (the risk of an event occurring at a particular point in time) comparing the different exposure groups remains constant over time (Kirkwood and Sterne, 2007). (Kirkwood and Sterne, 2007). Specifically, the model assumes that each covariate has a multiplicative effect in the hazards function that is constant over time (Kirkwood and Sterne, 2007). The proportional hazards assumption was based on the scaled Schoenfeld residuals (Grambsch and Therneau, 1994). A residual measures the difference between the observed and expected data under the model assumptions, in the case of Schoenfeld residuals. Schoenfeld residuals are calculated at every failure time and under the PH assumption are independent of time (Kirkwood and Sterne, 2007).

3.6.3 Accounting for confounding

The effects of confounding on each of the risk of cancer study outcomes was accounted for using confounder-adjusted Cox-regression models. The two approaches considered in this thesis were the multivariable-adjusted method and the propensity score-adjusted method. The methods used to build each model are described below.

3.6.3.1 Selection of the confounders

For each of the study outcomes, the inclusion of the potential confounders to the analysis models were tested using univariable analyses. For categorical variables, the log-rank test for equality of survivor function across strata was performed. The log rank test is used to test the null hypothesis that there is no difference between two groups in the probability of an event (cancer) at any time point (Bland and Altman, 2004). The long-rank test calculates

the observed number of events in each group and the expected number of events if there were in fact no difference between the two groups (Bland and Altman, 2004). The null hypothesis was tested using the x^2 test statistic. If the difference between the number of observed and expected events between the two groups was statistically significant, the categorical variable was included in the Cox-regression model. For continuous variables, univariable Cox-proportional hazard regressions were performed. Similarly, the continuous variable was selected for inclusion if x^2 test statistic was statistically significant. For both the categorical and continuous variables, the threshold for inclusion for each confounder was $p \leq 0.25$ (UCLA, 2021). Where a potential confounder did not test significantly, the variable could still be forced in to the model if there was evidence for an association with the study outcome in the literature.

3.6.3.2 Multivariable-adjusted Cox-regression model

The multivariable Cox-regression models included the exposure variable ('cohort') and all the confounder variables. The possibility of an interaction effect, defined as "…when the effect one explanatory variable on the outcome depends on the particular level or value of another explanatory variable" was also accounted for (Vetter and Mascha, 2017). Interaction terms were generated for each of the variables and tested for inclusion to the multivariable model in a stepwise fashion (UCLA, 2021). Each interaction terms was added to the multivariable model and assess for inclusion. Interaction terms were only included to the multivariable model if interaction effect was considered statistically significant ($p \leq 0.05$). The fit of the full multivariable Cox-regression model, including all the confounder variables, with and without the inclusion of the interactions term(s) were compared using the likelihood ratio test, a statistical test assessing the goodness of fit of two competing models (Glover and Dixon, 2004). The null hypothesis for this test, that both models fit the data equally well, was rejected if the test statistic was statistically significant ($p \leq 0.05$) and the interaction term(s) was included in the model.

The assumption of non-proportionality using Schoenfeld and scaled Schoenfeld residuals was assess statistically for each full Cox-regression model and the individual variables included each model in STATA using the 'stphtest' command. The model as a whole and the individual variables were deemed to have not violated the assumption of non-proportionality if the reported p-value for each was greater than 0.05.

3.6.3.3 Propensity score adjusted Cox-regression model

The primary method used to adjust for confounding in the risk of cancer study was by way of propensity score adjusted Cox-regression models. Propensity score methods are used to generate comparable populations such that the only real difference between them is the treatment received (McDonald et al., 2013). The propensity score, a single summary score between 0 and 1, is defined by Rosenbaum and Rubin as "…the conditional probability of assignment to a particular treatment given a vector of observed covariates" (Rosenbaum and Rubin, 1983). Patients in two cohorts with the same propensity score have the same likelihood of receiving the treatment of interest (biologic therapy) given their baseline characteristics (Desai et al., 2017). Differences in the measured baseline characteristics that could potentially act as confounders between patients in the two cohorts can be accounted for by comparing patients with the same propensity score (Austin, 2011). Therefore, the effect of treatment on developing the study outcomes can be compared directly between patients in the two groups while also mitigating for confounding by the measured baseline characteristics.

Propensity score methods are commonly used in pharmacoepidemiology to control for confounding and has a number of advantages over the more traditional multivariable adjusted regression models (Glynn et al., 2006). These include the ability to assess the balance of confounders between the cohorts and the improved estimation of treatment effect when outcomes are rare (Glynn et al., 2006). There are three main propensity score based methods used in survival analysis: propensity score matching; inverse probability of treatment weighting; stratification on the propensity score (Austin, 2011).

Propensity score matching consists of creating matched sets of patients treated with the therapy of interest (biologic therapy) and untreated (biologic-naïve) patients in the comparator group sharing a similar propensity score value (Austin, 2011). The treatment effect on developing the outcome of interest (cancer) can be estimated by directly compared between treated and untreated patients (Austin, 2011). However, this method has an import limitation deeming it unsuitable for the risk of cancer studies. Patients with most comparable propensity scores are matched 1-to-1 first. As the pool of patients needing to be matched decreases, patients in the treatment or comparator group are discarded if all the patients with comparable propensity scores are already matched up (Desai et al., 2017).

Given the considerably greater number of patients in the biologic cohort in the risk of cancer studies in this thesis, propensity score matching could lead to the exclusion of a large number of biologic-treated patients including those who developed the study outcome.

The inverse probability of treatment weighting (IPTW) method attempts to balance the distribution of the baseline confounders between two groups by calculating weights from the propensity scores for each patient such that they are the same as the distribution as the entire sample (Austin, 2011). In this approach, the IPTW for patients in the treatment group is calculated by the inverse of the conditional probability of receiving the treatment of interest (1/propensity score for receiving treatment) (Heinze and Jüni, 2011). For patients in the comparator group, the IPTW is calculated by the inverse of 1 minus their propensity score (1-(1/propensity score for receiving treatment) (Heinze and Jüni, 2011). The downside of using the IPTW method is that patients with extremely high propensity scores are disproportionally weighted higher than other patients which could lead to an imprecise estimate of the treatment effect (Glynn et al., 2006). To deal with this problem weights can be truncated at a threshold level, however the subsequent loss of patients in a study with rare outcome events is not desirable particularly when they could have been more likely to develop the outcomes of interest.

The propensity score method used in the risk of cancer studies was stratification on the propensity score. This method can be conceptualized as a meta-analysis of a set of quasi-RCTs, patients are ranked according to their propensity score and stratified in to groups with other patients with similar propensity scores (Desai et al., 2017). Within each of the strata, the effect of treatment on the study outcomes can be estimated by comparing risk of developing the outcome directly between treated and untreated patients (Austin, 2011). The stratum-specific estimates of treatment effect can then be pooled across the strata to estimate an overall treatment effect (Desai et al., 2017). The most common approach is divide the patients in to five groups equal in size using the quintiles of their estimated propensity score (Cochran, 1968). This approach was demonstrated to lead to a 90% reduction in bias with an increase in strata postulated to lead to further reductions due to the smaller strata (Cochran, 1968; Hullsiek and Louis, 2002). An advantage of using the stratification approach compared to the matching and IPTW methods is that by comparing patients within strata, the effect of small variations in the individual propensity scores on

the overall estimate is minimised (Rubin, 2004). A simulation study, using the stratification on the propensity score method, comparing the use of varying numbers of strata when assessing a binary outcome also concluded that using more than 5 strata led to increased power and reduced bias (Neuhäuser et al., 2018). However, the authors of the study concluded that using more than 10 strata yielded marginal benefits in terms of increasing power and reducing bias (Neuhäuser et al., 2018). Thus, the approach taken in the analyses was to divide patients in to ten strata using their propensity score with propensity score deciles generated.

The propensity score adjusted Cox-regression models were constructed in STATA using the guide written by Professor Mark Lunt from the University of Manchester (Lunt, 2014). In brief, the following steps were taken to construct the propensity score models. The initial balance of the confounders between the two cohorts were assessed using standardised difference (differences in the mean value of the confounder for patients in each cohort divided by their standard deviation) (Takeshima et al., 2014). For each study outcome, propensity scores were generated using a logistic regression model consisting of the treatment variable (cohort) and all the other confounders. The distribution of the propensity score for both study cohorts was assessed graphically using the log of the odds of the propensity score. The goodness of fit of the propensity scores was assess using a Hosmer-Lemeshow test where a significant p-value (≤ 0.05) indicating that logistic regression model did not fit the data well. The need for inclusion of interaction terms to improve the fit of the model was identified by generating interaction terms, including each one in the model and running the Hosmer-Lemeshow test.

Deciles were generated used the propensity score with patients in each cohort stratified in to one of the ten strata. The balance of confounders between the strata before and after adjustment using the propensity score methods were plotted using standardised differences and assessed graphically. The distribution of confounders was considered balanced between the cohorts if the standardised difference was 0.1 or less. The single propensity score decile summary variable took the place of the individual confounder variables in the Cox-regression model.

3.6.4 Subgroup analyses

Differences in the risk of developing the study outcomes between patients in the biologic cohort and the non-biologic systemic cohort were further explored using subgroup analyses. The purpose of performing these secondary analyses was to determine if particular segments of the biologic-treated study population had an increased or decreased risk of developing the study outcomes compared with corresponding patients in the non-biologic systemic cohorts. These analysis were performed for the following study outcomes: all cancer (excluding KC); cancers of infectious origin; BCC; SCC. Difference in risk by the following factors were of interested:

i. Age categories
ii. Fitzpatrick skin type (skin type I/II versus skin type III/IV)
iii. Comorbid PsA
iv. Obesity (BMI≥30 kg/m2)
v. biologic mechanism of the biologic therapy (TNFi-only versus ustekinumab-only versus mixed biologic exposure)
vi. Number of different biologic exposures (single exposure versus multiple exposure)

4 Risk of cancer in BADBIR patient cohorts

4.1 Outline

This chapter examines the risk of all cancer (excluding KC), hereafter referred to as 'all cancer' in patients with psoriasis treated with biologic therapy compared with patients treated with non-biologic systemic therapy only. The first part describes the study sample, their baseline demographic and disease characteristics, and the incidence of all cancer in the two therapy cohorts. The second part of the chapter reports the risk of all cancer, and specific risks of cancers of infectious origin and of common site-specific cancers (lung; breast; prostate).

4.2 Aims

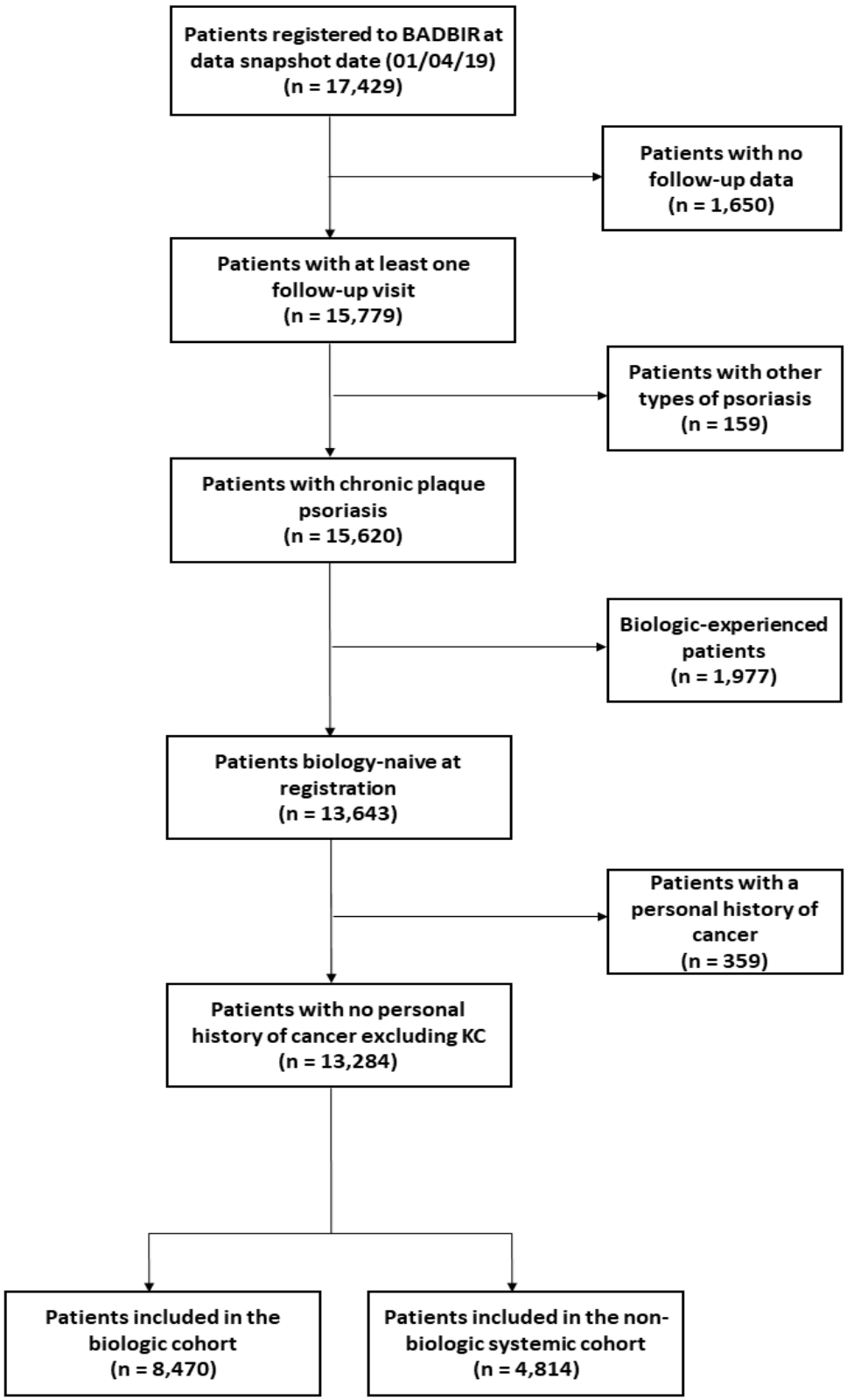
The aims of this chapter were to:

- Describe the study sample and compare the baseline and disease characteristics between the biologic and non-biologic systemic therapy cohorts
- Estimate and compare the incidence of total and site-specific cancers (excluding KC) for patients in the biologic and non-biologic systemic therapy cohorts
- Calculate the crude risk and adjusted risk of all cancer, cancers of infectious origin and common site-specific cancers (lung; breast; prostate) for patients in the biologic cohort compared with patients in the non-biologic systemic therapy cohort
- Determine if there are differences in risks of all cancer and cancers of infectious origin in biologic- versus non-biologic-treated patients according to: age categories; type of biologic therapy; cumulative biologic exposure; comorbid PsA; obesity (BMI≥30).

4.3 Study sample

A total of 17,429 patients with moderate-severe psoriasis were registered to BADBIR prior to 01/04/2019. Exclusions were as follows: 1,650 patients without follow-up data; 159 patients not having a diagnosis of chronic plaque psoriasis; 1,977 patients already using biologics; and 359 patients with a personal history of cancer other than KC. The final study population consisted of 13,284 patients: 8,470 patients in the biologic cohort and 4,814 patients in the non-biologic systemic cohort (Figure 4.1).

Figure 4.1: Patient inclusion and exclusion flow diagram for the risk of all cancer studies



4.4 Baseline demographic and disease characteristics

Differences between patients in the biologic cohort and the non-biologic systemic cohort for baseline demographic and disease characteristics, lifestyle factors and treatment history were assessed (Table 4.1). Differences in patient demographics between the two cohorts were small and unlikely to be clinically significant with respect to risk of cancer, despite being statistically significant. Patients in the biologic cohort were slightly older at registration than the non-biologic systemic cohort (44 years vs 42 years respectively) with slightly higher proportions of patients being male (60% vs 57%) and identifying as White (86% vs 84% respectively). Baseline disease severity measured by PASI was also very similar in the two therapy cohorts (14.2 vs 14.0). However, patients in the biologic cohort had a diagnosis of psoriasis for a longer number of years (19 vs 16) with a greater proportion of patients in the biologic cohort having comorbid PsA (21% vs 10%) (Table 4.1).

In terms of lifestyle factors, a greater proportion of patients in the biologic cohort than in the non-biologic systemic cohort were obese (BMI≥30) at baseline (46% vs 41%). Although the median baseline BMI for patients in the biologic cohort (29.8) was slightly higher than for patients in the non-biologic systemic cohorts (28.9), this difference was not clinically relevant in relation to cancer risk. Similarly there were only small baseline differences between the therapy cohorts regarding consumption of alcohol (65% vs 62%) and number of units of alcohol consumed per week (9 vs 8 units), prevalence of previous or current smoking (59% vs 62%) and number of cigarettes smoked per day (8 vs 6) (Table 4.1).

The greatest differences at baseline between patients in the biologic and non-biologic systemic cohorts were their previous exposures to non-biologic systemic therapy. Greater proportions of patients in the biologic (versus non-biologic) cohort were previously exposed to methotrexate (74% vs 23%), ciclosporin (58% vs 18%), acitretin (44% vs 22%) and FAEs (18% vs 4%). The proportions of missing data for baseline BMI, number of cigarettes smoked per day and number of units of alcohol consumed per week were similar between the two cohorts. Data were imputed for the missing values using MI (described in Section 3.5.5).

Table 4.1: Baseline patient demographics and disease characteristics

Baseline characteristics	Biologic cohort (n = 8,470)	Non-biologic systemic cohort (n = 4,814)	P-value
Demographics			
Age (years), median (IQR)	44.0 (34.0, 53.0)	42.0 (32.0, 53.0)	**0.000** [a]
Female, n (%)	3,388 (40.0)	2,085 (43.3)	**0.000** [c]
White ethnicity, n (%)	7,317 (86.4)	4,064 (84.4)	**0.002** [c]
Disease			
Disease duration (years), median (IQR)	19.0 (11.0, 29.0)	16.0 (8.0, 26.0)	**0.000** [b]
Baseline PASI score, median (IQR)	14.2 (11.0, 19.3)	14.0 (11.0, 18.8)	0.480 [b]
PsA, n (%)	1,792 (21.2)	501 (10.4)	**0.000** [c]
Lifestyle factors			
BMI (kg/m^2) category, n (%)			**0.000** [d]
Underweight (<18.5)	68 (1.0)	65 (1.4)	-
Normal (18.5-24.9)	1,462 (17.3)	1,000 (20.8)	-
Overweight (25.0-29.9)	2,522 (29.8)	1,475 (30.6)	-
Obese (≥30.0)	3,906 (46.1)	1,933 (41.0)	-
BMI (kg/m^2) score, median (IQR)	29.8 (26.0, 34.8)	28.9 (25.2, 33.7)	**0.000** [b]
Missing, n (%)	512 (6.0)	341 (7.0)	-
Smoking status, n (%)			**0.000** [d]
Never smoked	3,467 (40.9)	1,842 (38.3)	-
Previous smoker	2,791 (33.0)	1,523 (31.6)	-
Current smoker	2,212 (26.1)	1,449 (30.1)	-
Average number of cigarettes smoked per day, median (IQR)	6 (0, 15)	8 (0, 15)	**0.014** [b]
Missing, n (%)	745 (8.8)	418 (8.7)	
Currently drinks alcohol, n (%)	5,520 (65.2)	2,964 (61.6)	**0.000** [c]
Average units of alcohol per week, median (IQR)	9 (3, 15)	8 (3, 15)	**0.000** [b]
Missing, n (%)	431 (5.1)	241 (5.0)	-
Treatment history			
Previous methotrexate, n (%)	6, 294 (74.3)	1,112 (23.1)	**0.000** [c]
Previous ciclosporin, n (%)	4,938 (58.3)	844 (17.5)	**0.000** [c]
Previous acitretin, n (%)	3,760 (44.4)	1,051 (21.8)	**0.000** [c]
Previous FAEs, n (%)	1,549 (18.3)	213 (4.4)	**0.000** [c]

Abbreviations: n (number); standard deviation (SD); interquartile range (IQR); psoriasis area and severity index (PASI); body max index (BMI); [a] two-sample t-test for continuous variables; [b] Wilcoxon rank-sum test for continuous variables; [c] chi-squared test for binary variables; [d] Kruskal-Wallis for categorical variables.

4.5 Frequency of cancer

A total of 244 incident cancers (excluding KC) were reported during the study period. One-hundred and seventy three cancers, representing 70% of all incident cancers, were reported for patients in the biologic cohort (n= 8,470) with the remaining 71 cancers reported for patients in the non-biologic systemic cohort (n= 4,814). Biologic-treated and non-biologic systemic-treated patients with incident cancer represented 2.0% and 1.5% of all patients in their respective cohorts. Of the 173 incident cancers reported for the biologic cohort, 99 were in male patients (2.0% of males in the biologic cohort) and 74 in female patients (2.2% of females in the biologic cohort). For the non-biologic systemic cohort, the distribution of incident cancers was more balanced between male patients (n=36, 1.3% of males in the cohort) and female patients (n=35, 1.7% of females in the cohort). There were 58 cancers of infectious origin of which 41 were reported for patients in the biologic cohort (0.6% of the cohort) and 19 in the non-biologic cohort (0.4% of the cohort) (Table 4.2).

Gastrointestinal cancers were the most common group of incident cancers in the biologic cohort comprising 16.0% of all cancers, compared with 13.0% of all cancers in non-biologic systemic cohort, while respiratory and mediastinal cancers comprised 14.0% of each cohort. Breast cancer was the most common cancer for female patients in the biologic cohort (n=13) and non-biologic cohort (n=13), comprising 31% of all cancers in the female population for each cohort. Female reproductive cancers were the second most common group of cancers in the female patients in the biologic cohort (n=15, 20% of all cancers in females) and the non-biologic cohort (n=8, 23% of cancers in females). Male reproductive cancers represented 14% of all cancers reported for men in the biologic cohort and 25% of all cancer reported for men in the non-biologic cohort (Table 4.2).

Regarding common site-specific cancers (excluding KC), breast cancer was the most common site-specific cancer for female patients in both the biologic (31%) and non-biologic (31%) cohorts, while lung cancer was second most common cancer for patients in the biologic (12%) and non-biologic (13%) cohorts. Prostate cancer was the most common cancer reported for male patients in the biologic cohort (13%) and the non-biologic cohort (25%). Although melanoma (10%) and colorectal (8%) cancer represented the third and fifth most common cancers for patients in the biologic cohort, respectively, less than 5 events for

either cancer were reported for patients in the non-biologic cohort so they were not included in the analysis of common site-specific cancers (Table 4.2).

Table 4.2: Frequency of all incident cancers (excluding keratinocyte carcinomas)

Cancer sites (MedDRA *HLGT*)		Biologic cohort; (n = 8,470)			Non-biologic systemic cohort; (n = 4,814)		
		Total; n (%)	**Male; n (%)**	**Female; n (%)**	**Total; n (%)**	**Male; n (%)**	**Female; n (%)**
		173	**99**	**74**	**71**	**36**	**35**
Gastrointestinal	**Total**	**27 (16)**	**22 (22)**	**5 (7)**	**9 (13)**	<5	**5 (14)**
(Gastrointestinal neoplasms	Colorectal	13 (8)	8 (8)	5 (7)	<5	<5	<5
malignant and unspecified)	Pancreas	6 (3)	<5	<5	<5	<5	<5
Breast	**Total**	**23 (13)**		**23 (31)**	**11 (15)**		**11 (31)**
(Breast neoplasms malignant and unspecified (incl nipple)							
Respiratory and mediastinal	**Total**	**24 (14)**	**16 (16)**	**8 (11)**	**10 (14)**	**5 (14)**	**5 (14)**
(Respiratory and mediastinal neoplasms malignant and unspecified)	Lung	20 (12)	12 (12)	8 (11)	9 (13)	5 (14)	<5
Reproductive (female)	**Total**	**15 (9)**		**15 (20)**	**8 (11)**		**8 (23)**
(Reproductive neoplasms	Cervix	9 (5)		9 (12)	<5		<5
female malignant and unspecified)	Endometrium	<5		<5	<5		<5
Reproductive (male)	**Total**	**14 (8)**	**14 (14)**		**9 (13)**	**9 (25)**	
(Reproductive neoplasms	Prostate	13 (8)	13 (13)		9 (13)	9 (25)	
male malignant and unspecified)							

Melanoma *(Skin neoplasms malignant and unspecified)*	**Total**	**17 (10)**	**8 (8)**	**9 (12)**	**<5**	**<5**	**<5**
Renal and urinary tract (*Renal and urinary tract neoplasms malignant and unspecified)*	**Total** Kidney Bladder	**16 (9)** 11 6) 5 (3)	**9 (9)** <5 <5	**7 (9)** 7 (9) <5	**<5** <5 <5	**<5** <5 <5	**<5** <5 <5
Lymphoma (*Lymphomas non-Hodgkins B-cell*) (*Lymphomas Hodgkins disease*) (*Lymphomas NEC*)	**Total** NHL HL	**13 (8)** 8 (5) <5	**12 (12)** 7 (7) 4 (4)	**<5** <5 <5	**5 (7)** <5 <5	**<5** <5 <5	**<5** <5 <5
Haematopoietic (excluding lymphoma) *(Haematopoietic neoplasms [excl leukaemias and lymphomas]*) (*Leukaemias)*	**Total** Leukaemia	**8 (4)** 5 (3)	**6 (6)** <5	**<5** <5	**<5** <5	**<5** <5	**<5** <5
Hepatobiliary (*Hepatobiliary neoplasms malignant and unspecified*)	**Total** Liver	**7 (4)** 5 (3)	**<5** <5	**<5** <5	**<5** <5	**<5** <5	**<5** <5
Other*	**Total**	**10 (6)**	**6 (6)**	**<5**	**7 (10)**	**5 (14)**	**<5**
Cancers of infectious origin	**Total**	**41 (24)**	**27 (27)**	**14 (19)**	**17 (24)**	**9 (25)**	**8 (23)**

Abbreviations: Hodgkin Lymphoma (HL); Non-Hodgkin Lymphoma (NHL); Medical Dictionary for Regulatory Activities (MedDRA) ; Higher Level Group Term (HLGT)

* The other category included the following MedDRA HLGT: "*Miscellaneous and site unspecified neoplasms malignant and unspecified* " (n=8); *"Endocrine neoplasms malignant and unspecified"* (n=3); "*Mesotheliomas"* (n=2); *"Nervous system neoplasms malignant and unspecified"* (n=2); *"Skeletal neoplasms malignant and unspecified"* (n=1); *"Soft tissue neoplasms malignant and unspecified"* (n=1)

4.6 Risk of all cancer in study cohorts

4.6.1 Follow-up time and incidence rates

Total person-time for patients in the biologic and non-biologic systemic cohorts were 34,552.07 years and 14,381.26 years, respectively. The incidence rates for all cancer per 1,000 person-years of follow-up were very similar: 5.01 (95% CI 4.31-5.81) and 4.94 (95% CI 3.91-6.23) for patients in the biologic and non-biologic systemic cohorts, respectively (Table 4.3).

4.6.2 Multivariable and propensity score models

Univariable analyses, using log-rank tests and Cox-proportional hazards regression, of the *a priori* identified confounders identified the following variables for inclusion to the multivariable Cox-proportional hazards model: age; sex; average number of cigarettes smoked per day; average units of alcohol consumed per week and previous exposure to ciclosporin (Appendix 18). Although BMI was not significant after testing (p=0.84), it was included based on its known association with a number of site-specific cancer outcomes (Bhaskaran et al., 2014). Testing for multiplicative interaction terms between the variables included in the multivariable Cox-proportional hazards model identified the interactions terms age*sex (p=0.02) and units of alcohol consumed per week*number of cigarettes smoked per day (p=0.04) as statistically significant and these were subsequently included in the final multivariable model. The fit of the model including the interaction terms was found to fit the data better than the model without the interaction terms after performing a likelihood-ratio test (p=0.00). The proportional hazards assumption for the full multivariable model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.99) (Appendix 28).

The propensity score model for this analysis included the treatment variable (cohort) and all the confounders included in the multivariable Cox-proportional hazards model: age; sex; number of cigarettes smoked per day; units of alcohol consumed per week; previous exposure to ciclosporin; BMI. Interaction terms were not included in the propensity score model. After generating the propensity score for each participant and balancing the confounders between the two cohorts, propensity score deciles were generated for use in the propensity score adjusted model (Appendix 19).

4.6.3 Crude and adjusted risks: all cancer

The crude and age-sex adjusted hazard ratios for developing any cancer in patients treated with biologic therapy compared with patients treated with non-biologic systemic therapy were 0.99 (95% CI 0.75-1.31) and 1.08 (0.82-1.42), respectively. The multivariable-adjusted risk and propensity score decile-adjusted risk estimates for developing any cancer were each non-significant and fell on either side of unity: aHR 1.20 (95% CI 0.88-1.61) and aHR 0.96 (95% CI 0.70-1.30), respectively.

Table 4.3: Follow-up time, incidence rates, crude and adjusted Cox-proportional hazard ratios for the outcome all cancer

	Biologic cohort	Non-biologic systemic cohort
Cancers (n, %)	173 (2.0)	71 (1.5)
Follow-up time (years), median (IQR)	3.69 (1.99, 6.00)	2.49 (1.27, 4.22)
Total person-years of follow-up	34,552.07	14,381.26
IR/1000 pyrs (95% CI)	5.01 (4.31-5.81)	4.94 (3.91 - 6.23)
Crude HR (95% CI)	0.99 (0.75-1.31)	Reference
Age-sex aHR (95% CI)	1.08 (0.82-1.42)	Reference
Multivariable†* aHR (95% CI)	1.20 (0.88-1.61)	Reference
PSD† aHR (95% CI)	0.96 (0.70-1.30)	Reference

Abbreviations: interquartile range (IQR); incidence rate per 1,000 person-years of follow-up (IR/1000 pyrs); hazard ratio (HR); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); propensity score deciles (PSD)

† Confounders: age; sex; BMI; number of cigarettes; units of alcohol; previous ciclosporin.

* Interaction terms included with confounders in the multivariable model: age and sex; units of alcohol consumed per week and number of cigarettes smoked per day

4.6.4 Subgroup analyses

Subgroup analyses were performed to determine if the risk of all cancer for patients in the biologic cohort compared with the non-biologic systemic cohort differed according to the following factors: age categories; comorbid PsA status; presence of obesity (BMI≥30 kg/m2); biologic mechanism of the biologic therapy and number of different biologic exposures. The hazard ratios showed no consistent pattern of risk for biologic-treated patients compared to patients in non-biologic systemic cohort in relation to age. No difference in risk was detected between biologic-treated and non-biologic patients when considering biologic mechanism of their biologic therapy or the number of biologic exposures. Similarly, there were no meaningful differences in corresponding risk estimates between treatment cohorts according to comorbid PsA status or presence of obesity (Table 4.4).

Table 4.4: Subgroup analyses for the outcome all cancer

Subgroup analyses		Biologic cohort; n	Non-biologic systemic cohort; n	PSD aHR (95% CI)
Age categories (years)	<40	17	10	0.55 (0.22-1.39)
	40-49	39	10	1.48 (0.70-3.13)
	50-59	59	24	1.23 (0.74-2.05)
	≥60	58	27	1.18 (0.73-1.92)
Biologic mechanism	TNFi-only	108	71	0.90 (0.65-1.26)
	Ustekinumab-only	29	71	0.97 (0.60-1.57)
	Mixed biologic exposure	33	71	1.00 (0.62-1.65)
Number of different biologic exposures	Single biologic exposure	127	71	0.96 (0.70-1.32)
	Multiple biologic exposures	46	71	0.90 (0.57-1.40)
Prevalent PsA	No PsA	133	64	0.98 (0.70-1.37)
	PsA	40	7	0.85 (0.37-1.95)
Obesity	BMI<30 kg/m^2	81	39	0.87 (0.57-1.33)
	BMI≥30 kg/m^2	92	32	1.05 (0.68-1.64)

Abbreviations: Body Mass Index (BMI); Psoriatic arthritis (PsA); propensity score deciles (PSD); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); Tumour necrosis factor inhibitor (TNFi)

4.7 Risk of cancers of infectious origin

4.7.1 Follow-up time and incidence rates

Total person-time for patients in the biologic and non-biologic systemic cohorts were 34,797.86 years and 14,491.50 years, respectively. The incidence rates for cancers of infectious origin per 1,000 person-years of follow-up for patients in the biologic and non-biologic systemic cohorts were almost identical: 1.18 (95% CI 0.87-1.60) and 1.17 (95% CI 0.73-1.89), respectively (Table 4.5).

4.7.2 Multivariable and propensity score models

Univariable analyses identified the following variables for inclusion to the multivariable and propensity score adjusted Cox-proportional hazards models: age; average number of cigarettes per day; previous exposure to ciclosporin (Appendix 18). The variables for sex, BMI and average units of alcohol per week were not considered significant after testing but included in the model due to their associations with a number of cancers of infectious origin (Thun et al., 2018). Three interaction terms were identified for inclusion to the final multivariable model: age*sex (p=0.03); sex*BMI (p=0.01); sex*number of cigarettes smoked per day (p=0.03). The likelihood ratio test was significant (p=0.00), indicating that the model with the interaction terms fit the data better than the model without the interaction terms. The proportional hazards assumption for the full multivariable model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.95) (Appendix 29).

The propensity score model for this analysis included the treatment variable (cohort) and all the confounders included in the multivariable Cox-proportional hazards model described above. Interaction terms were not included in the propensity score model. Propensity scores were generated for patients in each cohort using logistic regression, confounders were balanced between the cohorts and propensity score deciles were generated for use in the propensity score adjusted model (Appendix 20).

4.7.3 Crude and adjusted risks: cancers of infectious origin

There was no evidence of a statistically significant increased risk of developing cancers of infectious origin for the biologic cohort compared with the non-biologic systemic cohort, with both crude and age-sex adjusted risk estimates close to unity: HR 1.02 (95% CI 0.58-1.80) and aHR 1.06 (95% CI 0.60-1.87), respectively (Table 4.5). Similarly, the multivariable-adjusted and propensity score decile-adjusted risk estimates for developing cancers of infectious origin were close to null: aHR 1.10 (95% CI 0.59-2.04) and aHR 0.95 (95% CI 0.70-1.77), respectively.

Table 4.5: Follow-up time, incidence rates, crude and adjusted Cox-proportional hazard ratios for the outcome cancers of infectious origin

	Biologic cohort	Non-biologic systemic cohort
Cancers (n, %)	41 (>1%)	17 (>1%)
Follow-up time (years), median (IQR)	3.75 (2.02, 6.00)	2.51 (1.29, 4.25)
Total person-years of follow-up	34,797.86	14,491.50
IR/1000 pyrs (95% CI)	1.18 (0.87-1.60)	1.17 (0.73 -1.89)
Crude HR (95% CI)	1.02 (0.58-1.80)	Reference
Age-sex aHR (95% CI)	1.06 (0.60-1.87)	Reference
Multivariable†* aHR (95% CI)	1.10 (0.59-2.04)	Reference
PSD†* aHR (95% CI)	0.95 (0.70-1.77)	Reference

Abbreviations: interquartile range (IQR); incidence rate per 1,000 person-years of follow-up (IR/1000 pyrs); hazard ratio (HR); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); propensity score deciles (PSD)

† Confounders: age; sex; BMI; number of cigarettes; units of alcohol; previous ciclosporin.

* Interaction terms included with confounders in the multivariable model: age and sex; sex and BMI; units of alcohol consumed per week and number of cigarettes smoked per day.

4.7.4 Subgroup analyses

Subgroup analyses were performed to determine if the risk of developing cancers of infectious origin for patients in the biologic cohort compared with the non-biologic systemic cohort differed by any of the following factors: age categories; comorbid PsA; obesity (BMI≥30 kg/m^2); biologic mechanism of the biologic therapy and number of different biologic exposures. Due to the very small number of events (<5) reported for the non-biologic systemic cohort, no analysis was performed for the stratum 'prevalent PsA' comparing patients with comorbid PsA. Subgroup analyses indicated no meaningful differences in risk or raised risk estimates for developing cancers of infectious origin in patients in the biologic cohort versus in the non-biologic systemic cohort across strata for any of the other factors (Table 4.6).

Table 4.6: Subgroup analyses for the outcome cancer of infectious origin

Subgroup analyses		Biologic cohort; n	Non-biologic systemic cohort; n	PSD ahr (95% CI)
Age categories (years)	<50	16	7	1.05 (0.89-1.23)
	≥50	25	10	0.96 (0.83-1.11)
Biologic mechanism	TNFi-only	28	17	0.99 (0.50-1.94)
	Ustekinumab-only	7	17	0.78 (0.30-2.04)
	Mixed biologic exposure	5	17	0.72 (0.22-2.31)
Number of different biologic exposures	Single biologic exposure	34	17	0.99 (0.52-1.90)
	Multiple biologic exposures	7	17	0.72 (0.25-2.07)
Prevalent PsA	No PsA	32	15	0.99 (0.50-1.98)
	PsA	9	<5	-
Obesity	BMI<30 kg/m^2	18	7	1.19 (0.46-3.13)
	BMI≥30 kg/m^2	23	10	0.80 (0.35-1.83)

Abbreviations: Body Mass Index (BMI); Psoriatic arthritis (PsA); propensity score deciles (PSD); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); Tumour necrosis factor inhibitor (TNFi)

4.8 Risk of common site-specific cancers

The study population for assessing the risk of lung cancer was the same as that of the risk of all cancer and risk of cancers of infectious origin analyses (described in Section 4.3), while the study populations for assessing risks of breast and prostate cancers were restricted to female and male patients, respectively (Section 3.4.1).

4.8.1 Lung cancer

The study population for the lung cancer analysis consisted of 8,470 patients in the biologic cohort and 4,814 patients in the non-biologic systemic cohort. Total person-time for patients in the biologic and non-biologic systemic cohorts were 34,875.06 years and 14,519.62 years, respectively. The incidence rates for lung cancer per 1,000 person-years of follow-up for patients in the biologic cohort were 0.57 (95% CI 0.37-0.89) and 0.62 (95% CI 0.32-1.19) for patients in the non-biologic systemic cohort (Table 4.7).

Univariable analyses identified the following confounders for inclusion to the propensity score adjusted Cox-regression model: age; average number of cigarettes per day (Appendix 18). Previous exposure to methotrexate (p=0.73) and previous exposure to ciclosporin (p=0.48) were not considered significant so were not included in the analysis. The variable for sex was also not significant after testing, however, the variable was included in the model due to the well-described sex difference in the incidence of lung cancer (Hellyer and Patel, 2019). No interaction terms were identified for inclusion to the model. Propensity scores were generated for patients in each cohort using logistic regression and confounders were balanced between the two cohorts (Appendix 21). Propensity score deciles were generated and included in the propensity score-adjusted model. The proportional hazards assumption for the adjusted model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.99) (Appendix 30).

Neither the crude nor propensity score decile-adjusted hazard ratios for developing lung cancer were raised in the biologic-treated versus the non-biologic systemically-treated patients in this study, with estimates of 0.86 (95% CI 0.39-1.91) and 0.83 (95% CI 0.36-1.94), respectively (Table 4.7).

4.8.2 Breast cancer

The study population for the breast cancer analysis consisted of 3,338 female patients in the biologic cohort and 2,085 female patients in the non-biologic systemic cohort. Total person-time for female patients in the biologic cohort was 13,814.26 and 6,295.53 for female patients in the non-biologic systemic therapy. The incidence rates of breast cancer per 1,000 person-years of follow-up for female patients were 1.74 (95% CI 0.97-3.16) and 1.66 (95% CI 1.11-2.51) for patients in the non-biologic and biologic cohorts, respectively.

Age, units of alcohol consumed per week and previous exposure to ciclosporin were identified for inclusion to the propensity score adjusted model after univariable analyses (Appendix 18). BMI was not significant after testing but was included in the model due to the known association between obesity and development of breast cancer in women (Engin, 2017). No interactions were included to the propensity score model. After generating the propensity scores for patients using logistic regression, the confounders were balanced between the cohorts and propensity score deciles were generated for inclusion in the propensity score-adjusted model (Appendix 22). The proportional hazards assumption for the adjusted model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.67) (Appendix 31).

The crude and propensity score decile-adjusted hazard ratios were 0.98 (95% CI 0.48-2.02) and 1.02 (95% CI 0.46-2.26), indicating no difference in risk for developing breast cancer between female patients in the biologic cohort and the non-biologic systemic cohort (Table 4.7).

4.8.3 Prostate cancer

The study population for the prostate cancer analysis consisted of 5,082 male patients in the biologic cohort and 2,729 male patients in the non-biologic systemic cohort. Total person-time for male patients in the biologic cohort was 20,989.85 and 8,179.26 for male patients in the non-biologic systemic therapy. The incidence rates of prostate cancer per 1,000 person-years of follow-up for male patients in the biologic cohort was 0.62 (95% CI 0.36-1.07) and 1.10 (95% CI 0.57-2.11) for patients in the non-biologic systemic cohort (Table 4.7).

Univariable analyses of the potential confounders identified the following for inclusion to the propensity score model: age, previous exposure to methotrexate and previous exposure to ciclosporin (Appendix 18). No interactions were identified for inclusion in the propensity score model. Propensity scores were generated for patients in each cohort using logistic regression and the confounders were balanced between the two cohorts (Appendix 23). Propensity score deciles were then generated and added to the Cox-regression model. The proportional hazards assumption for the adjusted model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.43) (Appendix 32).

The crude and propensity score decile-adjusted risk estimates for developing prostate cancer for male patients treated with biologic therapy compared with male patients treated with non-biologic systemic therapy were 0.55 (95% CI 0.23-1.29) and 0.53 (95% CI 0.16-1.94), respectively. The results indicate a possible decreased risk of prostate cancer for biologic-treated patients, however this decrease was not statistically significant (Table 4.7).

Table 4.7: Follow-up time, incidence rates, crude and adjusted Cox-proportional hazard ratios for the outcomes lung cancer, breast cancer and prostate cancer

Outcome	Cohort (n)	Cancers	Follow-up time (years), median (IQR)	Total person-years of follow-up	IR/1000 pyrs (95% CI)	Crude HR (95% CI)	PSD aHR (95% CI)
Lung cancer	Biologic (**8,470**)	20	3.80 (2.02, 6.00)	34,875.06	0.57 (0.37-0.89)	0.86 (0.39-1.91)	**0.83 (0.36-1.94)**†
	Non-biologic systemic (**4,814**)	9	2.52 (1.29, 4.25)	14,519.62	0.62 (0.32-1.19)	Reference	Reference
Breast cancer	Biologic (**3,388**)	23	3.73 (2.03, 6.00)	13,814.26	1.66 (1.11-2.51)	0.98 (0.48-2.02)	**1.02 (0.46-2.26)**‡
	Non-biologic systemic (**2,085**)	11	2.58 (1.29, 4.31)	6,295.53	1.74 (0.97-3.16)	Reference	Reference
Prostate cancer	Biologic (**5,082**)	13	3.84 (2.02, 5,98)	20,989.85	0.62 (0.36-1.07)	0.55 (0.23-1.29)	**0.53 (0.19-1.50)***
	Non-biologic systemic (**2,729**)	9	2.48 (1.30, 4.21)	8,179.26	1.10 (0.57-2.11)	Reference	Reference

Abbreviations: incidence rate per 1000 person-years (IR/1000 pyrs); hazard ratio (HR); propensity score decile (PSD); adjusted hazard ratio (aHR); 95% confidence interval (95% CI).

† Propensity score adjusted confounders: age, sex and number of cigarettes smoked per day

‡ Propensity score adjusted confounders: age, BMI, units of alcohol consumed per week, previous exposure to ciclosporin

* Propensity score adjusted confounders: age, previous exposure to methotrexate, previous exposure to ciclosporin

5 Risk of keratinocyte carcinomas in BADBIR patient cohorts

5.1 Outline

Chapter 5 presents the results examining the risk of KC in patients with psoriasis treated with biologic therapy compared with patients treated with non-biologic systemic therapy only. This chapter includes a description of the study sample, their baseline demographic and disease characteristics, and incidence of BCC and cutaneous SCC in the two therapy cohorts. This is followed by the results for the risk of BCC and SCC analyses.

5.2 Aims

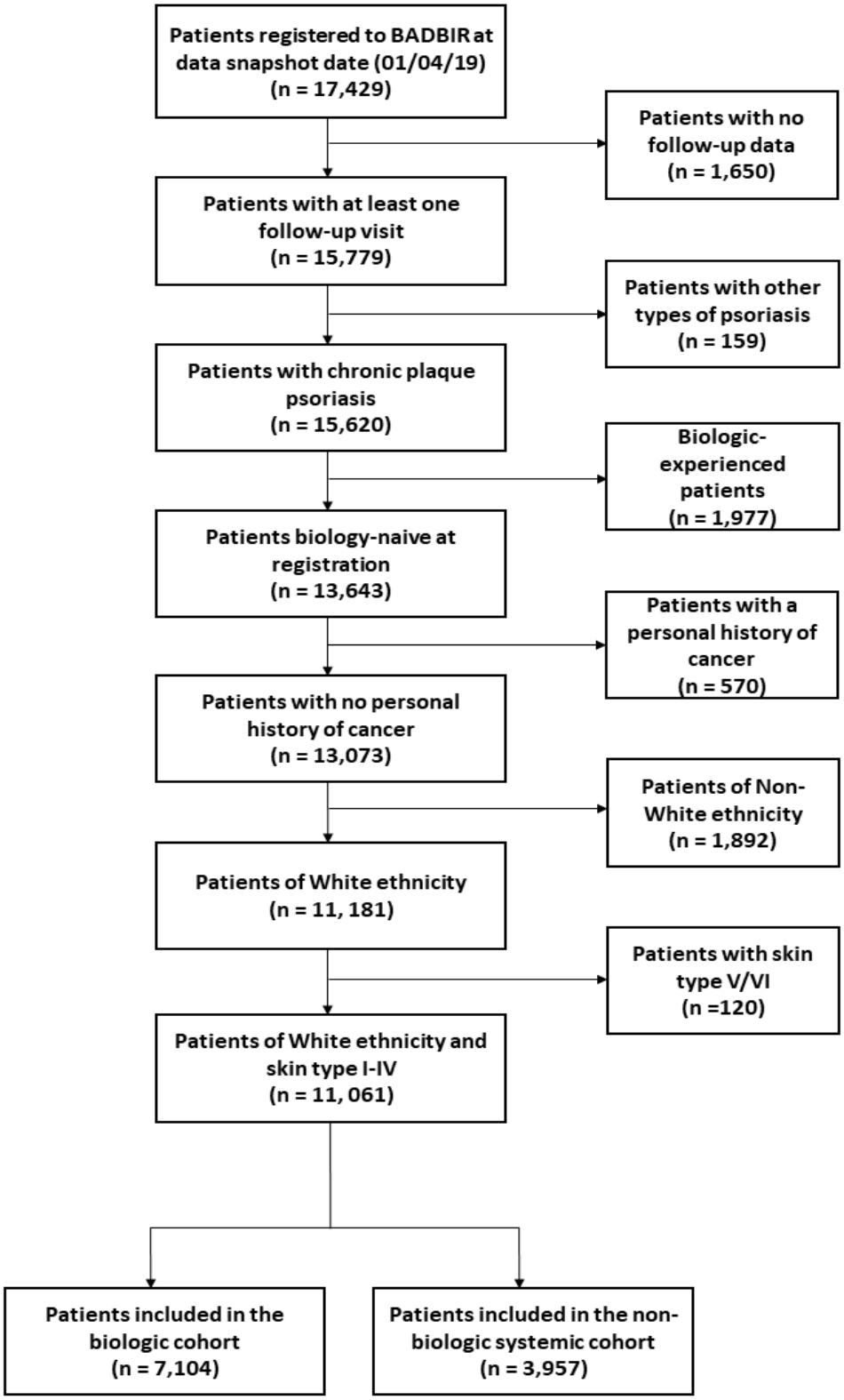
The aims of this chapter were to:

- Describe the KC study population and compare the baseline and disease characteristics between the biologic and non-biologic systemic cohorts
- Determine and compare the incidence of BCC and SCC for patients in the biologic and non-biologic systemic cohorts
- Determine the crude and adjusted risks of BCC and SCC for patients in the biologic cohort compared with patients in the non-biologic systemic cohort.
- Determine if there is a difference in risk of BCC or SCC for patients in the biologic vs non-biologic cohort according to: age categories; Fitzpatrick skin type; biologic mechanism of the biologic therapy; number of different biologic exposures.

5.3 Study sample

A total of 17,429 patients with moderate-severe psoriasis were registered to BADBIR prior to 01/04/2019. In addition to the main exclusions applied to the study population in the risk of all cancer study (described in Section 4.3), the following additional exclusions were made for this risk of KC study: 1,892 patients belonging to non-White ethnic groups; a further 120 patients who self-identified as belonging to a White ethnic group were also excluded as they had a Fitzpatrick skin types V/VI (Figure 5.1). The reasons for these additional exclusions were described in Section 3.4.1.

Figure 5.1: Patient inclusion and exclusion flow diagram for the risk of keratinocyte carcinoma studies



5.4 Baseline patient demographics and disease characteristics

Patients in the biologic cohort were slightly older at registration than their counterparts in the non-biologic systemic cohort (44 years versus 42 years) with a slightly greater proportion of male patients in the biologic cohort (58% versus 55%) and slightly more of the biologic cohort had skin types I and II (49% versus 46%) (Table 5.1). Although these differences between the two therapy cohorts were statistically significant, the magnitude of the differences was small and unlikely to be clinically significant with respect to risk of BCC or SCC (Table 5.1).

In terms of disease characteristics, baseline disease severity measured by PASI were nearly identical between patients in the biologic cohort and the non-biologic systemic cohort (14.1 versus 13.9). However, patients in the biologic cohort had a diagnosis of psoriasis for longer (20 years versus 17 years) with a greater proportion of patients in the biologic cohort having comorbid PsA (21% versus 10%). When considering lifestyle factors, patients in the non-biologic systemic cohort were slightly more likely to be current smokers at baseline than patients in the biologic cohort (30% versus 26%) and on average to have smoked a greater number of cigarettes per day than patients in the biologic cohort (10 versus 8), but again these were not likely to be clinically important difference with respect to KC (specifically SCC) risk (Table 5.1).

Similar proportions of patients in the two cohorts were reported to have had previous treatment with narrowband UVB (notwithstanding a statistically significant difference), however a higher proportion of patients in the biologic cohort were historically treated with PUVA (28% versus 21%). The largest differences between patients in the two therapy cohorts at baseline were seen in previous exposure to conventional systemic therapy. Greater proportions of patients in the biologic cohort were previously exposed to methotrexate (74%), ciclosporin (58%), acitretin (44%) and FAEs (18%), compared with corresponding proportions in the non-biologic cohort (23%, 17%, 21% and 5%) (Table 5.1).

Large difference were also seen in the proportion of missing data for some of the baseline variables between the two therapy cohorts. Greater proportions of patients in the biologic cohort were reported to have missing data for the number of narrowband UVB courses

(10% versus 8%) and PUVA courses (7% versus 4%) compared with patients in the non-biologic cohort (Table 5.1).

Table 5.1: Baseline patient demographics and disease characteristics

Baseline characteristics	Biologic cohort (n = 7,104)	Non-biologic systemic (n = 3,957)	P-value
Demographics			
Age (years), median (IQR)	44.0 (35.0, 53.0)	43.0 (32.0, 53.0)	**0.000** [a]
Female, n (%)	2,899 (40.8)	1,760 (44.5)	**0.000** [c]
Outdoor occupation, n (%)	2,176 (30.6)	1,227 (31.0)	0.680 [c]
Lived in a tropical country, n (%)	591 (8.3)	345 (8.7)	0.469 [c]
Skin type, n (%)			**0.001** [d]
Skin type I	1,076 (15.2)	521 (13.2)	
Skin type II	2,379 (33.5)	1,288 (32.6)	
Skin type III	2,305 (32.5)	1,348 (34.1)	
Skin type IV	1,344 (18.9)	800 (20.2)	
Disease			
Disease duration (years), median (IQR)	20.0 (12.0, 29.0)	17.0 (9.0, 27.0)	**0.000** [b]
Baseline PASI score, median (IQR)	14.1 (11.0, 19.0)	13.9 (11.0, 18.7)	0.996 [b]
PsA, n (%)	1, 494 (21.0)	396 (10.0)	**0.000** [c]
Lifestyle factors			
Smoking status, n (%)			**0.000** [d]
Never smoked	2,855 (40.2)	1,456 (36.8)	
Previous smoker	2,436 (34.3)	1.311 (33.1)	
Current smoker	1, 813 (25.5)	1,190 (30.1)	
Number of cigarettes smoked per day, median (IQR)	8 (0, 15)	10 (0, 15)	**0.011** [b]
Missing, n (%)	623 (8.8)	348 (8.8)	
Treatment history			
Previous NB-UVB, n (%)	4,416 (61.2)	2,520 (63.7)	**0.000** [c]
Number of NB-UVB courses, median (IQR)	2 (1, 3)	2 (1, 3)	0.342 [b]
Missing, n (%)	700 (9.9)	304 (7.7)	
Previous PUVA, n (%)	1,973 (27.8)	846 (21.4)	**0.000** [c]
Number of PUVA courses, median (IQR)	1 (1, 2)	1 (1, 2)	**0.000** [b]
Missing, n (%)	466 (6.6)	156 (3.9)	
Previous methotrexate, n (%)	5,247 (73.9)	890 (22.5)	**0.000** [c]
Previous ciclosporin, n (%)	4,117 (58.0)	688 (17.4)	**0.000** [c]
Previous acitretin, n (%)	3,130 (44.1)	843 (21.3)	**0.000** [c]
Previous FAEs, n (%)	1,328 (18.7)	180 (4.6)	**0.000** [c]

Abbreviations: n (number); standard deviation (SD); inter-quartile range (IQR); psoriasis area and severity index (PASI); narrowband ultraviolet B (NB-UVB); psoralen plus ultraviolet A (PUVA); two-sample t-test for continuous variables (a); Wilcoxon rank-sum test for continuous variables (b); chi-squared test for binary variables (c); Kruskal-Wallis for categorical variables.

5.5 Frequency of keratinocyte carcinomas

A total of 91 incident KCs were reported for patients in the biologic cohort of which 68 (75%) were reported for male patients and 23 (25%) reported for female patients. For the non-biologic systemic cohort, a total of 27 incident KCs were reported of which 17 (63%) were reported for male and 10 (27%) for female patients. Overall, incident KCs were infrequent with only 1% of patients in the biologic cohort and <1% of patients in non-biologic systemic cohort diagnosed with either BCC or SCC (Table 5.2).

As expected BCCs were the more commonly reported KCs for patients in both the biologic cohort (n=58, 64%) and the non-biologic systemic cohort (n=17, 63%). BCCs were more likely to occur in male patients in both the biologic cohort (n=41, 71%) and non-biologic cohort (n=9, 53%). SCCs were less common with a total of 33 (77%) and 8 (23%) reported for patients in the biologic and non-biologic cohorts, respectively. As was the case with BCCs, SCCs occurred more commonly in male patients than female patients in both the biologic cohort (n=27, 82%) and non-biologic system cohort (n=8, 80%).

Table 5.2: Frequency of incident keratinocyte carcinomas

Keratinocyte Carcinoma (MedDRA *HLGT*)		**Biologic cohort; (n = 7,104)**			**Non-biologic systemic cohort; (n = 3,957)**		
		Total; n (%)	**Male; n (%)**	**Female; n (%)**	**Total; n (%)**	**Male; n (%)**	**Female; n (%)**
		91	**68**	**23**	**27**	**17**	**10**
Skin (*Skin neoplasms malignant and unspecified*)	**Basal cell carcinoma**	**58 (64)**	41 (60)	17 (74)	**17 (63)**	9 (53)	8 (80)
	Squamous cell carcinoma	**33 (36)**	27 (40)	6 (26)	**10 (37)**	8 (47)	<5

Abbreviations: KC; Medical Dictionary for Regulatory Activities (MedDRA);
Higher Level Group Term (HLGT)

5.6 Risk of basal cell carcinoma

5.6.1 Follow-up time and incidence rates

Total person-time for patients in the biologic and non-biologic systemic cohorts were 34,552.07 years and 14,381.262 years, respectively. The incidence rates for BCC per 1,000 person-years of follow-up were 1.99 (95% CI 1.54-2.57) and 1.43 (95% CI 0.89-2.30) for patients in the biologic and non-biologic cohorts, respectively (Table 5.3).

5.6.2 Multivariable and propensity score models

Univariable analyses, using log-rank tests and Cox-regression, of the *a priori* identified confounders identified the following variables for inclusion in the multivariable Cox-regression models: age; sex; previous exposure to ciclosporin; previous exposure to acitretin; outdoor occupation; number of PUVA courses; number of narrowband UVB courses (Appendix 18). Following testing for multiplicative interaction terms between the variables included in the multivariable Cox-regression model, no interaction terms were identified for inclusion. The proportional hazards assumption for the full multivariable model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.64) (Appendix 33).

The propensity score model for BCC included the treatment variable (cohort) and all the confounders included in the multivariable model: age; sex; previous exposure to ciclosporin; previous exposure to acitretin; outdoor occupation; number of PUVA courses; number of narrowband UVB courses. Interaction terms were not included in the propensity score model. After generating the propensity score for each participant and balancing the confounders between the two cohorts, propensity score deciles were generated for use in the propensity score-adjusted model (Appendix 24).

5.6.3 Crude and adjusted risks: basal cell carcinoma

The crude and age-sex-adjusted hazard ratios for developing BCC in biologic-treated patients compared with non-biologic systemic-treated patients were 1.35 (95% CI 0.79-2.34) and 1.48 (0.86-2.55), respectively. The corresponding multivariable-adjusted and propensity score decile-adjusted hazard ratios for developing BCC were 1.44 (0.81-2.59) and 1.27 (0.70-2.32), respectively. Although both the multivariable and propensity score adjusted hazard ratios indicate a possible small increase in risk of developing BCC for biologic-treated patients compared with non-biologic systemic-treated patients, the increase was not statistically significant (Table 5.3).

Table 5.3: Follow-up time, incidence rates, crude and adjusted Cox-proportional hazard ratios for the outcome basal cell carcinoma

	Biologic cohort (n=7,104)	**Non-biologic systemic cohort (n=3,957)**
BCC (n, %)	58 (1%)	17(<1%)
Follow-up time (years), median (IQR)	3.83 (2.06, 5.99)	2.51 (1.29, 4.26)
Total person-years of follow-up	29,169.51	11,895.84
IR/1000 pyrs (95% CI)	1.99 (1.54-2.57)	1.43 (0.89-2.30)
Crude HR (95% CI)	1.35 (0.79-2.34)	Reference
Age-sex aHR (95% CI)	1.48 (0.86-2.55)	Reference
Multivariable† aHR (95% CI)	1.44 (0.81-2.59)	Reference
PSD† aHR (95% CI)	1.27 (0.70-2.32)	Reference

Abbreviations: incidence rate per 1,000 person-years of follow-up (IR/1000 pyrs); hazard ratio (HR); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); propensity score deciles (PSD)

† Confounders: age; sex; previous exposure to ciclosporin; previous exposure to acitretin; outdoor occupation; number of PUVA courses; number of narrowband UVB courses.

5.6.4 Subgroup analyses

Subgroup analyses were performed to determine if the risk of BCC for patients in the biologic cohort compared with the non-biologic systemic cohort differed for the following factors: age categories; Fitzpatrick skin type; biologic mechanisms of the biologic therapies, and number of different biologic exposures (Table 5.4). The hazard ratios for each of the two age strata varied greatly from the overall propensity score adjusted hazard ratio (1.27 [95% CI 0.70-2.32]), with an aHR of 0.79 (0.07-9.08) in those under 60, and 2.22 (0.90-5.51) in those aged 60 or more. The subgroup analyses also indicated a positive but non-significant association between biologic-treatment and BCC in patients with Fitzpatrick skin type III or IV (aHR 1.61 [0.72-3.63]), treatment with only TNFi (aHR 1.35 [0.70-2.57]), treatment with only ustekinumab (aHR 1.45 [0.56-3.72]) and mixed biologic exposure (aHR 1.26 [0.50-3.14]).

Although the hazard ratios for developing BCC in relation to the biologic mechanism and number of biologic exposures indicated varying levels of possible increased risks for biologic-treated patients (HR 1.26-1.45), number of BCCs in the non-biologic cohort was small and confidence intervals were wide. Thus, there was suggestive evidence of effect modification by several factors, especially with a possible increase in risk for developing BCC with age over 60, Fitzpatrick skin type III/IV, exposure to only TNFi, exposure to only ustekinumab and treatment with a single biologic therapy.

Table 5.4: Subgroup analyses for the outcome basal cell carcinoma

Subgroup analyses		Biologic cohort; n	Non-biologic systemic cohort; n	PSD aHR (95% CI)
Age categories (years)	<60	38	10	0.79 (0.07-9.08)
	≥60	20	7	2.22 (0.90-5.51)
Fitzpatrick skin type	Skin type I/II	23	8	0.92 (0.37-2.37)
	Skin type III/IV	35	9	1.61 (0.72-3.63)
Biologic mechanism	TNFi-only	39	Reference	1.35 (0.70-2.57)
	Ustekinumab-only	8	Reference	1.45 (0.56-3.72)
	Mixed biologic exposure	11	Reference	1.26 (0.50-3.14)
Number of different biologic exposures	Single biologic exposure	45	Reference	1.41 (0.75-2.63)
	Multiple biologic exposures	13	Reference	1.04 (0.43-2.51)

Abbreviations: propensity score deciles (PSD); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); Tumour necrosis factor inhibitor (TNFi)

5.7 Risk of squamous cell carcinoma

5.7.1 Follow-up time and incidence rates

Total person-time for patients in the biologic and non-biologic systemic cohorts were 29,243.26 years and 11,912.71 years, respectively. The incidence rates for SCC per 1,000 person-years of follow-up were 1.13 (95% CI 0.80-1.59) and 0.84 (95% CI 0.45-1.56) for patients in the biologic and non-biologic systemic cohorts, respectively (Table 5.5).

5.7.2 Multivariable and propensity score models

The following *a priori* identified confounders were included in the multivariable Cox-regression model after univariable analyses: age; sex; previous exposure to acitretin; outdoor occupation; number of cigarettes smoked per day; number of PUVA courses; number of narrowband UVB courses (Appendix 18). Although the variable for previous exposure to ciclosporin was not significant after testing, it was included in the multivariable model as there is some evidence of an association with the development of SCC in patients with psoriasis (Paul et al., 2003). Following testing for multiplicative interaction terms between the variables included in the multivariable Cox-regression model, no interaction terms were identified for inclusion. The proportional hazards assumption for the full multivariable model was found not to be violated after testing time-dependent variables using Schoenfeld residuals (p=0.69) (Appendix 34).

The propensity score model for SCC included the treatment variable (cohort) and all the confounders included in the multivariable model: age; sex; previous exposure to ciclosporin; previous exposure to acitretin; outdoor occupation; number of cigarettes smoked per day; number of PUVA courses; number of narrowband UVB courses. Interaction terms were not included in the propensity score model. After generating the propensity score for each participant and balancing the confounders between the two cohorts, propensity score deciles were generated for use in the propensity score-adjusted model (Appendix 25).

5.7.3 Crude and adjusted risk of squamous cell carcinoma

The crude and age-sex adjusted hazard ratios for developing SCC were 1.28 (95% CI 0.63-2.62) and 1.51 (0.74-3.09), respectively. The multivariable-adjusted hazard ratio for developing SCC was slightly and non-significantly raised in biologic-treated patients compared with non-biologic systemic-treated treated patients (aHR 1.24 [95% CI0.57-3.09]), while the corresponding propensity score decile adjusted hazard ratio was non-significantly reduced (aHR 0.93 [95% CI 0.42-2.07]) (Table 5.5).

Table 5.5: Follow-up time, incidence rates, crude and adjusted Cox-proportional hazard ratios for the outcome squamous cell carcinoma

	Biologic cohort (n=7,104)	**Non-biologic systemic cohort (n=3,957)**
SCC (n, %)	33 (<1%)	10 (<1%)
Follow-up time (years), median (IQR)	3.79 (2.06, 5.99)	2.51 (1.29, 4.26)
Total person-years of follow-up	29,243.26	11,912.71
IR/1000 pyrs (95% CI)	1.13 (0.80-1.59)	0.84 (0.45-1.56)
Crude HR (95% CI)	1.28 (0.63-2.62)	Reference
Age-sex aHR (95% CI)	1.51 (0.74-3.09)	Reference
Multivariable† aHR (95% CI)	1.24 (0.57-3.09)	Reference
PSD† aHR (95% CI)	0.93 (0.42-2.07)	Reference

Abbreviations: incidence rate per 1,000 person-years of follow-up (IR/1000 pyrs); hazard ratio (HR); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); propensity score deciles (PSD)

† Confounders: age; sex; previous exposure to acitretin; previous exposure to ciclosporin; outdoor occupation; number of cigarettes smoked per day; number of narrowband UVB courses.

5.7.4 Subgroup analyses

Subgroup analyses to detect possible differences in SCC risk according to age group, Fitzpatrick skin type, biological mechanisms of the biologic therapies, and cumulative exposure to biologic therapy and number of different biologic exposures were performed. Due to the very small number of events (<5) reported for the non-biologic systemic cohort, no analysis was performed for the strata of age category ≥60 and Fitzpatrick skin type I/II.

Risk estimates varied across the strata with the adjusted hazard ratios indicating a possible decreased risk for biologic-treated patients with skin type III/IV (aHR 0.47 [95% CI 0.17-1.30]); those treated with only TNFi (aHR 0.66 [95 % CI 0.27-1.61]); and those exposed to just one biologic therapy (aHR 0.73 [95% CI 0.31-1.73]); compared with patients in the non-biologic systemic cohort. In contrast, the adjusted hazard ratios indicated a possible increase in risk of SCC for biologic-treated patients treated with ustekinumab only (aHR 1.32 [95% CI 0.44-3.99]) and those exposed to more than one biologic therapy (aHR 1.31 [95% CI 0.43-3.93]). However, with the small number of SCCs in the non-biologic systemic cohort, there was a lack of statistical power to adequately assess for differences in risk for these factors, and the risk estimates for all strata were imprecise with wide confidence intervals.

Table 5.6: Subgroup analyses for the outcome squamous cell carcinoma

Subgroup analyses		Biologic cohort; n	Non-biologic systemic cohort; n	PSD aHR (95% CI)
Age categories (years)	<60	15	6	1.14 (0.95-1.83)
	≥60	18	<5	-
Fitzpatrick skin type	Skin type I/II	19	<5	-
	Skin type III/IV	14	8	0.47 (0.17-1.30)
Biologic mechanism	TNFi-only	18	Reference	0.66 (0.27-1.61)
	Ustekinumab-only	7	Reference	1.32 (0.44-3.99)
	Mixed biologic exposure	8	Reference	0.89 (0.27-2.95)
Number of different biologic exposures	Single biologic exposure	21	Reference	0.73 (0.31-1.73)
	Multiple biologic exposures	12	Reference	1.31 (0.43-3.93)

Abbreviations: propensity score deciles (PSD); adjusted hazard ratio (aHR); 95% confidence interval (95% CI); Tumour necrosis factor inhibitor (TNFi)

6 Discussion

6.1 Outline

The overarching aim of the thesis was to investigate the risk of cancer in patients with psoriasis treated with biologics, previously treated with non-biologic systemic therapy, compared with biologic-naïve patients treated with non-biologic systemic therapy only. In chapter 6, the main findings and their contribution to the literature are discussed. This is followed by a review of the strengths and limitations of the research. Finally, the implications of these findings on clinical practice are discussed with avenues for future research opportunities also presented.

6.2 Main study findings

6.2.1 Risk of all cancer in BADBIR

In this thesis, the main analyses were based on prospectively-collected data from the BADBIR cohort of 8.470 patients treated with biologic therapy (34,552.07 person-years of follow-up) and 4,814 patients treated with non-biologic systemic therapy only (14,381.26 person-years of follow-up). The median follow-up periods for patients in the biologic and non-biologic systemic cohorts were 3.69 years and 2.49 years, respectively. The following outcomes were studied and compared between the treatment groups: all cancer (excluding KC); cancers of infectious origin; and as secondary outcomes, common site-specific cancers (lung cancer, breast cancer and prostate cancer). Patients treated with biologic therapies were found to have no statistically significant increase or decrease in their risk of developing all cancer (excluding KC) or cancers of infectious origin compared with patients treated with non-biologic systemic therapies. Furthermore, no differences in risk of these two collective cancer outcomes were detected between the treatment groups when the study population was stratified by age, type of biologic therapy received and the number of biologic therapies received, comorbid PsA or obesity (BMI≥30 kg/m^2). In secondary analyses, treatment with biologic therapy was not associated with any statistically significant increase or decrease in risks of developing lung cancer, breast cancer or prostate cancer compared with non-biologic systemic therapy.

The results for risk of all cancer mirror those of the only other cohort study comparing the risks of all cancer (excluding KC) between biologic-treated and biologic-naïve systemically

treated patients with psoriasis (Asgari et al., 2017). Conducted using the KPNC health insurance database, Asgari et al found that treatment with biologic therapy did not result in an increased risk of all cancer compared with patients treated with conventional systemic therapy (aHR 0.86 [95% CI 0.66-1.13]) However, there are a number of important differences between the analyses in this thesis and the study by Asgari et al that merit discussion.

Firstly, the analyses in this thesis represent a more current and up-to-date study of cancer risk in biologic-treated patients. The study period for the Asgari et al (2017) was between 1998 and 2011 whereas the study period for this study was 2007 to 2019. Biologics were launched for treating psoriasis only in 2006, with the early years of use being dominated by TNFi. Since 2007, there have been major advances in the understanding of the pathogenesis of psoriasis, particularly the centrality of the IL-23/17 axis. This led to the introduction of a number of biologic therapies targeting sites other than TNF-α: ustekinumab in 2009, then a gap to 2015 that saw the launch of IL-17 blocking agents (Rønholt and Iversen, 2017). These progressive shifts resulted in differences in the biologic therapies to which patients in the two studies were exposed. In the earlier study conducted in the USA (Asgari et al., 2017), 3% of patients in this study were exposed to biologic therapies other than TNFi compared to 36% of patients in BADBIR (Appendix 27). Specifically, BADBIR patients were exposed to biologic therapies targeting IL-12/23 (ustekinumab, 29.6%) and IL-17A (secukinumab, 8.9%) (Appendix 27). Secondly, the BADBIR biologic cohort in the risk of all cancer analyses was significantly larger than the study by Asgari et al, both in terms of number of patients recruited (8,470 vs 2,285) and total person-years of follow-up (34,552 vs 9,175) (Asgari et al., 2017). The ability to recruit patients exposed to more novel biologic therapies and the larger cohort size meant that that the analysis of risk of all cancer among patients exposed to only TNFi (yielding an aHR 0.90 [95% CI 0.65-1.26]) as well as among those exposed to only ustekinumab (giving an aHR 0.97 [95% CI 0.60-1.57]) was better powered in the present study.

A further important difference between the two studies was the lack of inclusion of alcohol consumption as a confounder in analyses of risk of all cancer (excluding KC) in the study by Asgari et al. Alcohol consumption is classified as a group 1 carcinogen by the IARC for a number of major site-specific cancers including female breast cancer and colorectal cancer

(Secretan et al., 2009). Alcohol is also causally associated with squamous cell carcinomas of the oral cavity/ pharynx and oesophagus and liver cancer (Secretan et al., 2009). The exclusion of this confounder from their multivariable-adjusted model could have masked a potential increased or decreased risk of all cancer if alcohol consumption differed greatly between the two cohorts. Furthermore, the methods used to account for the significant proportion of missing data for the baseline confounders BMI (50%) and cigarette use (65%) in the Asgari et al study was not clear despite the inclusion of these variables in their analysis (Asgari et al., 2017). If complete case analysis were used to account for missing data, more than half the study population would have been excluded from the analysis resulting in a substantial loss of power and precision.

It appears that no other study to date has investigated the risk of developing cancers of infectious origin or the major site-specific cancers, namely of the lung, breast or prostate, in biologic-treated patients with psoriasis compared with biologic-naïve systemically-treated patients and therefore comparable data for these outcomes are lacking. Indeed there is a scarcity of similar studies in psoriasis populations overall, and so it is important to review the context of the present results more broadly, against similar studies conducted in other inflammatory disease populations where biologic therapies are used, namely PsA, IBD and RA. While some difference in baseline risk of cancer between psoriasis and these other common inflammatory conditions could be expected, immune dysregulation in the form of overexpression of cytokines such as is TNF-α play a central role in the pathogenesis of all these conditions (Kuek et al., 2007). Treatment guidelines typically dictate that patients with any of these conditions require conventional systemic therapy (e.g. methotrexate) as first line therapy. Treatment progresses to biologic therapy if conventional systemic therapies are contraindicated or response is considered inadequate. TNFi biosimilars are currently first line for patients with PsA, RA and IBD (Gossec et al., 2020; Harbord et al., 2017; Smolen et al., 2020; Torres et al., 2020).

The largest study investigating risk of cancer in TNFi-treated PsA patients was a population-based nationwide cohort study conducted in Danish and Swedish biologic registries (Hellgren et al., 2017). This study included 3,833 patients treated with TNFi and 15,908 biologic-naïve patients treated with non-biologic system therapy (Hellgren et al., 2017). No statistically significant difference in risk of all cancer was seen in TNFi-treated patients

compared with biologic-naïve patients after adjusting for age and sex (RR 0.90 [95% CI 0.70-1.10]); (Hellgren et al., 2017).

This Scandinavian study had a number of strengths, namely the large cohort sizes and long patient follow-up (median follow-up: 5.6 years) enabling the study of both risk of all cancer and the major site-specific cancers (lung; breast; prostate; colorectal; melanoma) (Hellgren et al., 2017). This cohort study benefited from linkage to the national cancer and mortality registries in each country, enabling accurate outcome assessment and verification. The major limitation of the study was the absence of adjustment for baseline confounders strongly associated with the development of cancer, namely smoking, alcohol consumption and previous exposure to systemic therapies (Hellgren et al., 2017). In addition, the results were not completely generalizable to both the Swedish and Danish populations as the comparator cohort only included RA patients from the Swedish population.

Few studies have been conducted in patients with IBD to assess cancer risk associated with treatment, with a recently published systemic review identifying only three (Muller et al., 2021). The largest study in an IBD population was a nationwide register-based cohort study in Denmark, comprising 56,000 patients with IBD which investigated the risk of overall and site-specific cancer in 4,553 TNFi-treated patients (18,440 person-years of follow-up) compared with 51,593 conventional systemic-treated patients (469,874 person-years of follow-up) (Nyboe Andersen et al., 2014). TNFi-treated patients did not have an increased or decreased risk of overall cancer compared with their biologic-naïve systemically-treated counterparts (aRR 1.07 [0.85-1.36]) (Nyboe Andersen et al., 2014). Similarly, when assessing the risk of developing major site-specific cancer, no statistically significant increased risk was detected for TNFi-treated patients compared with the biologic-naïve systemically-treated comparator cohort (Nyboe Andersen et al., 2014). The study had high external validity as the source population consisted of all people aged 15 and older living in Denmark during the study period (1999-2012). Information on drug exposure for systemically-treated IBD patients was from hospital records and national drug prescriptions registries (Nyboe Andersen et al., 2014). Outcome verification was achieved through linkage to the national Danish cancer registry containing detailed information on all incident cancers occurring in Denmark. Again the major limitation of this study was the absence of adjustment for a number of risk factors strongly associated with cancer risk. Unlike the risk of all cancer

analyses in this thesis, smoking, BMI and alcohol consumption was not collected for all patients in the study and not included in the propensity-score adjusted analyses (Nyboe Andersen et al., 2014).

The most recently published population-based cohort study investigating risk of cancer in biologic-treated RA patients was conducted in the Swedish biologics registry (Huss et al., 2021). This study is the largest to date comprising 21,365 TNFi-treated patients (224,661 person-years of follow-up) and comparator cohort of 58,233 biologic-naïve RA patients treated with conventional systemic therapy (Huss et al., 2021). TNFi-treated patients were found to have no statistically significant increased or decreased risk of all cancer (excluding KC) compared with non-biologic systemic therapy (aHR 1.0 [95% CI 0.9-1.0]) after adjusting for confounders (Huss et al., 2021). The result of the Swedish study is in keeping with earlier registry and national health insurance-based cohort studies conducted in the same population (Sweden) and in Denmark (aHR 1.02 [95% CI 0.80-1.30) and Australia (aHR 0.71 [95% CI 0.46-2.08]) comparing TNFi-treated patients with their biologic-naïve systemically-treated counterparts (Dreyer et al., 2013; Staples et al., 2019; Wadstrom et al., 2017).

The key strengths of the Swedish study include the use of a nationwide population-based registry capturing the majority of RA patients in Sweden treated with systemic therapies, the large sample sizes and long-term follow-up (median 6.6 years) (Huss et al., 2021). The large patients cohorts in this study also enabled the study of cancer risk in those treated with the biologic therapies rituximab, tocilizumab and abatacept compared with non-biologic systemically-treated patients (Huss et al., 2021). Similar to the studies conducted in the PsA and IBD populations, linkage to national drug prescription and cancer registries enabled accurate exposure and outcome verification for patients in this study (Huss et al., 2021). Beyond adjustment for the main confounders performed for the analyses in this thesis project, the authors of the Swedish study were also able to adjust for a number of demographic and socio-economic factors associated with deprivation through linkage to national social insurance and labour market databases (Huss et al., 2021). Although like all other observational studies. It was limited by the inability to exclude residual or unmeasured confounding, it serves as an example of what can be achieved within large, well-designed registry-based studies investigating risk of cancer in biologic-treated patients.

The evidence provided by the risk of all cancer analysis in this thesis and by the major registry-based cohort studies in PsA, IBD and RA show no increased risk associated with TNFi-treatment compared with non-biologic systemic therapy. However, limited sample sizes mean there are unanswered questions about risk of specific cancers. In addition, the introduction of new biologic therapies targeting sites other than TNF-α also necessitates future work as very few studies have assessed risk and some of these new therapies are specific to psoriasis.

6.2.2 Risk of keratinocyte carcinomas in BADBIR

The second prospective cohort study of risk of cancer investigated the risk of developing BCC or SCC and consisted of 7,104 biologic-treated patients (34,552 person-years of follow-up) and 3,957 biologic-naïve patients treated with non-biologic systemic therapy only (14,381 person-years of follow-up). Patients treated with biologic therapy experienced no statistically significant increased or decreased risk of developing BCC or SCC compared with patients treated with non-biologic systemic therapy. Although the HRs for some of the strata in the subgroup analyses (aged 60 and over, Fitzpatrick skin type III/IV, exposure to only ustekinumab), suggest a potential increased risk of BCC and SCC, confidence intervals were wide as a result of the small number of BCC events (Sections 5.6.4 and 5.7.4).

Asgari et al (2017) also studied the risk of developing KC and reported no statistically significant increased risk of BCC in biologic-treated patients (HR 1.23 [95% CI 0.91-1.66]) compared with patients treated with conventional systemic therapy. However, patients in this study were reported to have an increased risk of developing SCC (HR 1.81 [95% CI 1.23-2.67]) compared with patients treated with conventional systemic therapies (Asgari et al., 2017). There are a number of differences between the Asgari et al study and the risk of SCC in this analysis that could have contributed to this discrepancy in addition to these mentioned in Section 6.2.1. Firstly, patients with a previous history of SCC or BCC were not excluded from the study nor was past KC history adjusted for in their multivariable Cox-regression analysis (Asgari et al., 2017). Previous history of KC is the strongest predictor of future BCC or SCC (Whiteman et al., 2016). The inclusion of patients with a previous history of KC could have largely driven the increased risk of SCC in biologic-treated patients. Another possible factor was the absence of adjustment for differences in previous exposure to non-biologic systemic therapy between the two cohorts, including ciclosporin which is

associated with an increased risk of SCC (Paul et al., 2003). Although previous exposure to these systemic therapies at baseline for patients in the Asgari et al study was not detailed, patients in the biologic cohort were older so were likely to have experienced greater exposure to ciclosporin and other non-biologic systemic therapies before initiating treatment with biologic therapy, thereby contributing to the observed increased risk of SCC.

DeShazo et al conducted a cohort study investigating the risk of KC in biologic-treated patients in PSOLAR (deShazo et al., 2019). They reported no increased risk of BCC or SCC for patients treated with biologic therapy (TNFi and ustekinumab combined) or ustekinumab-only compared with patients treated with only non-biologic systemic therapy (deShazo et al., 2019). However, TNFi-treated patients did have an increased risk of BCC (aHR 2.54 [95% CI 1.08-5.98]) (deShazo et al., 2019). There are a number of possible reasons why there was a difference in reported BCC risk in TNFI-treated patients in the PSOLAR study and the BADBIR analysis. PSOLAR is a large, single pharmaceutical company-sponsored registry set in over 300 community and hospital-affiliated practices across 16 countries in North America, Latin America, and Europe (K. Papp et al., 2015). The majority of participating centres were in the USA (67%) and Canada (13%) with limited coverage in the other 14 countries (Papp et al., 2012). Physicians in each centre adhere to their own state and national prescribing practices, raising the question of comparability of patients in the registry given differences in prescribing practices (Papp et al., 2012). Data collected included exposure details and adverse events (including cancer) from the participating centres, however information regarding several established risk factors for skin cancer (e.g. occupational/recreational exposure to UV, Fitzpatrick skin type) was not collected systematically (Fiorentino et al., 2017). Outcome ascertainment via medical records and pathology reports or via linkage to national cancer registries was not performed for all malignancy reports (Fiorentino et al., 2017).

The PSOLAR analysis (deShazo et al., 2019) included a biologic cohort consisting of both prevalent and incident users at baseline. The exclusion of prevalent users from their analyses in the same study led to TNFi exposure no longer being associated with a statistically significant increase in risk of BCC (aHR 2.45 [95% CI 0.79-7.63) (deShazo et al., 2019). The non-biologic systemic comparator cohort in PSOLAR also excluded patients treated with the most commonly prescribed non-biologic systemic therapy, namely

methotrexate. Patients treated with methotrexate in the PSOLAR study in had an 8.5-fold increased risk of BCC compared with patients treated with other non-biologic systemic therapies (aHR 8.58 [95% 3.29-22.4) (deShazo et al., 2019).

Risk of BCC and SCC in biologic-treated patients compared with biologic-naive non-biologic systemically treated patients has also been explored in RA populations. Mercer et al investigated the risk of KC in TNFi-treated patients in the British Society for Rheumatology Biologics Register (BSRBR-RA) (L. K. Mercer et al., 2012). The BSRBR-RA shares many similarities with BADBIR in both its design and pharmacovigilance function as the latter was modelled on the former (Burden et al., 2012). In this large prospective BSRBR-RA cohort of 11,704 TNFi-treated patients (42,798 person-years of follow-up) and 3,523 non-biologic systemic-treated patients (9,342 person-years of follow-up), no statistically significant difference in risk of SCC was seen (aHR 0.96 [95% CI 0.28]) (L. K. Mercer et al., 2012). Similarly, no statistically significant difference in risk of developing BCC was observed for TNFi-treated patients (aHR 0.81 [95% 0.45 to 1.48]) compared with their biologic-naïve counterparts (L. K. Mercer et al., 2012). Key strengths of the BSRBR-RA study were the large cohort sizes and person-years of follow-up, and the use propensity-score methods to balance confounders between the two cohorts and adjust for confounders. However, information on Fitzpatrick skin type and UV exposure was not collected for BSRBR-RA patients so the analyses did not adjust for these important skin cancer risk factors (L. K. Mercer et al., 2012).

6.3 Strengths and limitations

6.3.1 Strengths

The main strength of this research project is its prospective cohort design set in a large disease-specific national pharmacovigilance registry of patients with similar disease characteristics. BADBIR is the largest and most comprehensive psoriasis registry in the world, enrolling over 19,500 patients at 168 dermatology centres as of February 2022. With the support of the BAD, external validity is maintained by urging all dermatologists in the UK to be involved in the registration process of eligible participants as part of normal clinical practice (BADBIR, 2020a). Guidelines from the BAD and guidance from NICE state that all patients treated with biologic therapy or small molecules be offered the opportunity to participate in the BADBIR study (NICE, 2017a; Smith et al., 2020).

The initiation of and changes to biologic and non-biologic systemic therapies were captured prospectively ensuring that patients were followed-up in their exposure-specific cohorts thus avoiding treatment misclassification. Baseline demographic and disease characteristics as well as treatment history were captured which enabled adjustment for these confounding factors in the risk of cancer studies. The comparator cohort in this research project consisted of patients with the same indication, recruited from the same population with similar disease severity at enrolment (BSA/PASI≥10, DLQI>10) and treated with a clinically meaningful alternative treatment (non-biologic systemic therapy). This is evidenced by the observed similarity between the biologic and non-biologic systemic cohorts across many of the baseline demographic and disease characteristics for both risk of cancer studies (Table 4.1 and Table 5.1). The robust design of BADBIR minimised some of the potential biases associated with comparator selection such as confounding by indication or severity and channelling bias, thus increasing the internal validity of this research. Moreover, the use of an active comparator cohort, rather than a cohort consisting of patients treated with non-systemic therapies enabled the study to ask a specific question: "Does treatment with biologic therapy increase the risk of cancer relative to non-biologic systemics? The results provide patients and clinicians direct insights into cancer risk between these two groups.

BADBIR has put in place a wide range of measures to ensure that data collected for each patient in this research project was accurate and complete. Database training centered on data entry is provided to clinical staff at participating dermatology centres. Data entry error is minimized through the use of drop-down menus and clinicians are provided with a 21-day edit period for each follow-up giving them ample time to complete, review and edit their entries. BADBIR administrators perform data quality checks of all data entries for accuracy and completeness. Where data are missing or incomplete, queries are raised and centres are asked to provide further information. In addition to these measures, a selection of participating centers are also audited each year by a dedicated member of staff.

Another major strength of this study was the analysis methodology. A robust process was put in place to identify and adjust for confounders. Potential confounders were identified using a combination of literature review and expert advice, and assessed for inclusion using univariable analyses. Furthermore, effects of confounding were mitigated in these analyses by generating propensity score models in which patients were stratified by their probability of receiving biologic therapy at baseline, mimicking the random allocation component of a RCTs. Patients with similar distributions of baseline confounders in the biologic cohort and the non-biologic systemic cohort were grouped in the same stratum and compared, thereby reducing differences in outcome to differences in treatment. Finally, the inclusion of risk estimates for the crude, age-sex and multivariable adjusted Cox-proportional hazards models for the main outcomes allowed for comparisons between the various levels and methods of adjusting for confounders with the propensity score method.

6.3.2 Limitations

There were a number of potential limitations in thesis project. There is the question of whether this research could fully address the study aim: to determine if patients with chronic-plaque psoriasis treated with biologic therapy had an increased risk of cancer compared to with non-biologic systemic therapy (Section 2.1). The clinical pathway for psoriasis patients requiring treatment with systemic therapy in this study is that they first underwent treatment with the non-biologic systemic therapy before proceeding to biologic therapy (Figure 1.4). Patients in the biologic cohort in this study were thus much further along the treatment pathway and significantly more likely to have been exposed to non-biologic systemic therapy than their counterparts in the non-biologic systemic cohort. This is

evident when examining the baseline characteristics of the study population (Tables 4.1 and 5.1). Markedly higher proportions of patients in the biologic (versus non-biologic) cohort were previously exposed to methotrexate (74% vs 23%) and ciclosporin (58% vs 18%). This meant that biologic-treated patients, carrying a potentially increased background risk of cancer due to differential past exposure to non-biologic systemics at baseline, were compared with patients treated with only non-biologic systemic therapy. It would not be completely possible to determine if any observed difference in risk of cancer between the two cohorts was due to only the different immunosuppressive mechanisms of biologic therapy and non-biologic system therapy. In order to have adequately addressed the research question, patients in each cohort would needed to have identical levels of exposure to non-biologic systemics at baseline. Any difference in cancer risk between the two cohorts can then be attributed to the addition of biologic therapy, provided that other factors are also adjusted for.

Although this study was able to investigate risk of all cancer and some of the common site-specific cancer, the BABDIR registry at the time of performing the analyses presented in this thesis was not adequately powered to study the risk of most site-specific cancer. A sample size calculation, using the centre for disease control and prevention (CDC) Epi Info™ calculator, was performed by BADBIR *a priori* (BADBIR, 2006). The sample size required in each cohort for a 2 sided significance of alpha < 0.05 to be detected with 80% power was determined in person-years of follow-up. Based on these calculations, in order to determine or rule out a two-fold increase in risk, for a cancer with an incidence of 1 in 2000, there would need to be a total of 162,950 person-years in the biologic cohort and 91,475 person-years in the non-biologic cohort (Appendix 35) (Burden et al., 2012). This is significantly higher than the total number of person-years in the biologic (34,552.07) and non-biologic systemic (14,381.26) cohorts in the analyses in this thesis.

Assuming an annual recruitment rate of 1,000 new patients to the biologic cohort and continued follow up, the total number of person-years accrued for a ten year period will only be around 50,000 (Appendix 36). The average annual recruitment to BADBIR during the study period for the biologic cohort was just over 1,100 patients (Appendix 37). Given the low incidence of site-specific cancers in BABDIR (Table 4.2), the rate of recruitment to

BADBIR will need to substantially increase in order to accumulate the necessary person-years of follow-up required to investigate risk of developing these rare outcomes.

When considering cancer latency, the time between an exposure and the occurrence of cancer, follow-up of patients in this study might not have been long enough to attribute biologic exposure, in addition to previous treatment with photo/systemic therapy, to developing the outcomes of interest. The estimated latency period for site-specific cancers can range from a few years to a few decades (Nadler and Zurbenko, 2014). Although the extent to which other factors, such as past treatment with phototherapy and systemic therapy and the duration and intensity of exposure to these agent, might influence the latency period is not clear. The median follow-up period, from first exposure to cancer diagnosis, for biologic (3.83 years) and non-biologic systemic (2.57 years) cohorts were quite short. Particularly when compared with studies investigating cancer risk in the biologic-treated RA. PsA and IBD population reporting median follow-up periods longer than 6 years (Hellgren et al., 2017; Huss et al., 2021; Lemaitre et al., 2017). Expanding the study to also include patients with prevalent exposure to biologic and non-biologic systemic therapy, rather than just incident exposure, might have been warranted given the long latency of the cancer outcomes.

BADBIR was also not adequately powered to study the risk of cancer for each individual therapy compared with non-biologic systemic therapy, thus limiting the risk of cancers studies to comparing patients treated with any biologic with those treated with any non-biologic systemic therapy. Potential increases in risk for patients treated with one type of biologic therapy (e.g. IL-17A inhibitors) in the biologic cohort could have been masked by grouping them with other therapies (e.g. IL-23 inhibitors). Thereby leading to an underestimation of cancer risk for patients treated with these therapies. Although the stratified analyses for cancer outcomes did consider differences in risk by biologic mechanism for TNFi-treated and ustekinumab-treated patients, IL-17 and IL-23 inhibitors could not be studied due to small numbers treated with these therapies in this study owing to their recent introduction to BADBIR at the time of the study cut-off date (01//04/2019).

Due to the low incidence of cancers in BADBIR, risk of developing major, site-specific cancers including colorectal cancer and melanoma as well as more rare cancers could not be assessed. The composite outcomes of all cancer (excluding KC) and cancers of infectious

origin consisted of a number of heterogeneous cancers and presumed that mechanisms whereby biologic therapies might raise cancer risk is common across the different cancer types. Although the overall results indicate no statistically significant increased or decreased risk of cancer for biologic-treated patients, this could have been the result of risks for the different cancer types acting in opposite directions and in effect cancelling each other out. Thus the results for these composite outcomes cannot be used to rule out risk for all but three of the site-specific cancers (lung, breast, prostate).

Another important limitation in this thesis could be outcome misclassification. Access to linkage data from cancer and mortality registries, as a source of cancer diagnosis for patients in the dataset analysed in this thesis, was restricted to individuals employed by BADBIR (BADBIR, 2022a). The only cancers included in the analyses dataset were those confirmed by the participating dermatology centres. Adverse events reported as either neoplasms of unspecified malignancy or metastases (where there is no report of a previous incident cancer) were not included in the cancer definition (Table 3.5). To account for the possibility that these events should have been included in the outcomes, a sensitivity analysis was performed (Appendix 38). Crude, age-sex adjusted and propensity score decile adjusted point estimates for the outcome risk of all cancer (excluding KC) using the cancer definition excluding neoplasms of unspecified malignancy or metastases (restricted cancer definition) were compared with the point estimates after including these events in the outcomes (expanded cancer definition). The fully adjusted risk estimate for all cancer (excluding KC) for the restricted cancer definition (HR 0.96 [95% CI 0.70-1.30) and the expanded definition (HR 0.98 [95% CI 0.70-1.36]) were not significantly different. Although there were robust procedures put in place by BADBIR to ensure any adverse event reported for patients in each cohort that could be malignancies were investigated, significant underreporting of cancers for patients in this research project could not be ruled out without access to cancer diagnoses from linkage.

The use of MI to account for missing data in this thesis project was based on the assumption that data was ‘missing at random’ (Section 3.5.5). In other words, the distribution of the missing data for the variable can be predicted from the distribution of the variables without missing data. Although it could be argued that the variables with missing data (BMI, number of cigarettes smoked per day, units of alcohol consumed per week) are correlated and

therefore could be good predictors for each other, the assumption of missing at random could be incorrect. If data was missing not at random, the use of MI for could have led to misleading results similar to complete case analysis (Sterne et al., 2009).

Studies set in pharmacovigilance registries are limited by the voluntary nature of study participation. Data collection for demographics and lifestyle factors in BADBIR is performed using patient-completed questionnaires. For questionnaire items that captured previous history of smoking and alcohol drinking there was the possibility of recall bias and social desirability bias due to stigma associated with excessive smoking and drinking. Despite all attempts to adjust for confounding, data were not collected for genetic risk factors strongly associated with the development of cancer such as a patient's family history of cancer and hereditary cancer syndromes, or for socioeconomic factors such as deprivation, or for reproductive factors among women. This meant that these factors could not be accounted for in the analyses. As is the case with all observational studies, unmeasured confounding could not be ruled out.

Despite the attempts to maintain external validity, participation with the BADBIR study is voluntary for the dermatology centres. Participation to the study might be limited to hospitals with higher levels of staffing, namely those in large urban and affluent areas. Although BADBIR compensates the participating dermatology centres for each baseline registration and any subsequent follow-up, hospital sites in rural and deprived areas might be less likely to participate in the study (BADBIR, 2022b).

6.4 Implications for clinical practice

Based on the current study's findings regarding the risk of cancer, clinicians and patients with psoriasis can be reassured that treatment with biologic therapy in the short- to medium-term does not sizably increase the risk of cancer overall, or the risk of cancers of infectious origins or the risk of several major site-specific cancers compared with their biologic-naïve systemically treated counterparts. In terms of the clinical relevance of the precision of the estimated risk, a 1.3-fold increase in risk of all cancer (excluding KC) and a 1.8-fold increase in risk of cancers of infectious origin can be ruled out.

Stratified analysis of the biologic-treated population with a possible baseline increased risk of developing categories, namely those in the older age categories, Fitzpatrick skin type I/II, comorbid PsA or obesity (BMI≥30 kg/m^2), also revealed no increased risks. Similarly, treatment with TNFi-only, ustekinumab-only, or with biologic therapies with different mechanisms of action did not lead to an increased risk of cancer compared with non-biologic systemic therapy. These results are also reassuring for patients currently receiving non-biologic systemic therapy. Given the paucity of studies examining risk of cancer in psoriasis populations, policymakers are now provided with real-world evidence regarding the short- to medium-term risks which will aid decision making.

6.5 Future research opportunities

BADBIR continues to recruit and follow-up patients prospectively in the UK and the ROI. Future opportunities to address the long-term risk of cancer in patients with psoriasis treated with biologic therapy will occur through further accrual of events and person-years of follow-up. Longer follow-up of patients registered to BADBIR along with access to cancer diagnoses received via linkage will improve the study of these cancers in the future. This includes studying risk of developing common site-specific cancer, such as colorectal cancer and melanoma, which could not be explored in this thesis due the low incidence of these cancers in the comparator cohort.

Clarifying the long-term risk of incident cancer in patients treated with IL-17 and IL-23 biologics is of particular importance. In head-to-head trials these agents have been demonstrated to have superior clinical efficacy versus TNFi, establishing them one of the first-line biologic therapies within the treatment hierarchy (Smith et al., 2020; ten Bergen et

al., 2020). There are conflicting reports from preclinical and clinical models indicating both a pro-tumourigenic and anti- tumourigenic role for IL-17 and IL-23 cytokines (Section 1.4.3.3). The increased prominence of IL-17A, IL-17 Receptor A and IL-23p19 inhibitors and the absence of real-world evidence for the safety of these therapies as it pertains to risk of cancer in psoriasis populations presents a future opportunity to investigate this in BADBIR.

Another area of interest to both patients and clinicians that has yet to be explored in the psoriasis literature is the risk of cancer progression or recurrence in patients treated with biologic therapy. The latest clinical guidelines from the BAD urge that clinicians exercise caution when prescribing biologic therapy to patients with either a history of cancer or continuing treatment with biologic therapy in those who develop cancer (Smith et al., 2020). Decision to continue or cease treatment with biologic therapy are made after discussion with patients, their oncologist and multidisciplinary teams (Smith et al., 2020). Uncertainty regarding the risk of recurrence or progression of cancer could lead to cessation of treatment with biologic therapy, potentially exacerbating their psoriasis and significantly impacting quality of life, or make patients reluctant to continue, or adhere to, treatment after cancer remission. Therefore, clarifying this research question is of paramount importance for this patient group.

The RA literature provides a number of examples of large population-based cohort studies investigating the risk of cancer recurrence in biologic-treated patients compared with non-biologic systemic therapy (Onuora, 2021). The risk of developing BCC or SCC in patients with a previous history of skin cancer was recently investigated by a cohort study from BADBIR demonstrating no increased or decreased risk of BCC (aHR 0.89 [0.42-1.89]) or SCC (aHR 0.83 [0.37-1.89]) in biologic-treated patients with a previous history of KC compared with non-biologic systemic therapy (Mason et al., 2021). This study serves as a template for future studies investigating the risk of progression or recurrence of major, non-cutaneous site-specific cancers in patients treated with biologic therapy.

There are also future opportunities to study the risk of cancer in biologic-treated patients for the individual TNFi, IL-17 and IL-23 therapies. Recruitment of patients initiating or switching to each individual biologic therapy, including biosimilars, is expected to continue until adequate numbers (2000-4000 patients) are met (BADBIR, 2020a). Having large cohorts of patients treated with these individual therapies and long follow-up will enable

the study of cancer risk compared with non-biologic systemic therapy and comparison of cancer risk between patients treated with these therapies with differing biological mechanisms. This will enable clinicians and patients to make more informed choices in their choice of biologic therapy with respect to cancer risk.

Where BADBIR will not be adequately powered to study the risk of rare cancers, even in the long-term, there are opportunities to collaborate with other psoriasis registries and national healthcare databases. BADBIR is affiliated to PSONET, a network of psoriasis-specific independent national pharmacovigilance cohorts and healthcare databases in Europe (Lecluse et al., 2009). The potential of such collaboration is demonstrated by a study conducted in 11 European RA biologic registries investigating the risk of melanoma in patients treated with biologics compared with non-biologic systemic therapy (Mercer et al., 2017). Many of the individual registries were underpowered to investigate this within their own population, so the decision was made to conduct a collaborative project. The study, consisting of 130,315 patients contributing 579, 983 person-years, was able conclude no statistically significant increased risk in developing incident melanoma for TNFi-treated patients, and those treated with rituximab, abatacept or tocilizumab, compared with patients treated with only non-biologic systemics (Mercer et al., 2017).

The first PSONET study was a 2018 meta-analysis of nested case-control studies investigated cumulative exposure to biologics and cancer risk in patients (60,000 person-year of follow-up) enrolled in BADBIR and three other PSONET registries and healthcare databases (Garcia-Doval et al., 2018). The authors of this study were able to rule out an association between cumulative lengths of exposure to biologic therapy and risk of developing any cancer after adjusting for confounders (OR 1.02 [95% CI 0.92-1.13) (Garcia-Doval et al., 2018). Although there were some limitations to this study, including data quality and completeness, it has laid the ground work for future collaborations to study risk of rare site-specific cancer that cannot be addressed within a single registry.

Large, population-based cohort studies conducted in electronic health records (EHR) databases might be better placed to study to risk of cancer in patients with psoriasis. Population-based nationwide cohort studies conducted in RA and PsA patients living in Sweden and Denmark are model for studying risk of cancer in systemically-treated populations (Hellgren et al., 2017; Huss et al., 2021). These studies were able to include

virtually all patients in their respective countries diagnosed with RA or PsA through linkage to national health records (Hellgren et al., 2017; Huss et al., 2021). The large number of accrued person-years of follow-up enabled the study of risk of incident and recurrent site-specific cancers in the biologic-treated RA and PsA populations (Hellgren et al., 2017; Huss et al., 2021). Incident and prevalent exposure to biologic and non-biologic systemic therapies for patients was determined through linkage with national prescribing registries with accurate outcome verification made possible via linkage to national cancer registries (Hellgren et al., 2017; Huss et al., 2021).

A collaborative study utilising BADBIR and electronic medical records databases in the UK along with linkage to secondary care data can mimic the study design of the population-based cohort studies conducted in the RA and PsA populations. CPRD is a research service consisting of over 11 million primary care records for patients in the UK (Herrett et al., 2015; Wolf et al., 2019). THIN is an electronic medical records database contains medical records for 11.9 million patients across more than 400 GP practices the UK (Chiesa Fuxench et al., 2016). The validity of using CPRD and THIN in the research of psoriasis has been demonstrated in a number of studies (Huerta et al., 2007; Seminara et al., 2011; Springate et al., 2017a). Data captured for patients in CPRD and THIN includes demographics (including ethnicity), lifestyle factors (smoking, alcohol consumption and BMI), diagnoses, prescriptions and hospital referrals. Data for these patients can also be linked to secondary care and other healthcare data sources via NHS Digital (BADBIR, 2022a; CPRD, 2022). Hospital episode statistics (HES) is a database containing details of all admissions, accident and emergency attendances and outpatient appointments and diagnoses at discharge in NHS hospitals in England (Herbert et al., 2017; Thorn et al., 2016). Cancer diagnosis and death registration data can also be obtained, via linkage to NHS Digital, from the national disease registration service and the office for national statistics, respectively. Linking BADBIR data with these sources of primary and secondary care records can greatly enhance the study of cancer in patients with psoriasis.

6.6 Conclusion

In conclusion, this research project has demonstrated that patients with psoriasis treated with biologic therapy, previously treated with non-biologic systemic therapy, did not have a statistically significant increased or decreased risk of developing: all cancer (excluding KC), cancers of infectious origin, common site-specific cancers (lung; breast; prostate), or BCC or SCC in the short to medium term, compared with non-biologic systemic therapy only. While the results are reassuring, the potentially long latency between exposure to these relatively new therapies and cancer development means that the long-term risk of incident or recurrent site-specific cancer still needs to be clarified. This study lays the ground-work for future studies examining the long-term risk of cancer, and the risk of common cancers (including colorectal, melanoma and lymphoma) and the risk of developing a second primary or recurrent cancer or metastases for patients treated with biologic therapy.

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Appendices

Appendix 1: MOOSE checklist for meta-analyses of observational studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	88
2	Hypothesis statement	-
3	Description of study outcome(s)	89
4	Type of exposure or intervention used	88
5	Type of study designs used	89
6	Study population	88
Reporting of search strategy should include		
7	Qualifications of searchers (e.g., librarians and investigators)	-
8	Search strategy, including time period included in the synthesis and key words	89, Appendix 2
9	Effort to include all available studies, including contact with authors	89
10	Databases and registries searched	89, Appendix 2
11	Search software used, name and version, including special features used (e.g., explosion)	89, Appendix 2
12	Use of hand searching (e.g., reference lists of obtained articles)	90
13	List of citations located and those excluded, including justification	91, Figure 1.6
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	-
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	91, 92
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	-
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	-
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	92, Appendix 4
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	95, Appendix 6
22	Assessment of heterogeneity	95, Figure 1.7
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	90
24	Provision of appropriate tables and graphics	-
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 1.7
26	Table giving descriptive information for each study included	Table 1.5
27	Results of sensitivity testing (e.g., subgroup analysis)	95, Appendix 5
28	Indication of statistical uncertainty of findings	97-99

Appendix 2: Search Strategy in Embase, MEDLINE and Cochrane CENTRAL

		Medline & Embase	Cochrane CENTRAL
Population	**#1**	Exp Psoriasis/ OR Psoriasis af.	MeSH descriptor: [Psoriasis] explode all trees
	#2	Exp Arthritis, Rheumatoid/ OR Rheum* af.	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
	#3	Exp Colitis, Ulcerative/ OR Ulcerative colitis af.	MeSH descriptor: [Colitis, Ulcerative] explode all trees
	#4	Exp Crohn Disease/ OR Crohn?s af.	MeSH descriptor: [Crohn Disease] explode all trees
	#5	Exp inflammatory bowel diseases/ OR inflammatory bowel disease* af.	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
Intervention	**#1**	Exp infliximab/ OR infliximab af.	MeSH descriptor: [Infliximab] explode all trees
	#2	Exp etanercept/ OR etanercept af.	MeSH descriptor: [Etanercept] explode all trees
	#3	Exp adalimumab/ OR adalimumab af.	MeSH descriptor: [Adalimumab] explode all trees
	#4	Exp golimumab/ OR golimumab af.	golimumab;ti,ab,kw
	#5	Exp certolizumab pegol/ OR certolizumab af.	MeSH descriptor: [Certolizumab Pegol] explode all trees
	#6	Exp ustekinumab/ OR ustekinumab af.	MeSH descriptor: [Ustekinumab] explode all trees
	#7	Exp rituximab/ OR rituximab af.	MeSH descriptor: [Rituximab] explode all trees
	#8	Exp abatacept/ OR abatacept af.	MeSH descriptor: [Abatacept] explode all trees
	#9	Exp anakinra/ OR anakinra af.	anakinra;ti,ab,kw
	#10	Exp tocilizumab/ OR tocilizumab af.	tocilizumab;ti,ab,kw
	#11	Exp natalizumab/ OR natalizumab af.	MeSH descriptor: [Natalizumab] explode all trees
	#12	Exp vedolizumab/ OR vedolizumab af.	vedolizumab;ti,ab,kw
	#13	(Tumo?r or TNF*) adj2 (Inhibit* or Ant*).af.	(TNF near/1(antagonis* or inhibit*)) OR anti-TNFI;ti,ab,kw
Outcome	**#1**	Exp Melanoma/ OR melanoma af.	MeSH descriptor: [Melanoma] explode all trees
	#2	Exp Skin Neoplasms/ OR Skin cancer af.	MeSH descriptor: [Skin Neoplasms] explode all trees
Study Design	**#1**	Exp Randomized Controlled Trial/	
	#2	Exp Clinical Trial/	
	#3	Exp Observational Study/	
	#4	Exp Cohort Studies/	
	#5	Exp Case-Control Studies/	
	#6	(Nested adj3 (case or cohort)).af.	

Appendix 3: Newcastle-Ottawa scale of cohort studies checklist

Bias	Definition
Selection (maximum of one star per item	
Representativeness of the exposed cohort.	a) Truly representative of the average IBD, RA and psoriasis patients treated with biologic therapy.* b) Somewhat representative of the average IBD, RA and psoriasis patients treated with biologic therapy.* c) Selected group of users d) No description of the derivation of the cohort
Selection of the non-exposed cohort.	a) Drawn from the same community as the exposed cohort*. b) Drawn from a different source c) No description of the derivation of the non-exposed cohort
Ascertainment of exposure.	a) Secure record (e.g. surgical records)* b) Structured interview* c) Written self-report d) No description
Demonstration that outcome of interest was not present at baseline.	a) Yes* b) no
Comparability (maximum of two stars)	
Comparability of cohorts on the basis of the design or analysis.	a) Study controls for age and sex* b) Study controls for one more additional risk factors*; • UVR exposure • skin type/ethnicity • concomitant/historic immunosuppressive therapy (azathioprine, ciclosporin), • Psoralen + UVA (PUVA) in psoriasis.
Outcome (maximum of one star per item)	
Assessment of outcome.	a) Independent blind assessment* b) Record linkage* c) Self-report d) No description
Was follow-up long enough for outcomes to occur?	a) Yes (≥12 months)* b) No
Adequacy of follow-up of cohorts.	a) complete follow up – all subjects accounted for * b) Subjects lost to follow up unlikely to introduce bias – small number lost (%) * c) follow up rate <% and no description of those lost d) no statement

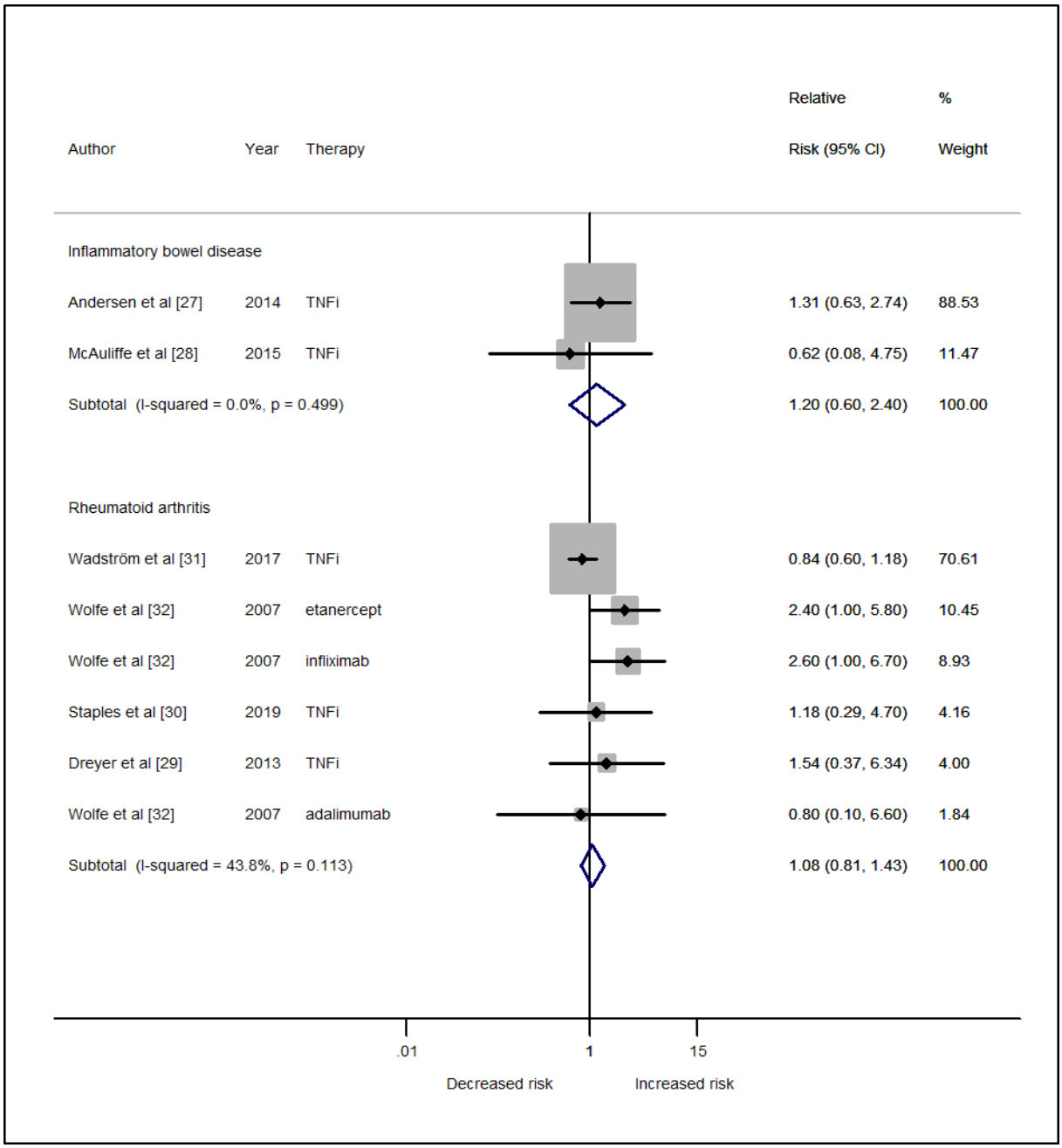
Appendix 4: Systematic review and meta-analysis – adjustment for confounding checklist

	Confounding Factors					
Study	**Age**	**Sex**	**UVR exposure**	**Concomitant/historic exposure to immunosuppressive therapy**	**Exposure to PUVA therapy**	**Skin colour / ethnicity**
Andersen 2014	✓	✓	☒	✓- concomitant	N/A	☒
McAuliffe 2015	✓	✓	☒	☒	N/A	☒
Wolfe 2007	✓	✓	☒	☒	N/A	☒
Dreyer 2013	✓	✓	☒	☒	N/A	☒
Staples 2019	✓	✓	☒	☒	N/A	☒
Wadström 2017	✓	✓	☒	☒	N/A	☒
Asgari 2017	✓	✓	☒	☒	? –UV light therapy	✓ - Race

N/A - Not Applicable

? – Unclear if adjustment was made

Appendix 5: Risk of melanoma in TNFi-treated IBD and RA patients compared with patients treated with conventional systemic therapies under a fixed-effects model.

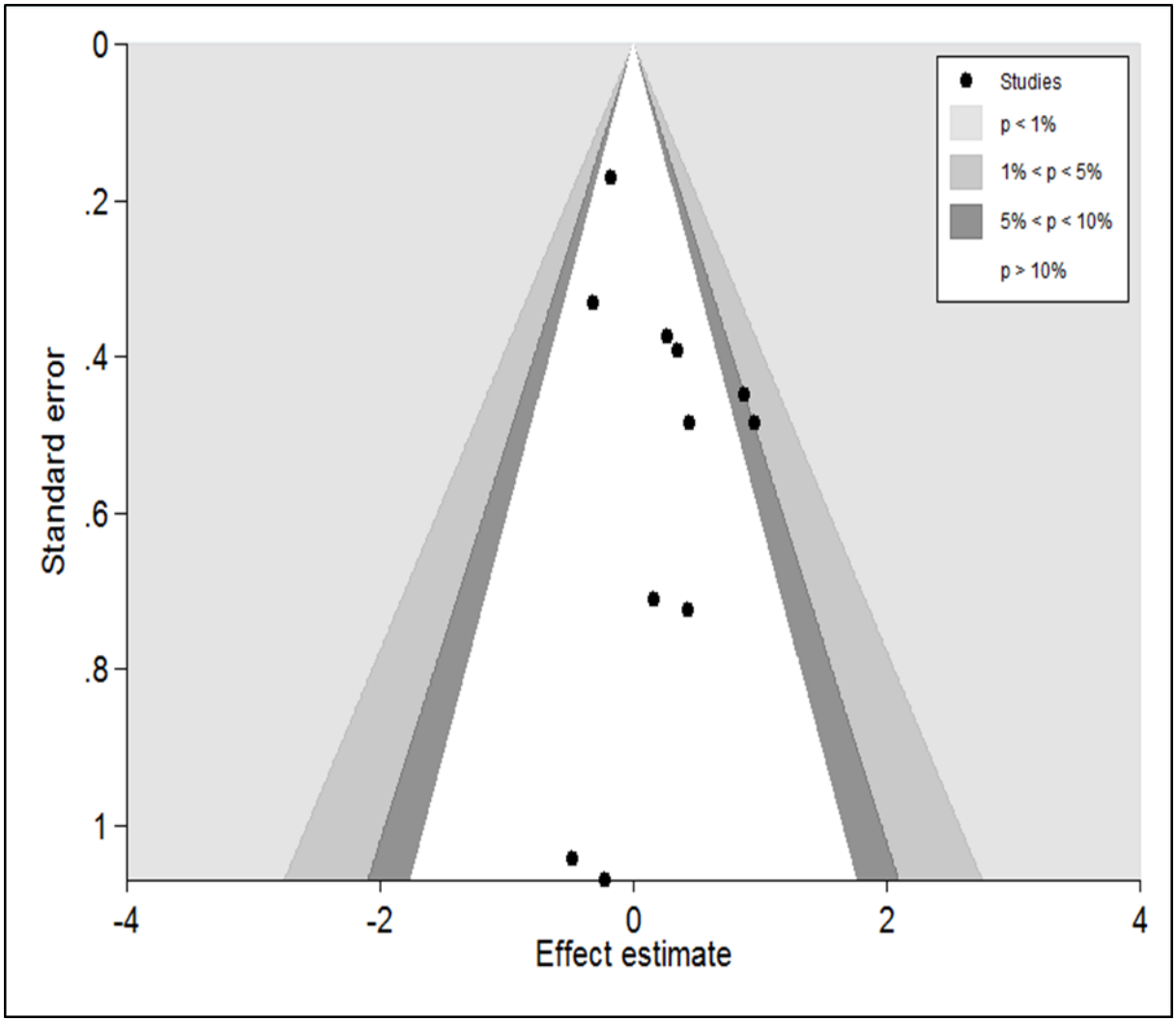


Caption: This forest plot includes a row for each individual study results with the point estimates presented as a diamond with a horizontal line (95% confidence interval). The grey box around each point estimate is proportional to the weight of the study

Appendix 6: Newcastle-Ottawa scale of cohort studies scores

	Andersen 2014	McAuliffe 2015	Wolfe 2007	Dreyer 2013	Staples 2019	Wadström 2017	Asgari 2017
Selection (maximum one star per item)							
Representativeness of exposed cohort	*(a)	*(b)	*(b)	*(a)	*(a)	*(a)	*(b)
Selection of non - exposed cohort	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)
Ascertainment of exposure	*(a)	*(a)	*(b)	*(a)	*(a)	*(a)	*(a)
Outcome not present at baseline	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)
Matching (maximum two stars)							
Matching	*(a) + *(b)	*(a)	*(a)	*(a)	*(a)	*(a)	*(a) +*(b)
Outcome (maximum one star per item)							
Assessment of outcome	*(b)	*(b)	*(b)	*(b)	*(b)	*(b)	*(b)
Length of follow -up	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)	*(a)
Adequacy of follow - up	(d)	(d)	(d)	(d)	(d)	(d)	(d)
Total score	**8/9***	**7/9***	**7/9***	**7/9***	**7/9***	**7/9***	**8/9***

Appendix 7: Funnel plot for the inspection of publication bias



Caption: Contour-enhanced funnel plot for the inspection of publication bias in studies examining the risk of melanoma in biologic-treated IBD, RA and psoriasis patients compared with patients treated with conventional systemic therapies.

Appendix 8: Systematic review and meta-analysis study protocol

Component	Description
Review question	What is the risk of melanoma in people with inflammatory bowel disease (IBD), rheumatoid arthritis (RA) or psoriasis treated with biologic therapy when compared with biologic-naïve IBD, RA or psoriasis patients treated with only conventional systemic therapies?
Objectives	To determine if psoriasis, RA and IBD patients treated with biologic therapy have a greater risk of developing melanoma than IBD, RA or psoriasis patients treated with only the conventional systemic therapies.
Population	All patients diagnosed as having IBD, RA and psoriasis with no personal history of cancer treated with biologic therapy
Subgroups	Factors to be considered for subgroup analysis: • Mechanism of biologic therapy • Treatment duration • Adjustment for confounders
Intervention	Biologics:- At least 5 years of European Medicines Agency licensing as of 07/02/19 TNF Inhibitors: infliximab, etanercept, adalimumab, golimumab, certolizumab pegol IL-12/23 antagonist: ustekinumab CD-20 :rituximab CTLA4: abatacept IL -1 antagonist: anakinra IL-6 antagonist: tocilizumab α4-integrin antagonist: natalizumab α4β7 -integrin antagonist: vedolizumab
Comparison	Biologic-naïve patients treated with conventional systemic therapies
Outcome	The risk of melanoma in studies with a follow up of at least 12 months since the onset of biological treatment.
Exclusion	• Studies comparing across diseases • Studies using biologic –treated /general population comparator groups. • Randomised controlled trials and open label extension studies • Case-control studies
Study design	• Randomised controlled trials and open label extension studies • Cohort – studies (prospective, retrospective) • Case-control studies nested within a cohort
Search Strategy	Embase, Medline, Cochrane Limits: human subjects, studies from 01-01-1995 onwards
Review strategy	Appraisal of methodological quality: • The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses Synthesis of Data • Meta-Analysis

Appendix 9: BADBIR patient information sheet

PATIENT INFORMATION SHEET

Title of Project: British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)

What is the purpose of this study?

The purpose of the research study is to assess whether new biologic or immunomodulator treatments (such as Benepali, Cosentyx, Taltz, Humira, Stelara) used in the treatment of psoriasis have a greater risk of serious side effects or long term health problems than established treatments such as ciclosporin, methotrexate and PUVA. As psoriasis is a long term condition requiring lifelong treatment it is important to establish how these drugs compare to the other treatment options available in terms of safety when used long-term (for a period of many years).

The biologic drugs and immunomodulators have been carefully tested in clinical trials before being approved for use. However, as clinical trials are run for a relatively short period of time (on average up to a year), have limited numbers of participants compared with those which will be ultimately treated with the drug and may exclude patients with additional diseases (co-morbidities), it may mean that the picture might not be complete in terms of long-term use. In contrast, BADBIR will collect information (data) on patients treated with biologics and immunomodulators attending regular dermatology clinics over a long period. Patients who have co-morbidities will also be included therefore the results are likely to be more representative of the "real world" use of these drugs. The study is designed such that a large group of patients being treated with biologics and immunomodulators are compared to an equally large group of patients treated with established therapies (conventional). The study team will observe how often side effects occur in all three groups of patients. Rates of untoward medical events will be compared between the groups and the results will then be used to provide patients with a better picture of any increased risk of the new therapies. The study is being funded by the British Association of Dermatologists (BAD), a society of dermatologists aiming to give the best patient care to individuals with skin diseases. The BAD receive funds from a number of pharmaceutical companies who manufacture the biologic therapies to support this study.

Why have I been chosen and what your contribution means?

You have been chosen to participate as you have been started on a biologic, immunomodulator therapy or one of the established treatments for psoriasis. By participating, you will help us build up the amount of data available for analysis.

Do I have to take part?

You do not have to take part. If you do decide to take part, you can keep this sheet and will be asked to sign a consent form. Your participation will not interfere with the standard of care you receive. By signing the consent form, you would be confirming your willingness to take part.

What are the risks of taking part?

The study will run alongside your routine clinical care at the hospital; it will not influence this process at all. Therefore, there are no foreseeable medical risks associated with participating in this study.

What are the benefits of taking part?

Although there is no clinical benefit gained by participation in the study, the information obtained from this study may result in changes in future treatment of patients with psoriasis and will help patients and doctors make more informed treatment decisions.

Will the research influence the treatment I receive?

The research does not alter the treatment you receive. Your specialist will start and stop treatments as determined by your clinical condition.

What will happen if I take part?

Your participation will involve the following:

i. Agreement to complete the questionnaires and other survey forms about your health. You should note that some of the questions may be of a sensitive or personal nature. You are not compelled to answer all of the questions.

ii. Agreement with your specialist to provide information of relevance to this study from your hospital medical records to the BADBIR study team at the University of Manchester. This will be information regarding the treatments you are receiving, assessments of your skin, details of any illnesses you have and body measurements including height and weight. Copies of the data collection questionnaires are available on the BADBIR website http://www.badbir.org/

iii. Agreement for your date of birth and NHS number (and also in Scotland your name) to be shared with national providers of healthcare data (including NHS Digital in England) for the purpose of linking to information held about any hospital admissions you have had, details if you are registered as having cancer or in the event of your death. This will enable these organisations to provide the BADBIR study team with information about these events that may not have been reported via the dermatology team. This will result in a more complete picture of your health experiences and will enable the study to provide more accurate results on the long-term safety of the biologic and immunomodulating drugs.

At this stage we do not know how long we will want to collect this information from you and about you. It is likely to be for at least five years. Research data will be stored for 15 years following study end and subsequently securely destroyed.

Appendix 10: BADBIR patient consent form

PATIENT CONSENT FORM

Title of Project: British Association of Dermatologists Biologics and Immunomodulators Register

Name of Chief Investigator: Professor Christopher Griffiths

		Please initial box
1.	I confirm that I have read and understand the information sheet dated 01/08/2017 (version 5.1) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical care or legal rights being affected.	☐
3.	I understand and agree that my identifiable details (date of birth and health service number, name in Scotland only) may be shared with national providers of healthcare data for the purpose of linking to information held about any hospital admissions I have had, details if am registered as having cancer or, in the event of my death. Details of the organisations linked to are available on the final page of the information sheet and at www.badbir.org	☐
4.	I agree to complete the questionnaires and other survey forms about my health.	☐
5.	I agree that my specialist Dr _____ may provide the researchers with information from my Health Records that is relevant to this Study.	☐
6.	I agree to information, from which I can be identified, being held by the research Team at the University of Manchester together with data collected during the study.	☐
7.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University Of Manchester, their representatives/ agents, the regulatory authorities and individuals from the Hospital. I give permission for these individuals to have access to my records which will include identifiable information.	☐
8.	I understand that some data, which will not contain information that could identify me, may be transferred out of the UK	☐

Name of patient	Date	Signature
Name of Person taking consent	Date	Signature

1 copy for patient; 1copy for researcher; 1 copy to be kept with hospital notes

Version 5.1 01/08/2017

Appendix 11: BADBIR patient baseline questionnaire

MANCHESTER 1824

The University of Manchester

BADBIR

PATIENT BASELINE QUESTIONNAIRE

Thank you for your participation in BADBIR. We would be grateful if you could complete the questionnaires below and hand them to your dermatology nurse / doctor

Name: _____ Date of Birth: _____ BADBIR ID: _____ *For office use only*

Where were you born? Town: _____ Country: _____

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 ☐ Student

☐ Unemployed but seeking work ☐ Not working due to ill health/disability ☐ Retired

Which of these ethnic groups do you belong to?

☐ White ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Chinese

☐ Black-African ☐ Black-Caribbean ☐ Black-British ☐ Black-other

☐ Other Please specify _____

Do you have an occupation or hobby which is mainly outdoors? ☐ Yes ☐ No

Have you ever lived in a tropical/subtropical (hot/sunny climate) country? ☐ Yes ☐ No

Have you EVER smoked more than one cigarette a day? ☐ Yes ☐ No

If you have ever smoked, what was the average number of cigarettes /day? _____ Cigarettes per day

Age started smoking _____ years **Age stopped smoking** _____ years

Do you CURRENTLY smoke more than one cigarette a day? ☐ Yes ☐ No

If YES, how many cigarettes do you smoke each day? _____ Cigarettes per day

Do you drink alcohol? ☐ Yes ☐ No

If yes, how many units do you drink in an average week? _____

For guidance please refer to the table below

Alcoholic Drink	No. of units
A pint of ordinary beer/lager (4%)	2.3
A pint of strong lager	3
A standard (175ml) glass of wine	2
A large (250ml) glass of wine	3
A small (25ml) glass of spirits	1
A 275ml bottled alcopop	1.5

Version 5 (*abridged*) 30/11/2007 **Signature:** _____ **Date:** ____/____/____

Appendix 12: BADBIR clinical baseline questionnaire

Please complete or attach patient sticker:

Name: **Address:**

Hosp. No.:

NHS/CHI:

DoB:

Gender: ☐ **Male** ☐ **Female**

BIR Biologic Interventions Register

BADBIR ID: ☐☐☐☐☐☐☐☐☐☐

BAD Biologic Interventions Register Baseline Clinical Questionnaire

Today's Date:_____ **Date of Consent:**_____ **Sent to BADBIR?** ☐

Date Entered on to Database:_____

Psoriasis

1. Does the patient have a past history of the following?

	No		No
Erythrodermic psoriasis	☐☐	Generalised pustular psoriasis	☐☐

2. What type of psoriasis does the patient currently have?

	Yes	No	
Chronic plaque psoriasis	☐	☐	→ **Small** (≤3cm diam) ☐ **Large** (>3cm diam) ☐
Flexural/intertriginous	☐	☐	
Seborrhoeic psoriasis	☐	☐	
Scalp	☐	☐	
Palms/soles (non pustular)	☐	☐	
Nails	☐	☐	→ Indicate number of nails affected ☐
Guttate psoriasis	☐	☐	
Unstable psoriasis	☐	☐	
Erythrodermic	☐	☐	
Generalised pustular psoriasis	☐	☐	
Localised pustular psoriasis	☐	☐	→ Acrodermatitis Hallopeau ☐☐ / Palmoplantar pustulosis ☐☐
Other (please specify below)	☐	☐	

(Yes / No)

☐

3. Please complete the following details:

Year of diagnosis (best approximation) ☐☐☐☐ Year first seen by a dermatologist ☐☐☐☐

4. Does the patient have a family history of psoriasis? (i.e. first-degree relative such as parent, sibling or child)

Yes ☐
No ☐
Don't know ☐

Disease Severity

5. Does the patient have diagnosis by a rheumatologist of psoriatic arthritis?

Yes ☐ → Year of Diagnosis ☐☐☐☐
No ☐

Please add details of any other inflammatory arthritis conditions to comorbidities

6. Please indicate the current disease severity (i.e. at the time the patient started the new drug)

Preferably a PASI from within 3 months prior to drug commencement

PASI ☐☐ ☐ **BSA** ☐☐ ***Only if the patient has pustular psoriasis***

Date of PASI ...../...../..... **Date of BSA** ...../...../.....

Psoriasis Global Assessment:

☐	Severe	☐	Mild
☐	Moderate to severe	☐	Almost clear
☐	Moderate	☐	Clear

Missing: ☐

Current Drug Therapy

7. Is the patient currently on any of the following topical treatments?

Topical pimecrolimus Yes ☐ No ☐ **Topical tacrolimus** Yes ☐ No ☐

8. Please list all the patient's current therapy for any *indication (Please note topical treatments apart from the two listed above are not required)*

DRUG	Date Started (d d m m y y)	DRUG	Date Started (d d m m y y)

Psoriasis Treatment

9. Is the patient currently receiving biologic treatment for their psoriasis? Yes ☐ No ☐

- ☐ Amgevita (adalimumab)
- ☐ Benepali (etanercept)
- ☐ Cimzia (certolizumab pegol)
- ☐ Cosentyx (secukinumab)
- ☐ Erelzi (etanercept)
- ☐ Humira (adalimumab)
- ☐ Hyrimoz (adalimumab)
- ☐ Kyntheum (brodalumab)
- ☐ Stelara (ustekinumab)
- ☐ Taltz (ixekizumab)
- ☐ Tremfya (guselkumab)
- ☐ Zessly (infliximab)

Commencement date of this episode of biologic therapy: d d m m y y

Is this the patient's first exposure to a biologic agent: Yes ☐ No ☐

Dose: ☐

Frequency: ☐

***If applicable*: Was the recommended opening schedule followed?**

Yes ☐ No* ☐ Currently unknown ☐

*If 'No', please provide details of deviation from schedule:

STELARA / ZESSLY ONLY: Provide administration dates

d d	m m	y y	Batch number

RECOMMENDED OPENING SCHEDULES:

Amgevita: 80mg loading dose week 0, 40mg from week 2
Cimzia: 400 mg at weeks 0, 2 and 4
Cosentyx: 300mg at weeks 0, 1, 2, 3 & 4
Humira: 80mg loading dose week 0, 40mg from week 2
Hyrimoz: 80mg loading dose week 0, 40mg from week 2
Kyntheum: 210 mg at weeks 0, 1 and 2
Taltz: 160mg at week0, 80mg at weeks 2, 4, 6, 8, 10, and 12
Tremfya: 100mg at week 0, 100mg at week 4

10. Is the patient currently receiving a small molecule immunomodulator therapy for their psoriasis? Yes ☐ No ☐

DRUG	(Please Tick)	Dose (mg)	Frequency	Date Started (d d m m y y)
Otezla (apremilast)				
Skilarance (dimethyl fumarate)			*Average Daily Dose*	

OTEZLA ONLY: Was the recommended opening schedule followed? Yes ☐ No ☐ Currently unknown ☐

11. Is the patient currently receiving conventional therapy for their psoriasis? Yes ☐ No ☐

DRUG	(Please Tick)	J/cm² or mg	Frequency	Date Started (d d m m y y)
Oral PUVA				
Methotrexate				
Ciclosporin			*Average Daily Dose*	
Acitretin				
Fumaderm			*Average Daily Dose*	
Hydroxycarbamide				

MTX Only: Oral ☐ Sub-Cut ☐

Previous Therapy

12. Please list <u>all previous</u> systemic anti-psoriatic therapy: **If none please tick** ☐

Drug	Start date	Stop date	Stop reason*

***Stop reasons:** Adverse Events, Clinical Trial, Contraindication, Death, Financial Consideration, Inefficacy, Inefficacy and Adverse Events, Other (please provide details), Patient Choice, Patient Non-Compliance, Remission, Titration*

Co-morbidities

13. Has the patient <u>ever</u> had (i.e. <u>required treatment for</u>) any of the following illnesses?

(please tick <u>all</u> that apply) **If none please tick** ☐

Hypertension	Yes	Year of Onset
Hypertension		

Cardiovascular Disease	Yes	Year of Onset
Angina		
Myocardial Infarction		
Stroke / Cerebrovascular Disease		
Peripheral Vascular Disease		
Dyslipidaemia		

Diabetes	Yes	Year of Onset
Type 1		
Type 2		

Autoimmune Disorders	Yes	Year of Onset
Thyroid Disease		
Alopecia Areata		
Vitiligo		
Psoriatic Arthritis		

Thrombosis	Yes	Year of Onset
Deep vein thrombosis		
Pulmonary embolism		
Asthma		
COPD (including chronic bronchitis, emphysema)		

Liver Disease	Yes	Year of Onset
NAFLD (non-alcoholic fatty liver disease, including fatty liver and NASH)		
Alcoholic Liver Disease		
Viral Hepatitis		
Autoimmune Hepatitis		
Inherited Liver Disease (inc. haemochromatosis)		

Kidney Disease	Yes	Year of Onset
Chronic Kidney Disease		
Glomerular Disease		
Renovascular Kidney Disease		
Inherited Renal Disease (polycystic kidney disease)		

Peptic Ulcer	Yes	Year of Onset
Peptic Ulcer		

Demyelination	Yes	Year of Onset
Optic Neuritis		
Multiple Sclerosis		
Transverse Myelitis		
Chronic Inflammatory De-myelinating Polyneuropathy		
Guillain-Barre Syndrome		

Epilepsy	Yes	Year of Onset
Epilepsy		

Peptic Ulcer	Yes	Year of Onset
Peptic Ulcer		

Non-Skin Cancer	Yes	Year of Onset
Please specify type / site:		

Psychiatric	Yes	Year of Onset
Depression		
Anxiety		

Inflammatory Bowel	Yes	Year of Onset
Crohns		
Ulcerative Colitis		

Other (please specify)	Yes	Year of Onset

Skin

Skin Cancer risk factors:

14a) Please indicate Fitzpatrick skin type in box below

Description	Fitzpatrick Skin Type	Please tick
Burns easily, never tans	1	
Burns easily, tans minimally	2	
Burns moderately, tans gradually	3	
Burns minimally, tans well	4	
Rarely burns, tans profusely	5	
Never burns, deeply pigmented	6	

14b) History of prior neoplastic or pre-cancerous lesions? Yes ☐ No ☐

(Please indicate number) and site below)

Type	Site	Number
SCC		
BCC		
Melanoma		
Melanoma in situ		
Actinic keratosis		
Bowen's disease		
Keratoacanthoma		

UV Therapy

15. Has the patient ever had UV therapy? Yes ☐ No ☐ **If YES, please complete the following:**

UV Therapy Details	Yes	No. of Courses	No. of Treatments	Cumulative Dose (J/cm^2)	Data Known to be Accurate?
Broadband UVB					
Narrowband UVB					
TOTAL BODY PUVA					
Oral PUVA					
Topical PUVA					
HAND AND FOOT PUVA					
Oral PUVA					
Topical PUVA					

Lab Values

16. Please complete the following laboratory values (recent i.e. within last 6 months):

LABORATORY VALUES	Result	Date
Haemoglobin count (g/dL)		
White cell count (x10^9/L)		
Platelet count (x10^9/L)		
Creatinine (µmol/L)		
Transaminase ALT (U/L)		
Cholesterol (mmol/L)		
Triglyceride (mmol/L)		
HDL (mmol/L)		

Additional Information

17. What is the patient's current (i.e. at the time that the biologic/systemic agent was started) blood pressure?

Systolic ☐☐☐ mm

Diastolic ☐☐☐ mm

15. What is the patient's current (i.e. at the time that the biologic/systemic agent was started) height, weight and waist circumference?

Height ☐☐☐ cm

Weight ☐☐☐ kg

Waist circumference ☐☐☐ cm

PBQ & QoL Questionnaires

The following patient questionnaires should also be completed:

PBQ ☐
(1)DLQI ☐
EuroQol ☐

CAGE ☐
(2)HAQ ☐

If paediatric patient:

cDLQI ☐
EQ-5D-y ☐

PBQ ☐
(2)cHAQ ☐

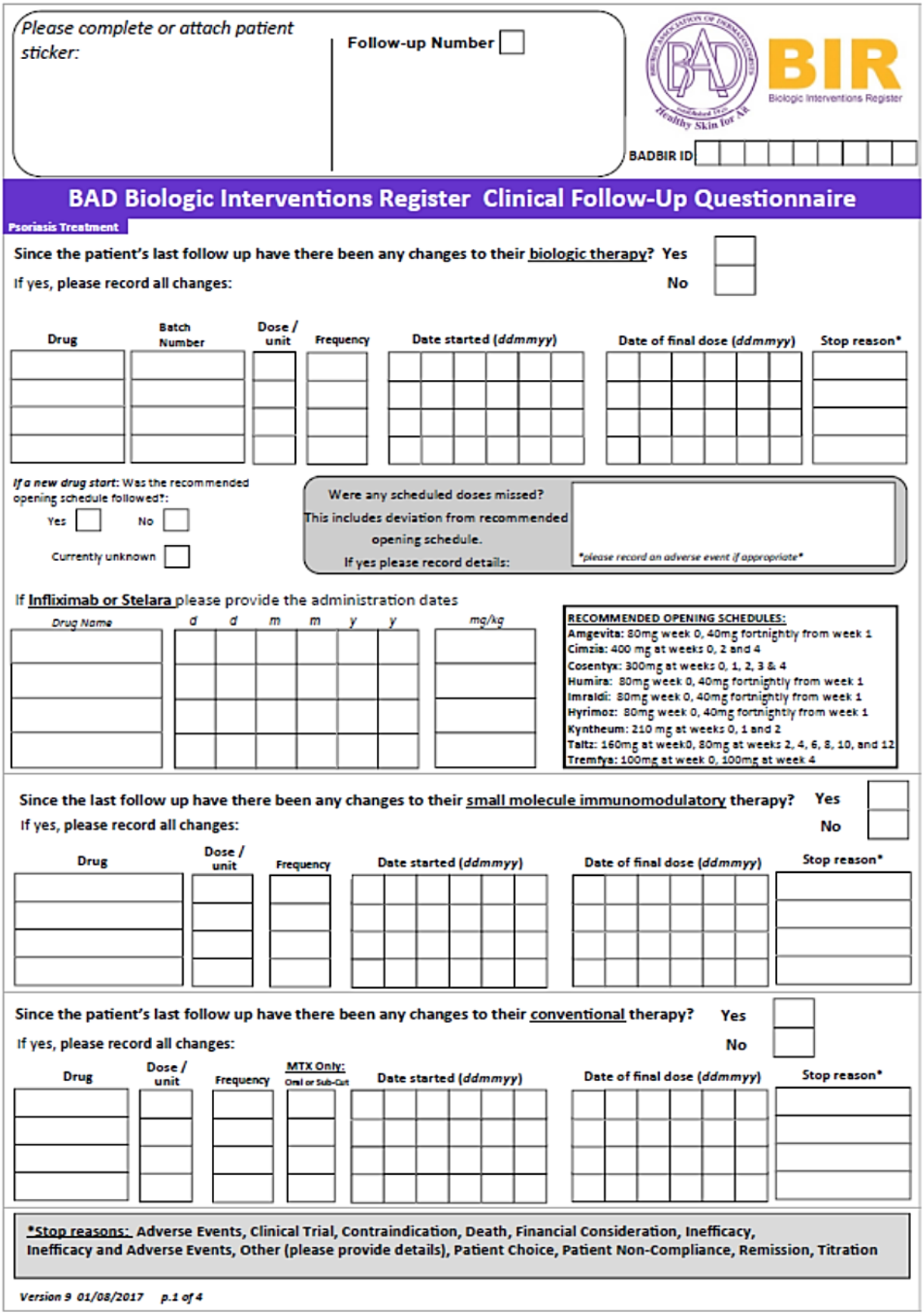
(1) It is not essential but a DLQI taken prior to drug commencement is preferred
(2) (Only if patient has a rheumatologist's diagnosis of inflammatory arthritis)

Signature

Please sign and date below:

Name: _____ **Signature:** _____ **Date:** _____

Appendix 13: BADBIR clinical follow-up questionnaire



Please complete or attach patient sticker:

Follow-up Number ☐

BIR Biologic Interventions Register

BADBIR ID ☐☐☐☐☐☐☐☐☐☐

BAD Biologic Interventions Register Clinical Follow-Up Questionnaire

Psoriasis Treatment

Since the patient's last follow up have there been any changes to their biologic therapy? Yes ☐ No ☐

If yes, please record all changes:

Drug	Batch Number	Dose / unit	Frequency	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

If a new drug start: Was the recommended opening schedule followed?:

Yes ☐ No ☐

Currently unknown ☐

Were any scheduled doses missed? This includes deviation from recommended opening schedule.

If yes please record details:

please record an adverse event if appropriate

If **Infliximab or Stelara** please provide the administration dates

Drug Name	d d m m y y	mg/kg

RECOMMENDED OPENING SCHEDULES:
Amgevita: 80mg week 0, 40mg fortnightly from week 1
Cimzia: 400 mg at weeks 0, 2 and 4
Cosentyx: 300mg at weeks 0, 1, 2, 3 & 4
Humira: 80mg week 0, 40mg fortnightly from week 1
Imraldi: 80mg week 0, 40mg fortnightly from week 1
Hyrimoz: 80mg week 0, 40mg fortnightly from week 1
Kyntheum: 210 mg at weeks 0, 1 and 2
Taltz: 160mg at week0, 80mg at weeks 2, 4, 6, 8, 10, and 12
Tremfya: 100mg at week 0, 100mg at week 4

Since the last follow up have there been any changes to their small molecule immunomodulatory therapy? Yes ☐ No ☐

If yes, please record all changes:

Drug	Dose / unit	Frequency	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

Since the patient's last follow up have there been any changes to their conventional therapy? Yes ☐ No ☐

If yes, please record all changes:

Drug	Dose / unit	Frequency	MTX Only: Oral or Sub-Cut	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

***Stop reasons:** Adverse Events, Clinical Trial, Contraindication, Death, Financial Consideration, Inefficacy, Inefficacy and Adverse Events, Other (please provide details), Patient Choice, Patient Non-Compliance, Remission, Titration*

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UV Therapy

Since the patients last follow-up have they had any UV therapy? Yes ☐
If yes, please complete the following: No ☐

UV Therapy Details	Yes	No. of Courses	No. of Treatments	Cumulative Dose (J/cm^2)	Data Known to be Accurate?
Broadband UVB					
Narrowband UVB					
TOTAL BODY PUVA					
Oral PUVA					
Topical PUVA					
HAND AND FOOT PUVA					
Oral PUVA					
Topical PUVA					

Concomitant Therapy

Since the patient's last follow up have they had any changes to their concomitant therapy? Yes ☐
If yes, please complete the following: *(please note we do not need details of topical therapy for psoriasis except for tacrolimus and pimecrolimus)* No ☐

Drug	Start date	Stop date	Are these dates estimated?

Lab Values

Please complete the following laboratory values (recent i.e. within last 6 months):

LABORATORY VALUES	Result	Date
Haemoglobin count (g/dL)		
White cell count (x10^9/L)		
Platelet count (x10^9/L)		
Creatinine (µmol/L)		
Transaminase ALT (U/L)		
Cholesterol (mmol/L)		
Triglyceride (mmol/L)		
HDL (mmol/L)		

FUP7 + : Lab Values not required

Adverse Events Since date of last data entry has your patient experienced any adverse events)?

Yes ☐

No ☐

An <u>adverse event</u> (AE) is defined as any medically untoward event occurring in a patient whether or not related to any treatment or medication

A <u>serious adverse event</u> (SAE) is defined by the classifications in the box below

Please enter details of <u>ALL</u> adverse events (both serious and non-serious) from this follow-up period

Event No.	Description of event (Symptoms, Diagnosis, Treatment)	Start date	Start Date Estimated?	Stop date	Stop Date Estimated?	Is the event ongoing?	Is the event related to biologic/ biosimilar or small molecule drug therapy? Yes, No or Don't Know Not required for conventional cohort patients	Yellow Card Sent?	Is the event a SAE ? If yes please select code (see below)	Is the event an ESI? If yes please record)	Outcome of the event?
	Symptoms - Diagnoses - Treatment -						If 'Yes' Name of drug:___		If 'Hospitalisation' Admission Date:________ Discharge Date:________	*List of ESI categories moved to AE summary page / BADBIR website*	☐ Resolved ☐ Resolved w/ Sequelae ☐ Not Resolved ☐ Unknown ☐ Death
	Symptoms - Diagnoses - Treatment -						If 'Yes' Name of drug:___		If 'Hospitalisation' Admission Date:________ Discharge Date:________		☐ Resolved ☐ Resolved w/ Sequelae ☐ Not Resolved ☐ Unknown ☐ Death
	Symptoms - Diagnoses - Treatment -						If 'Yes' Name of drug:___		If 'Hospitalisation' Admission Date:________ Discharge Date:________		☐ Resolved ☐ Resolved w/ Sequelae ☐ Not Resolved ☐ Unknown ☐ Death
	Symptoms - Diagnoses - Treatment -						If 'Yes' Name of drug:___		If 'Hospitalisation' Admission Date:________ Discharge Date:________		☐ Resolved ☐ Resolved w/ Sequelae ☐ Not Resolved ☐ Unknown ☐ Death
	Symptoms - Diagnoses - Treatment -						If 'Yes' Name of drug:___		If 'Hospitalisation' Admission Date:________ Discharge Date:________		☐ Resolved ☐ Resolved w/ Sequelae ☐ Not Resolved ☐ Unknown ☐ Death

Code	SAE Classification
1	Death
2	**Overnight** Hospitalisation
3	IV antibiotics/antivirals/antifungal
4	Significant loss of function or disability
5	Congenital malformation
6	Immediately Life Threatening
7	Medically Important Event

If any of the Serious Adverse events you have listed include any of the following, an Event of Special Interest (ESI) form needs to be completed:

- ***Aplastic anaemia, pancytopaenia or serious neutropenia***
- ***Cerebrovascular Accident (CVA)***
- ***Hepatitis B Reactivation***
- ***Lymphoproliferative Disease***
- ***Malignancy (not inc. skin)***
- ***Melanoma / Skin Cancer (inc. Bowens Disease)***
- *Drug misuse, abuse, overdose and medication error*
- ***Myocardial Infarction/Acute Coronary Disease***
- ***Pregnancy***
- ***Pulmonary Embolism***
- ***Serious Congestive Heart Failure***
- *Serious Demyelination/Optic Neuritis*
- ***Serious Hepatic Dysfunction/Failure***
- **Serious Hypersensitivity Reaction**
- **Serious Infection (excl. TB)**
- **Serious Lupus/Lupus like illness**
- **Serious Psoriasis Flare** ***(Overnight Hospitalisation Only)***
- **Serious Skin Reaction**
- **Surgery** ***(Overnight Hospitalisation Only)***
- **Tuberculosis (Not Latent)**

Current Disease Severity

Please indicate the current disease severity

BSA ☐☐ ***Only if the patient has pustular psoriasis***

Date of BSA ...../...../.....

Please enter the details of all PASI's that have been completed since the patients last follow-up.

Please note at least one PASI must be collected during a follow-up period to be eligible for payment

PASI	Date of PASI	Psoriasis Global Assessment

Psoriasis Global Assessment score:

- Severe
- Moderate to severe
- Moderate
- Mild
- Almost clear
- Clear

Has the patient been diagnosed with psoriatic arthritis by a rheumatologist? **Yes** ☐ **No** ☐

if this is a new diagnosis please remember to add this as an adverse event

Additional Information

What is the patient's current weight and waist circumference?

Weight ☐☐☐ kg

Waist circumference ☐☐☐ cm

FUP9 + : Weight / Waist not required

If the patient is under 16 year of age on the date of this follow-up, please provide a height measurement: ☐☐☐ cm

Patient Follow-up Questionnaire

The patient questionnaire should also be completed containing:

Occupation Qus ☐
DLQI ☐
EuroQol ☐

Lifestyle Qus ☐
CAGE ☐
***HAQ** ☐

If paediatric patient:

cDLQ ☐
EQ-5D-y ☐
***cHAQ** ☐

FUP 7+ : Patient Questionnaire is not required

(*Only if patient has a rheumatologist's diagnosis of inflammatory arthritis)

Signature

Please sign and date below:

Clinician's signature:_____ **Date:**_____

Appendix 14: Event of Special Interest form – Malignancy (not including skin)

PATIENT:	BADBIR ID:	BIR Biologic Interventions Register
HRN:	DOB:	
BIOLOGIC / CONVENTIONAL TREATMENT:		

Event of Special Interest: Malignancy (not including skin)

Diagnosis - *please include site(s)*:

Histopathological classification:

Treatment regime: ☐ **Surgery** ☐ **Chemo** ☐ **Other** *(specify)*

Details

Family history of cancer **Yes** ☐ **No** ☐ **Unknown** ☐

If Yes - Relationship _____

If you have any questions please call the Register office on: 0161 306 1911

Form completed By: _____ On: ____/____/____	Please note this ESI form needs to be entered directly onto the BADBIR database in the adverse section

Appendix 15: Event of Special Interest form – Lymphoproliferative Disease

PATIENT:	BADBIR ID:
HRN:	DOB:
BIOLOGIC / CONVENTIONAL TREATMENT:	

Event of Special Interest: Lymphoproliferative Disease

Diagnosis: (please include site)

Histopathological classification:

(if known, please enter the results below)

Treatment regime: ☐ Surgery ☐ Chemo ☐ Rituximab

Tissue EBV status: ☐ Positive ☐ Negative ☐ Unknown

Family history of cancer: ☐ Yes ☐ No ☐ Unknown

If you have any questions please call the Register office on: 0161 306 1911

Form completed By: _____

On: ____/____/____

Please note this ESI form needs to be entered directly onto the BADBIR database in the adverse section

Appendix 16: Event of Special Interest form – Melanoma or Skin Cancer including Bowen's Disease

PATIENT: **BADBIR ID:**

HRN: **DOB:**

BIOLOGIC / CONVENTIONAL TREATMENT:

BIR Biologic Interventions Register

Event of Special Interest: Melanoma Or Skin Cancer including Bowen's Disease

Diagnosis - *please include site(s)*:

Details of any previous UV/Photo therapy:

UV Therapy Details	No. of courses	No. treatments	Cumulative Dose (J/cm^2)	Dose unknown *(please tick)*
Broadband UVB				
Narrowband UVB				

Histopathological classification:

Treatment regime: ☐ Surgery ☐ Chemo ☐ Other *(specify)*

Details

Family history of cancer Yes ☐ No ☐ Unknown ☐

If Yes - Relationship _____

If you have any questions please call the Register office on: 0161 306 1911

Form completed By: _____

On: ____/____/____

Please note this ESI form needs to be entered directly onto the BADBIR database in the adverse section

Appendix 17: BADBIR NHS research ethics committee approval form

NHS

North West Research Ethics Committee

NHS North West
Room 155 - Gateway House
Piccadilly South
Manchester
M60 7LP

Telephone: 0161 237 2152
Facsimile: 0161 237 2383

14 March 2007

Professor C E M Griffiths
Professor of Dermatology
The University of Manchester
Dermatology Centre
Hope Hospital
Stott Lane
SALFORD M6 8HD

RECEIVED
16 MAR 2007

Dear Professor Griffiths

Full title of study: **British Association of Dermatologists Biological Interventions Register**

REC reference number: **07/MRE08/9**

Thank you for your letter of 05 March 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair (Dr Donal Manning) and Mr James Bruce (Consultant Surgeon).

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised].

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

The Central Office for Research Ethics Committees is Responsible for the operational management of Multi-Centre Research Ethics Committees

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	5.2	18 December 2006
Investigator CV - for Professor C E M Griffiths		19 December 2006
Protocol	10	05 December 2006
Covering Letter		19 December 2006
Peer Review - from Professor Nils Feltenius, Director of ARTIS registry, Karolinska University Hospital Solna - August 2006		
Statistician Comments - Letter from Dr Chris Roberts, Senior Lecturer in Medical Statistics, The University of Manchester		25 October 2006
Questionnaire: Patient baseline questionnaire	4	08 December 2006
Questionnaire: Consultant 6-monthly follow-up questionnaire	4	08 December 2006
Questionnaire: Consultant baseline questionnaire	4	08 December 2006
Questionnaire: Patient 6-monthly follow-up questionnaire	4	08 December 2006
Questionnaire: Psoriasis Area and Severity Index - PASI (validated)		
Questionnaire: Dermatology Life Quality Index - DLQI (validated)		
Questionnaire: CAGE Questionnaire (validated)		
Questionnaire: Generic Health Utility Index - Patient Baseline EuroQol (validated)		
Questionnaire: Health Assessment Questionnaire (HAQ) - rheumatoid arthritis only) (validated)		
Questionnaire: BAD Biological Interventions Register - Patient 6-monthly diary	4	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Serious Infections (excluding TB)	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Lymphoproliferative tumours	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Congestive Heart Failure	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Central demyelinating disease	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Aplastic anaemia / pancytopaenia	1	08 December 2006
Questionnaire: Control Patient follow-up questionnaire	4	08 December 2006
Questionnaire: Pregnancy Outcome Questionnaire	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Tuberculosis	1	08 December 2006
Participant Information Sheet	1	08 December 2006
Participant Information Sheet	2	
Participant Consent Form	1	08 December 2006
Response to Request for Further Information - From Professor EM Griffiths		05 March 2007
Patient Follow-up Flow Chart		
Website content		
Letter from funder - British Association of Dermatologists		07 December 2006

R&D approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final approval from the R&D office for the relevant NHS care organisation.

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.

07/MRE08/9	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

p.p. **Dr Donal Manning**
Chair

Email: northwest.mrec@northwest.nhs.uk

Enclosures: Standard approval conditions

Copies to: -

Dr K D Watson
ARC Epidemiology Unit
The University of Manchester
Stopford Building
Oxford Road
MANCHESTER
M13 9PT

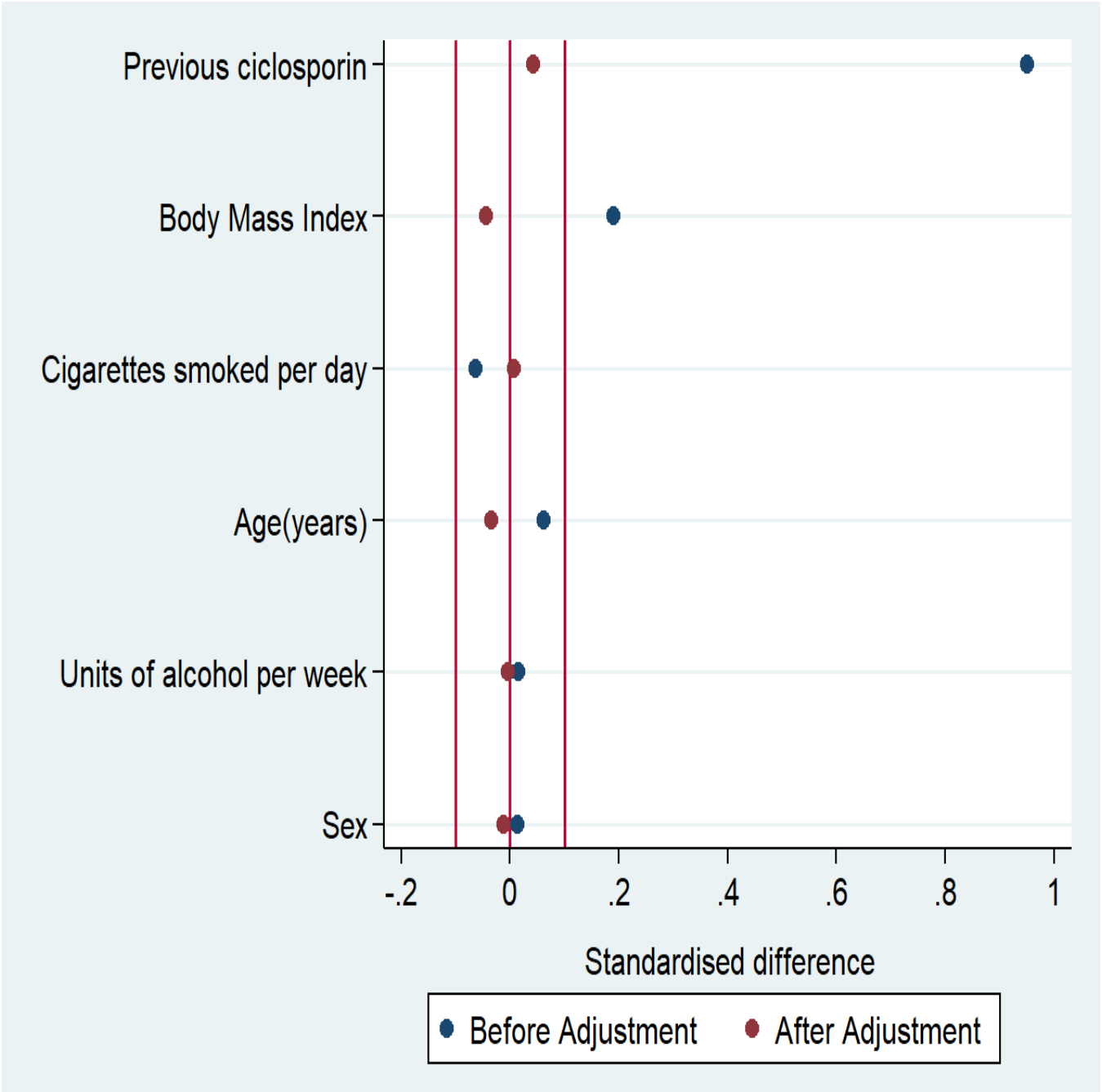
R&D Department for NHS care organisation at lead site: -

Dr K Shaw
Head of the University Research Office
University of Manchester
Christie Building
Oxford Road
MANCHESTER
M13 9PL

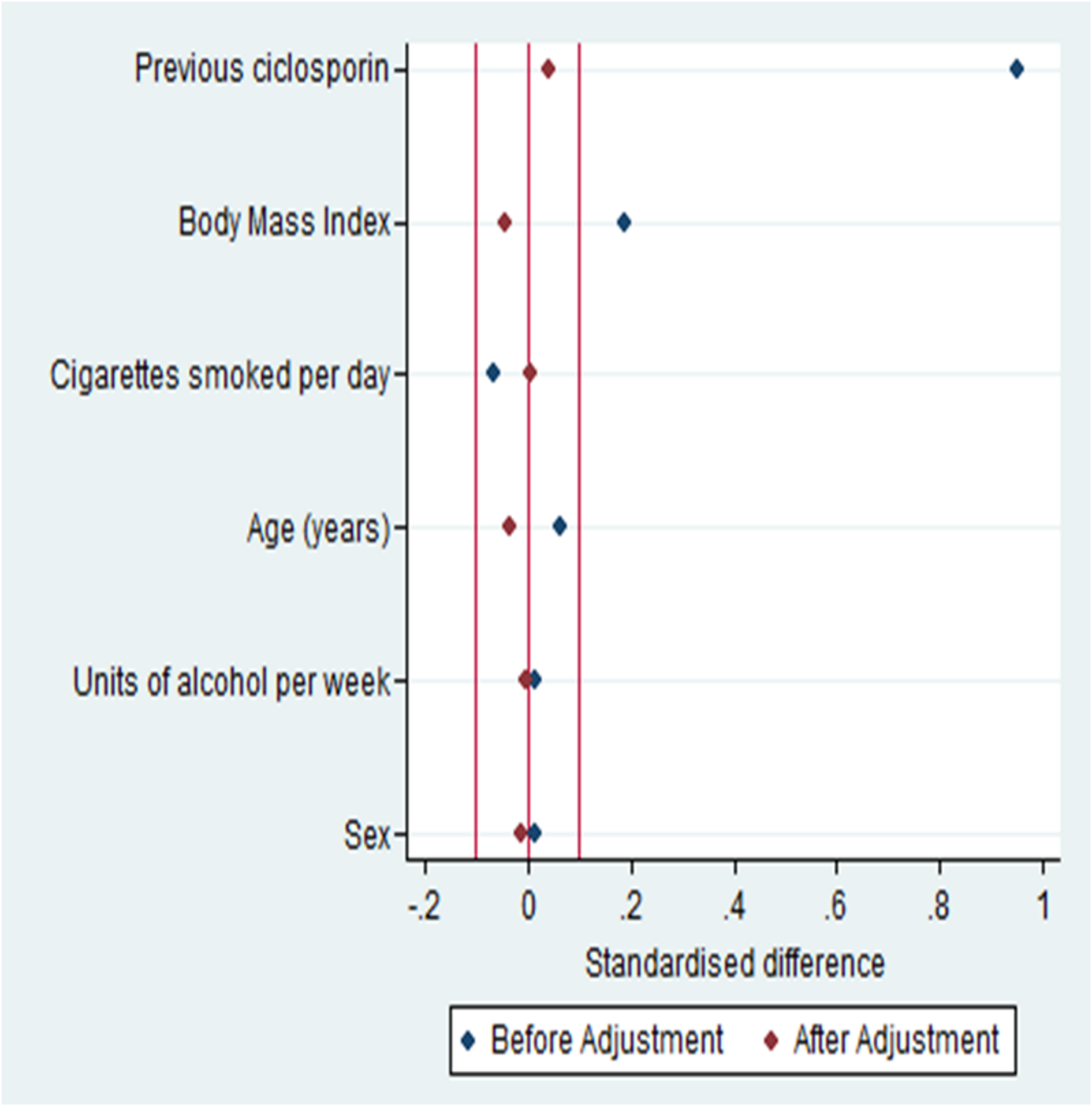
Appendix 18: Variables explored as confounding factors using tests for equality of survivor functions

	STUDY OUTCOMES						
	All cancer	**Cancers of infectious origin**	**Lung cancer**	**Breast Cancer**	**Prostate Cancer**	**Basal cell carcinoma**	**Squamous cell carcinoma**
Categorical variables	**Log-rank test for equality of survival function (Chi^2: p<0.25)**						
Sex	**0.22**	*0.64**	*0.96**	-	-	**0.13**	**0.00**
Previous exposure to methotrexate	0.48	0.66	0.73	0.45	**0.12**	-	-
Previous exposure to ciclosporin	**0.01**	**0.06**	0.48	**0.10**	**0.00**	**0.02**	*0.89**
Previous exposure to acitretin	-	-	-	-	-	**0.00**	**0.03**
Outdoor occupation	-	-	-	-	-	**0.00**	**0.06**
Lived in a tropical country	-	-	-	-	-	0.27	0.88
Continuous variables	**Univariate Cox-regression test for equality of survival function (p<0.25)**						
Age	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
BMI	*0.84**	*0.77**	**-**	*0.81**	-	-	-
Number of cigarettes smoked per day	**0.00**	**0.02**	**0.00**	**-**	-	-	**0.01**
Units of alcohol consumed per week	**0.00**	*0.56**	-	**0.04**	-	-	-
Number of PUVA courses	-	-	-	-	-	**0.00**	**0.00**
Number of narrowband UVB courses	-	-	-	-	-	**0.01**	**0.21**

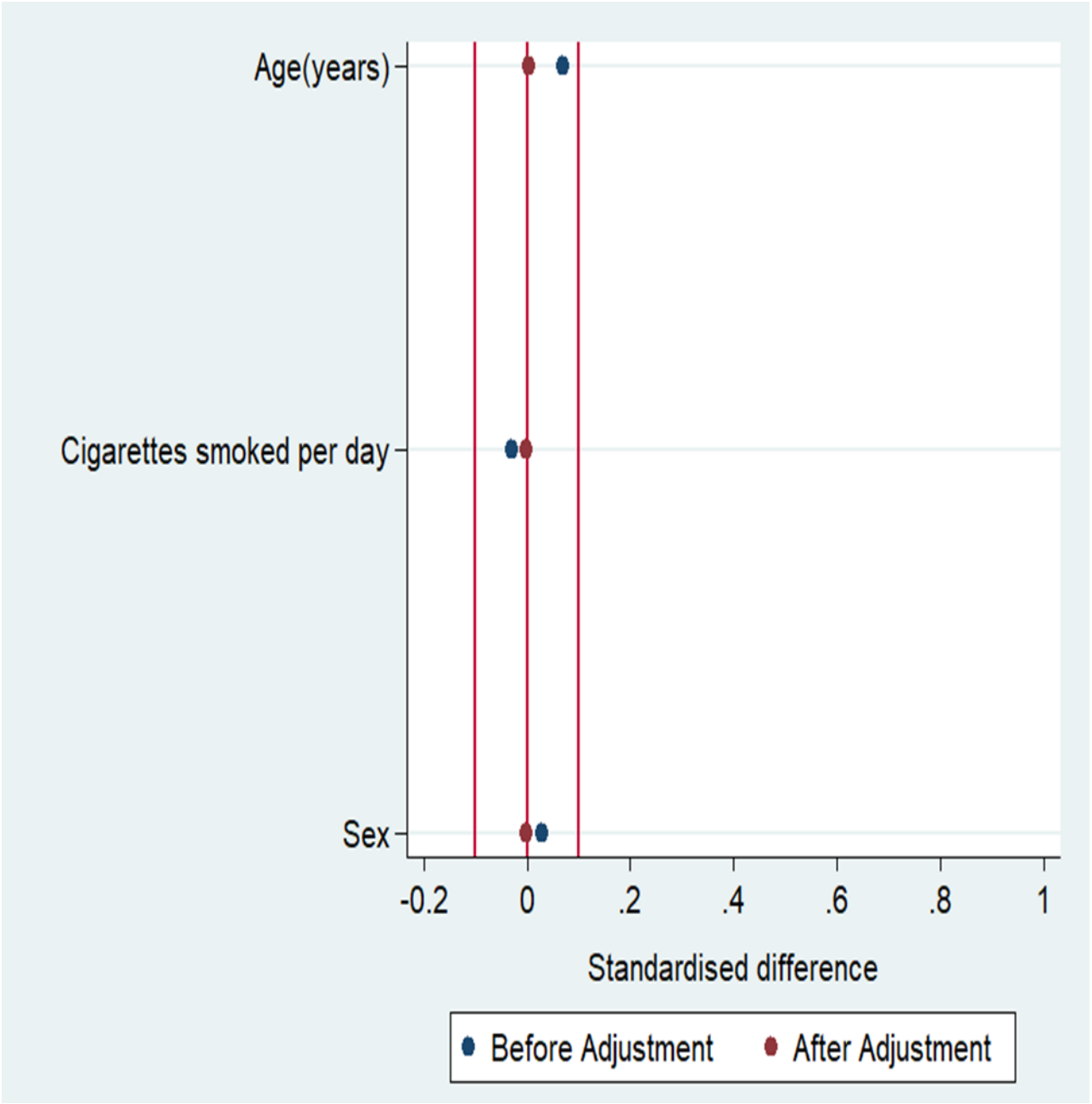
Appendix 19: Distribution of the confounders before and after propensity score balancing for the outcome all cancer (excluding KC)



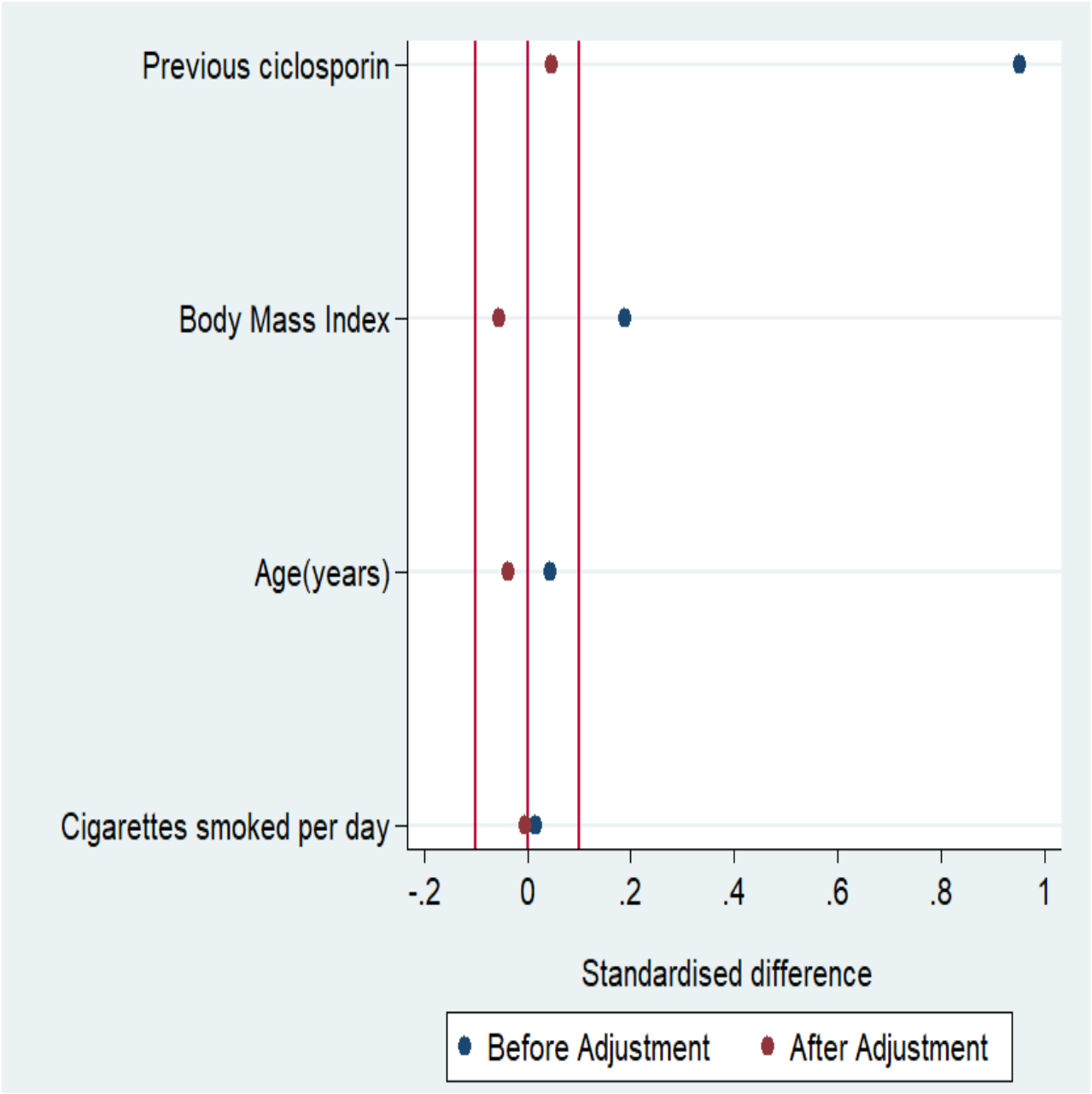
Appendix 20: Distribution of the confounders before and after propensity score balancing for the outcome cancers of infectious origin



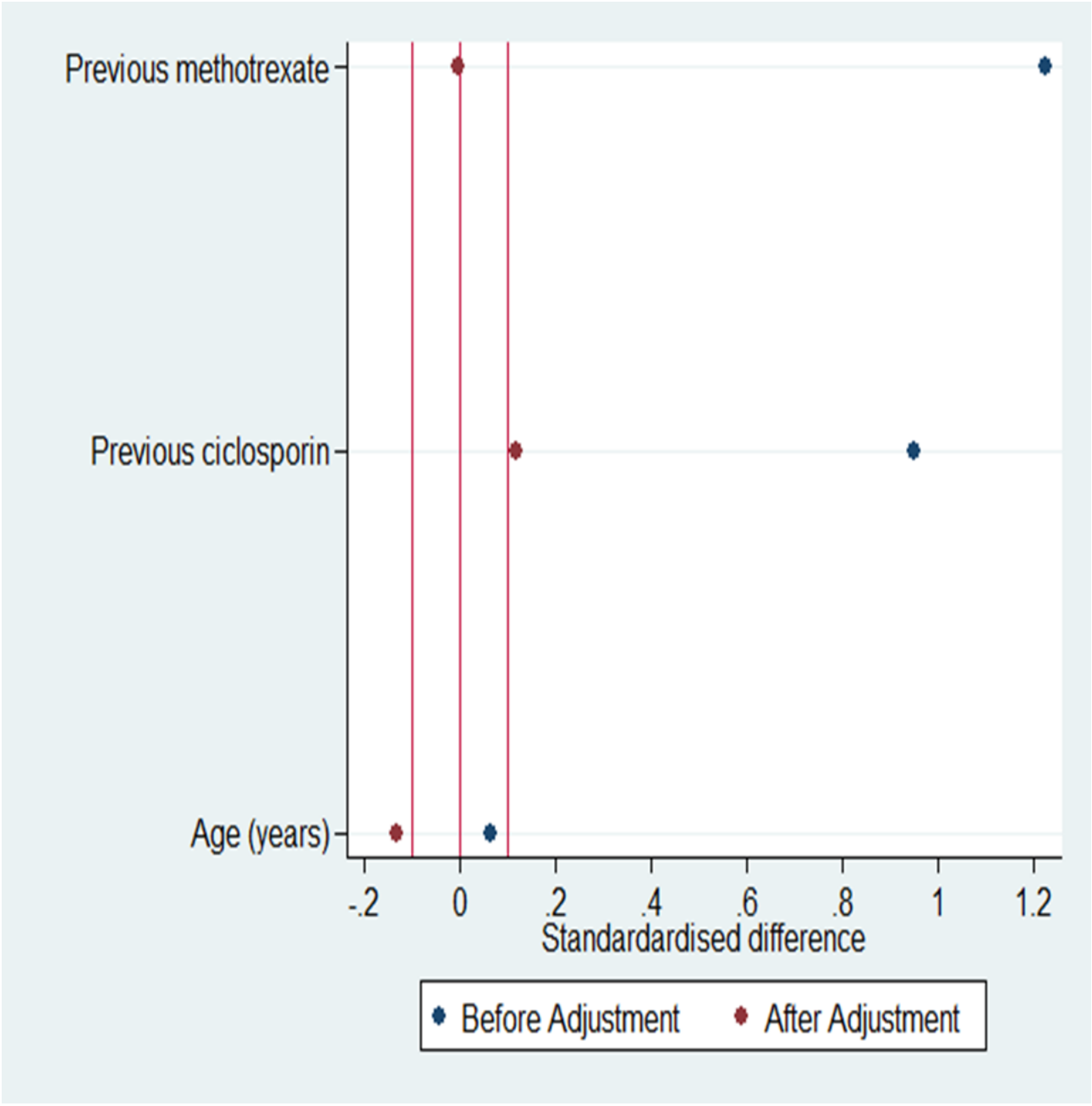
Appendix 21: Distribution of the confounders before and after propensity score balancing for the outcome lung cancer



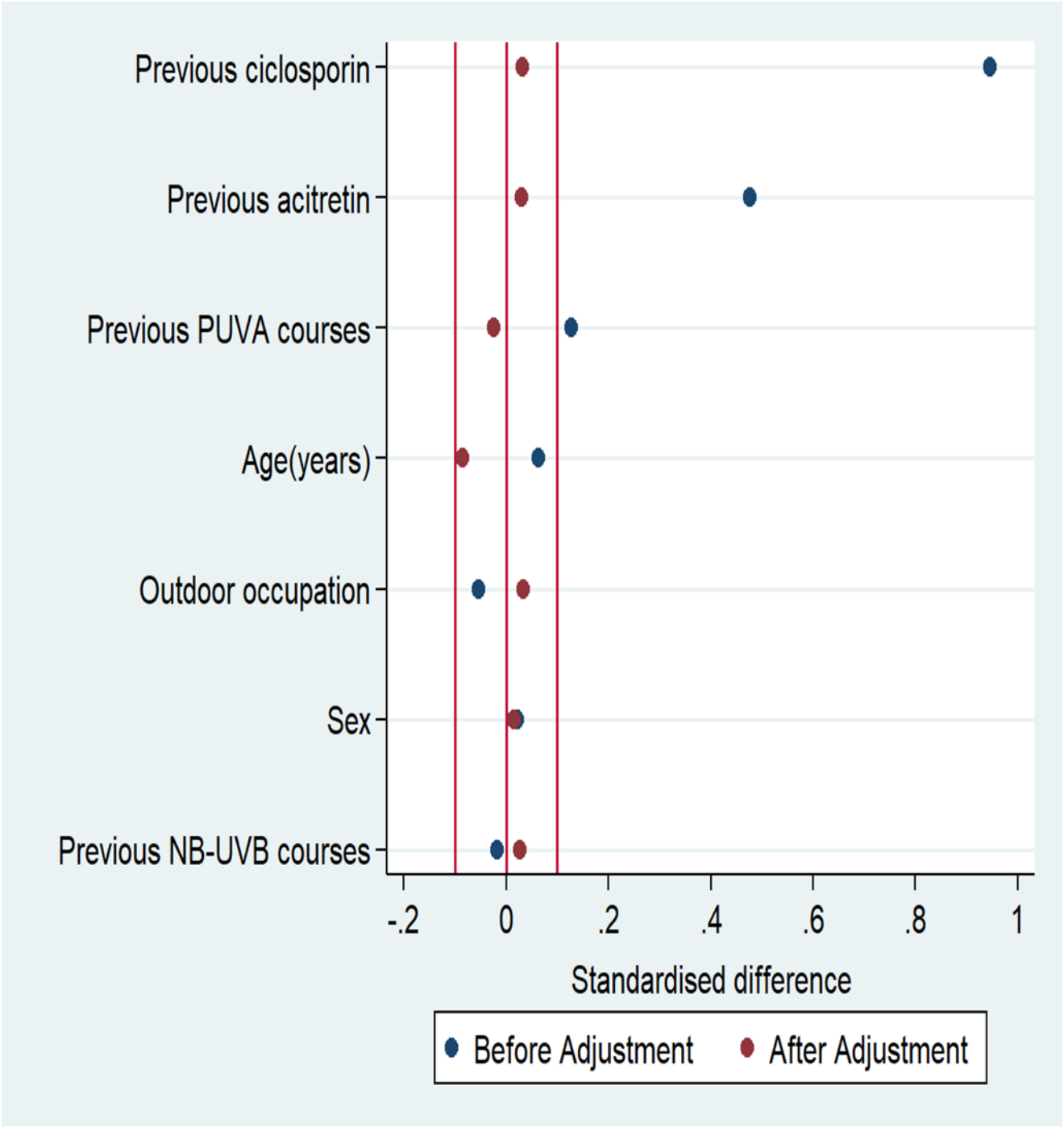
Appendix 22: Distribution of the confounders before and after propensity score balancing for the outcome breast cancer



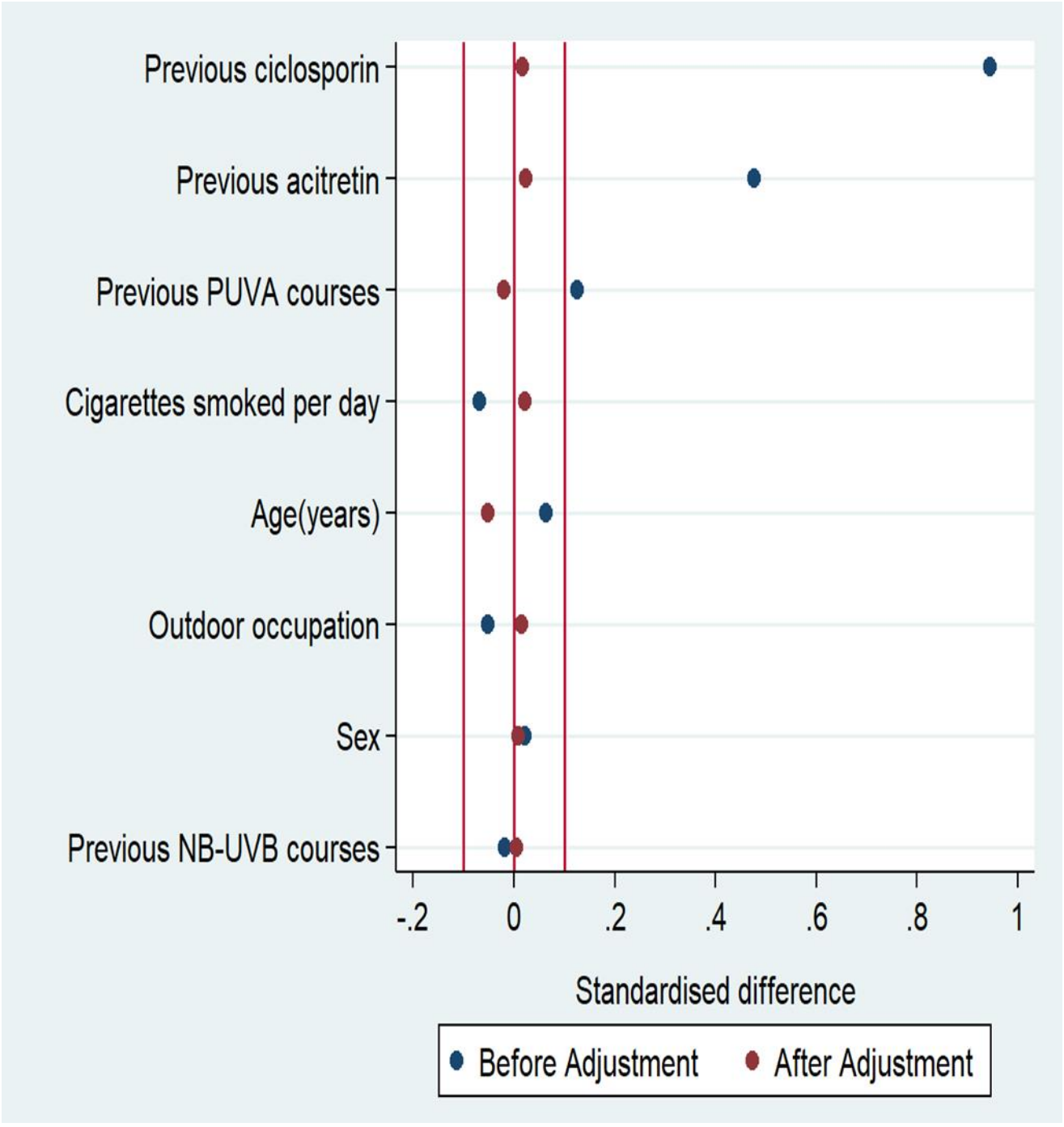
Appendix 23: Distribution of the confounders before and after propensity score balancing for the outcome prostate cancer



Appendix 24: Distribution of the confounders before and after propensity score balancing for the outcome basal cell carcinoma



Appendix 25: Distribution of the confounders before and after propensity score balancing for the outcome squamous cell carcinoma



Appendix 26: Registration therapies for patients entering the biologic and non-biologic systemic therapy cohorts in BADBIR during the study period

Cohort	Registration therapy	Number of patients	Proportion of the cohort (%)
Biologic	Enbrel	1341	15.8
	Remicade	131	1.5
	Humira	4428	52.3
	Cosentyx	516	6.1
	Stelara	1937	22.9
	Other biologic therapy†	117	1.2
Non-biologic systemic	Methotrexate	2232	46.4
	Ciclosporin	1214	25.2
	Acitretin	843	17.5
	FAEs	327	6.8
	PUVA	94	2.0
	Other non-biologic systemic therapy‡	104	2.2

Abbreviations: Fumaric Acid Esters (FAEs); Psoralen plus Ultraviolet A (PUVA)

† Other biologic therapies: etanercept biosimilar (Benepali, n=83); ixekizumab (Taltz, n=16); brodalumab (Kyntheum, n=4); certolizumab pegol (Cimzia, n=1); efalizumab (Raptiva, n=10); golimumab (Simponi, n=2), clinical trial biologic (n=1)

‡ Other non-biologic systemic therapies: dimethyl fumarate (Skilarence, n=36; apremilast (Otezla, n=35); hydroxycarbamide (n=33)

Appendix 27: Biologic therapies patients in BADBIR were exposed to at any point during the study period

Biologic mechanism	Drug name	Tradename	Proportion of patients ever exposed to the therapy (%)
Tumour necrosis factor inhibitors	adalimumab	Humira	54.1
	etanercept	Enbrel	16.0
	infliximab	Remicade	1.9
	etanercept (biosimilar)	Benepali	1.5
	Other TNFi†		<1.0
Interleukin-23 inhibitor	guselkumab	Tremfya	<1.0
Interleukin-12/23 inhibitor	ustekinumab	Stelara	29.6
Interleukin-17A inhibitors	secukinumab	Cosentyx	8.9
	ixekizumab	Taltz	<1.0
Interleukin-17 Receptor A inhibitor	brodalumab	Kyntheum	<1.0

† Other TNFi: infliximab biosimilar (Erelzi, 0.1%; Inflectra, 0.1%); Certolizumab pegol (Cimzia, 0.1%)

Appendix 28: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of all cancer (excluding keratinocyte carcinoma) model.

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	0.05594	0.59	1	0.4409
age	0.02006	0.08	1	0.7808
bmi	-0.05098	0.56	1	0.4550
numberofci~y	0.01287	0.03	1	0.8584
drnkunitsavg	0.03443	0.16	1	0.6931
genderid	0.02064	0.07	1	0.7978
prev1433	-0.03355	0.21	1	0.6466
age_genderid	-0.02199	0.08	1	0.7831
numberofci~g	-0.03379	0.18	1	0.6678
global test		1.43	9	0.9976

Appendix 29: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of cancers of infectious origin model.

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	0.16633	1.42	1	0.2327
age	0.04513	0.14	1	0.7075
bmi	0.04781	0.09	1	0.7614
numberofci~y	0.00979	0.00	1	0.9612
drnkunitsavg	0.12627	0.83	1	0.3625
genderid	0.10861	0.48	1	0.4866
prev1433	0.03627	0.07	1	0.7979
age_genderid	-0.07711	0.31	1	0.5754
bmi_genderid	-0.06845	0.18	1	0.6728
genderid_n~y	-0.04192	0.05	1	0.8169
global test		3.85	10	0.9538

Appendix 30: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of lung cancer model.

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	-0.07538	0.15	1	0.7016
age	0.05120	0.05	1	0.8276
numberofci~y	-0.04444	0.03	1	0.8691
genderid	-0.04749	0.06	1	0.8082
global test		0.32	4	0.9883

Appendix 31: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of breast cancer model.

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	0.14324	0.50	1	0.4813
age	-0.19359	0.54	1	0.4641
bmi	0.23229	1.39	1	0.2383
drnkunitsavg	0.07109	0.07	1	0.7855
prev1433	0.06779	0.11	1	0.7402
global test		3.21	5	0.6680

Appendix 32: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of prostate cancer model.

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	0.21110	0.69	1	0.4067
age	-0.19278	0.39	1	0.5330
prev16	0.11949	0.22	1	0.6371
prev1433	-0.37133	2.86	1	0.0910
global test		3.84	4	0.4284

Appendix 33: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of basal cell carcinoma model

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	0.09707	0.52	1	0.4701
age	-0.00589	0.00	1	0.9674
genderid	-0.05985	0.23	1	0.6331
prev1433	0.06214	0.21	1	0.6473
prev110	-0.10596	0.66	1	0.4182
outdoorocc~n	-0.22959	3.31	1	0.0688
UVAcourse	-0.02827	0.06	1	0.8035
UVBnarrowc~e	0.06937	0.28	1	0.5988
global test		6.10	8	0.6356

Appendix 34: Test of proportional-hazards assumption using Schoenfeld residuals for the risk of squamous cell carcinoma model

```
. stphtest, detail

      Test of proportional-hazards assumption

      Time:  Time
```

	rho	chi2	df	Prob>chi2
cohort	-0.17213	1.06	1	0.3044
age	0.04415	0.05	1	0.8169
genderid	-0.33393	3.43	1	0.0639
prev1433	0.17306	0.87	1	0.3501
prev110	0.08677	0.26	1	0.6096
outdoorocc~n	-0.11473	0.38	1	0.5356
UVAcourse	0.02537	0.02	1	0.8905
UVBnarrowc~e	-0.02917	0.02	1	0.8769
numberofci~y	-0.07084	0.18	1	0.6713
global test		6.48	9	0.6916

Appendix 35: Number of person-years of follow-up required in each cohort to determine risk of developing cancer

Incidence of cancer in the control group	Ratio of patients in the biologic cohort to non-biologic systemic cohort	Relative Risk 2.0	
		Biologic cohort	Non-biologic systemic cohort
1 in 500	1:1	12,717	12,717
	1:2	18,250	9,125
1 in 1000	1:1	23,471	23,471
	1:2	36,550	18,275
1 in 2000	1:1	127,501	127,501
	1:2	162, 950	91,475

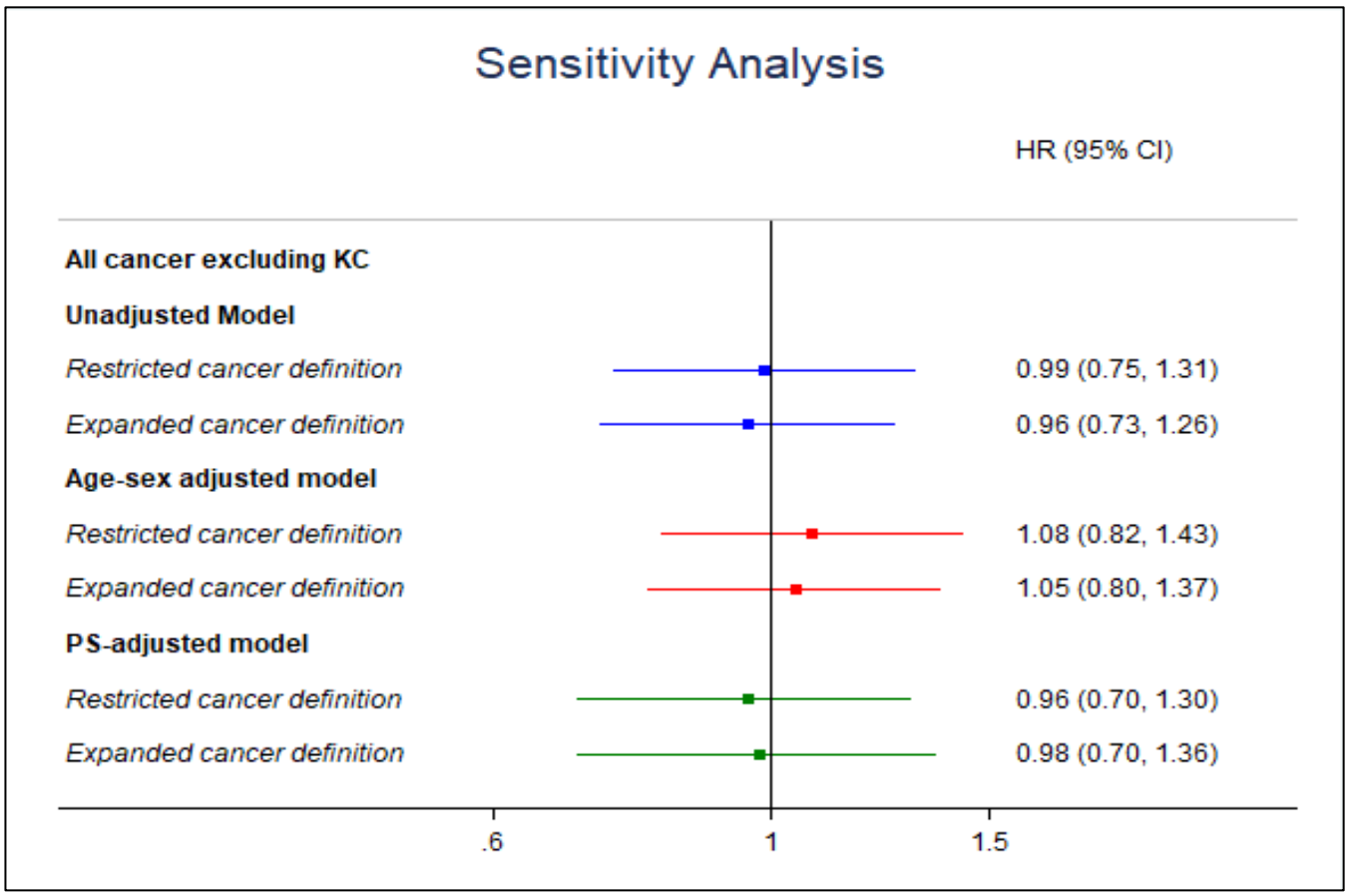
Appendix 36: Estimated number of person-years accrued in BADBIR given a scenario of 1,000 new patients per year registering to one of the cohorts over a period of 10 years.

	Number of years on BADBIR										
Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total number of person-years accrued**
1	500										**500**
2	1,500	500									**2,000**
3	2,500	1,500	500								**4,500**
4	3,500	2,500	1,500	500							**8,000**
5	4,500	3,500	2,500	1,500	500						**12,500**
6	5,500	4,500	3,500	2,500	1,500	500					**18,000**
7	6,500	5,500	4,500	3,500	2,500	1,500	500				**24,500**
8	7,500	6,500	5,500	4,500	3,500	2,500	1,500	500			**32,000**
9	8,500	7,500	6,500	5,500	4,500	3,500	2,500	1,500	500		**40,500**
10	9,500	8,500	7,500	6,500	5,500	4,500	3,500	2,500	1,500	500	**50,000**

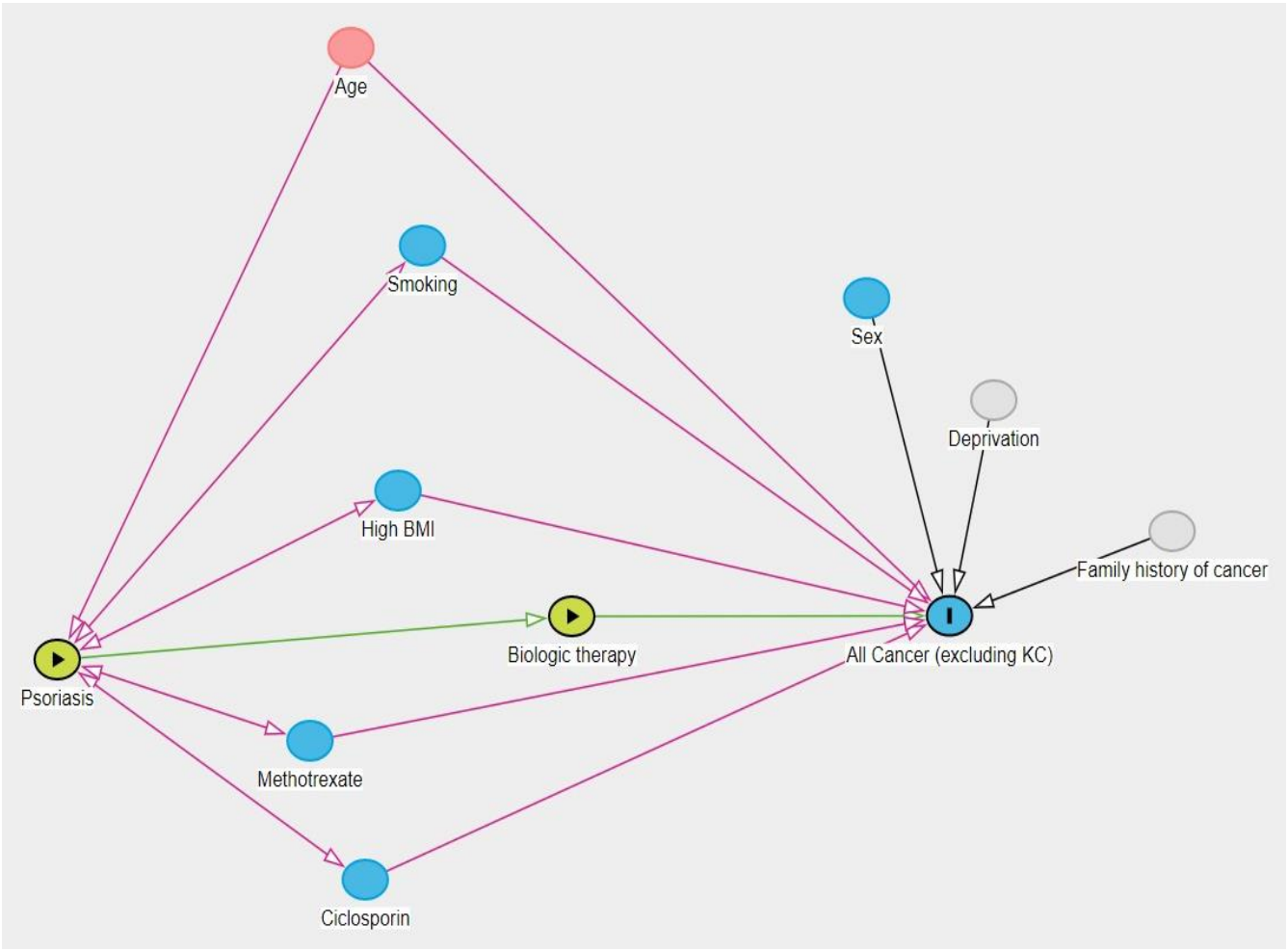
Appendix 37: Number of new registrations to BADBIR by cohort up to 1 April 2019.

Registration Year	Biologic cohort	Conventional systemic Cohort	Small molecule cohort	**Total**
2007	47	5	3	**55**
2008	206	26	1	**233**
2009	472	91	1	**564**
2010	814	384	2	**1,200**
2011	965	646	6	**1,617**
2012	1,265	925	1	**2,191**
2013	1,350	810	4	**2,164**
2014	1,211	626	8	**1,845**
2015	1,206	483	1	**1,690**
2016	1,398	532	2	**1,932**
2017	1,332	490	5	**1,827**
2018	1,307	407	111	**1,825**
2019	206	58	22	**286**
Total	**11,779**	**5,483**	**167**	**17,429**

Appendix 38: Sensitivity analysis comparing risk of all cancer (excluding KC) between the restricted and expanded cancer definitions

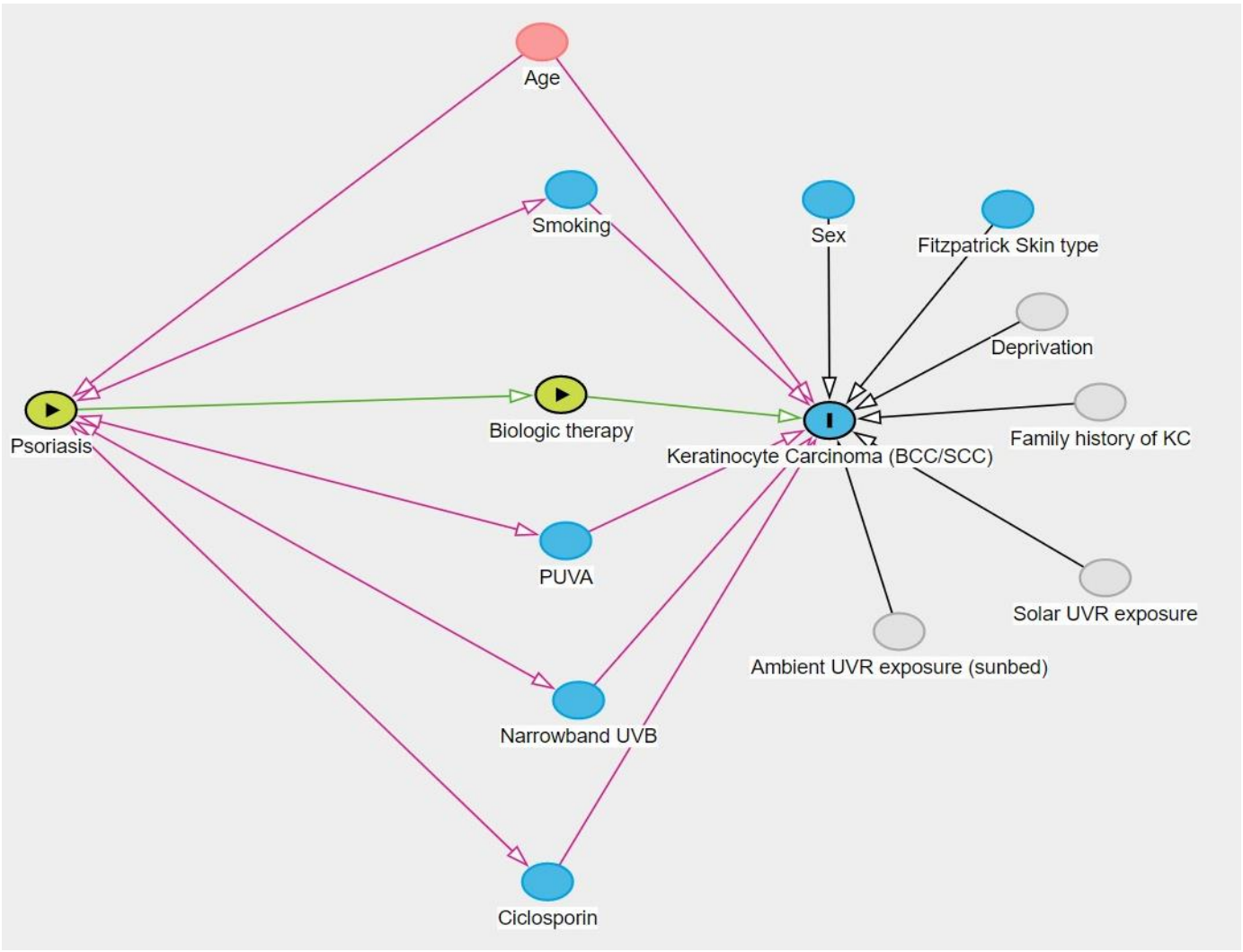


Appendix 39: Directed acyclic graph exploring the assumed relationships between psoriasis, the outcome of all cancer (excluding KC) and potential confounder and mediators.



Key: **Green node = exposure variable**
Pink node= confounder variable
Blue node=mediator variable
Grey node = unobserved variable

Appendix 40: Directed acyclic graph exploring the assumed relationships between psoriasis, the KC outcomes (SCC and BCC) and potential confounders and mediators.



Key: **Green node = exposure variable**
Pink node= confounder variable
Blue node=mediator variable
Grey node = unobserved variable