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Malignancy risk and recurrence with psoriasis and its treatments: a concise update

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Abstract

Psoriasis is a common inflammatory cutaneous disease that affects approximately 120 million people worldwide. Systemic treatments have significantly improved disease burden, but concerns persist regarding their association with increased risk of malignancy. Patients with psoriasis have a slightly elevated baseline risk of lymphoproliferative diseases. Studies on methotrexate and cyclosporine and older biological agents such as tumor necrosis factor inhibitors have found no increased risk of non-cutaneous solid tumors. However, there are positive associations found between cutaneous squamous cell carcinomas and certain therapies. There is conflicting evidence regarding risk of lymphoma and melanoma. Further studies are needed to determine the long-term safety of newer psoriasis treatments (IL-12/23, IL-17, Janus Kinase 1/3, and phosphodiesterase-4 inhibitors) and, specifically, their safety in patients with a history of cancer. This review summarizes the most recent studies on malignancy risk from psoriasis and its treatments in patients and cancer survivors with highest available level of evidence.

1 Introduction

Psoriasis is a common inflammatory disease affecting 3.2% of the United States (US) adult population[1]. Systemic treatments such as methotrexate (MTX), cyclosporine (CsA), and biological agents: tumor necrosis factor alpha (TNFα) inhibitors, ustekinumab and newer biologics[2, 3] have significantly improved burden of disease in patients with moderate to severe psoriasis, improving quality of life[4–6]. A review on psoriasis treatment and malignancy risk was published in 2009[7]. Since then therapeutic options have expanded and additional safety data has become available. Herein, we summarize the most recent

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meta-analyses, randomized control trials (RCTs) and prospective cohort studies on malignancy risk from psoriasis and its treatments in patients and cancer survivors.

2 Baseline risk of malignancy in psoriasis patients

2.1 Systemic malignancies

Assessing baseline cancer risk in psoriasis is challenging as most studies include both treated and untreated patients. In 2001, Margolis *et al.* published a landmark study, comparing 17,000 psoriasis patients to patients with hypertension, revealing an increased risk ratio of overall malignancy in patients with severe psoriasis (1.78, 95% CI 1.3 to–2.40) [8]. Most cancers identified in this cohort were lymphoproliferative malignancies and nonmelanoma skin cancers (NMSC)[8], highlighting the increased risk of malignancy prior to the biologics era.

Gelfand *et al.* conducted a population-based cohort study revealing an increased relative risk (RR) for lymphoma (RR 2.95, 95% CI 1.83–4.76)[9] that persisted after adjusting for age, sex, MTX treatment, and development of mycosis fungoides. In a follow up study, they reported a positive association between psoriasis and lymphoma (adjusted hazard ratio, aHR 1.35, 95% CI 1.17–1.55) with strongest association between severe psoriasis with Hodgkin's lymphoma (aHR 3.18, 95% CI 1.01–9.97) and cutaneous T-cell lymphoma (CTCL aHR 10.75, 95% CI 3.89–29.76)[10], though the latter association may be a result of misdiagnosing CTCL as psoriasis. Brauchli *et al.* confirmed an elevated risk of lymphohematopoietic cancer (odds ratio, OR 2.12, 95% CI 1.45–3.10) and in a nested case–control analysis, found overall cancer risk was increased in patients who did not receive oral treatment and had disease duration ≥2 years (adjusted OR 1.31, 95% CI 1.16–1.48)[11].

Most recently, a prospective, population-based cohort study of 200,000 psoriasis patients revealed minimally increased risk for all cancers excluding NMSC (aHR 1.06, 95% CI 1.02–1.09) and for lymphoma (aHR 1.34, 95%CI 1.18–1.51)[12]. In a meta-analysis conducted in 2013, the overall malignancy risk was elevated but consistent with previous studies (standard incidence ratio, SIR 1.16, 95% CI 1.07–1.25) with SIR 1.4 (95% CI 1.06–1.86) for non-Hodgkin lymphoma (NHL)[13]. A retrospective cohort study in biologic-naïve pediatric psoriasis patients found no significant increase in overall cancer risk compared to a matched pediatric population with no psoriasis, however increased lymphoma rate was observed when compared with the general population (SIR 5.42, 95% CI 1.62–12.94) [14]. Evidence for increase risk of solid tumors is inconsistent, but has been previously reported[11, 13, 12, 15] (Table 1).

2.2 Cutaneous malignancies

Baseline risk of skin cancer in psoriasis patients is difficult to assess due to confounding from phototherapy and immunosuppressive therapy. The rate of NMSC is increased[16], supported by a meta-analysis reporting SIR 5.3 for squamous cell carcinoma (SCC) (95% CI 2.63–10.71) and SIR 2.00 for basal cell carcinoma (BCC) (95% CI 1.83–2.20), whereas risk of melanoma was not increased[13]. A large population based cohort study confirmed these results, finding an aHR of 1.12 for NMSC (95% CI 1.07–1.16) in the overall psoriasis group,

and 1.62 (95% CI 1.16–2.28) in patients with severe psoriasis[12]. A Danish cohort reported modestly increased melanoma risk in patients with mild psoriasis but not severe psoriasis[17].

3 Risk of cancer with psoriasis treatments

3.1 Phototherapy

Several studies found oral psoralen and ultraviolet A (PUVA) to be associated with increased risk of skin cancer in a dose dependent fashion[18–21] but not for non-cutaneous malignancies[22]. The risk of NMSC is greatest with >350 treatments, genital SCC risk is increased and persisted after cessation of treatment[23, 24]. Melanoma risk is increased with >250 treatments in the US[20], but not demonstrated in retrospective European studies with smaller numbers of patients enrolled or shorter follow up[24]. The risk of Merkel cell carcinoma is also increased[25].

No increase in skin cancer is noted with broadband or narrowband-UVB, especially in <100 treatments[26, 27, 24, 23, 28] or with bath PUVA[29]. However, in patients treated with broadband UVB with previous PUVA exposure, >300 UVB treatment exposure is associated with modest but significant increase in NMSC (SCC incidence rate ratio IRR 1.37, 95% CI 1.03–1.83; and BCC IRR 1.45, 95% CI 1.07–1.96)[30]. In summary, PUVA phototherapy increases risk for skin cancer in a dose dependent fashion.

3.2 Systemic nonbiologic therapies

MTX and CsA have been associated with an increased risk of malignancies. The association of these agents and lymphoproliferative disorders, including rare EBV-positive lymphoma, has been observed in small case reports and series[31–33]. While 30-year follow-up PUVA study found an elevated risk of lymphoma in MTX treated patients (≥ 36 months), the control was general population (IRR 4.39, 95% CI 1.59–12.06)[34]. Additionally, recent data shows that low-dose MTX treatment (≤30 mg/week oral or 17.5–22.5mg/week subcutaneously) monotherapy compared to placebo in patients with psoriasis and other diseases revealed no increased malignancy risk[35, 36]. Exposure to MTX in patients receiving PUVA was reported to be an independent risk factor for developing SCC (RR 2.1, CI 95% 1.4–2.8) with potential for metastatic disease[37]. Increased risk for NMSC was reported in rheumatoid arthritis (RA) and psoriatic arthritis patients taking MTX and concurrent CsA[38]. In a nationwide Swedish registry, a small risk for melanoma was observed in MTX-exposed patients, however diagnosis, length of exposure and dose were not reported (HR 1.17, 95% CI 1.08–1.26)[39]. The PSOLAR registry, a postmarketing cohort examining the safety of systemic treatments in psoriasis, found no increased risk of malignancy in patients treated with MTX (excluding NMSC).[40]

Paul *et al.* prospectively followed 1252 psoriasis patients treated with CsA for up to 5 years, and reported an increased overall malignancy risk compared to the general population (SIR 2.1). However, non-cutaneous malignancy incidence was not increased, and the risk was attributed to a 6-fold higher incidence of skin malignancies, mostly SCC, affected by longer duration of treatment (>2 years) and previous therapies (PUVA and MTX)[41], confirming

the conclusions from a nested cohort showing high SCC risk with CsA treated patients, particularly after PUVA exposure[42].

In summary, MTX and CsA are generally considered safe. There is an elevated risk of SCC associated with CsA and MTX, increased by PUVA exposure.

3.3 TNF-alpha inhibitors

3.3.1 Systemic malignancies—In 2006, a meta-analysis suggested an increased risk of malignancy with infliximab and adalimumab (OR 3.7, 95% CI 1.0–13.2) analyzing RA RCTs[43]. However, subsequent data has not confirmed these findings. An updated meta-analysis including 64 RCTs of RA patients found no increased risk (OR 0.98, 95% CI 0.51–1.9)[44]. Additional meta-analyses pooling together malignancy cases in TNFα-inhibitors in rheumatologic, inflammatory bowel diseases (IBD) and psoriasis patients, failed to reveal increased cancer risk (see Table 2). In pooled clinical trial analyses of all indications, anti-TNFα treated RA patients were found to have a higher incidence of lymphoma[45, 10, 46, 47] compared to the overall population, however there is confounding from increased baseline lymphoma risk in RA patients[48, 49, 46, 47]. In a meta-analysis with Crohn's disease patients, anti-TNFα treatments demonstrated an elevated NHL risk compared to the general population (SIR 3.23, 95% CI 1.5–6.9), but not when compared to immunomodulator treated patients[50], suggesting contributory roles of traditional immunosuppressive agents[51].

The risk of malignancy in anti-TNFα exposed psoriasis patients examined in a meta-analysis did not find any increased risk (OR 1.26, 95% CI 0.39–4.15)[52]. Pariser *et al.* studied the risk of malignancy and etanercept therapy in psoriasis patients by an integrated analysis of short-term placebo-controlled clinical trials and long-term uncontrolled open-label trials, revealing no increase of cancer incidence for etanercept compared to the control group and the overall population (RR 1.11, 95% CI 0.16–12.23 and SIR 1.2, 95% CI 0.8–1.6, respectively). The risk did not increase with increasing dosage or exposures[53]. The PSOLAR registry examined the safety of anti–TNFα agents and ustekinumab and reported that long-term (>=12 months) anti–TNFα therapy, but not shorter-term treatment, may increase malignancy risk, excluding NMSC (OR 1.54, 95% CI 1.10–2.15), however analyses performed for individual anti–TNFα agents were not statistically significant and a monotherapy analysis that excluded cases with multiple exposures to study agents, observed no elevated risk[40]. The OBSERVE-5, a 5-year surveillance registry, studied "real-world" etanercept use in psoriasis patients and found cumulative incidences of 3.2% for malignancies excluding NMSC (95% CI 2.3%–4.1%) and 0.1% for lymphoma (95% CI 0.0%–0.3%), which were not higher than expected (SIR <1)[54]. The safety of adalimumab in psoriasis patients was demonstrated by the initial 7-year results of the ESPRIT registry[55]. Studying a large healthcare delivery system database, systemic malignancy and lymphoma rates were not increased for biologics in psoriasis patients[56].

3.3.2 Non-melanoma skin cancer—Association between biologics and NMSC has been reported in RA and IBD patients [57–59]; however, several meta-analyses found no increased risk for NMSC[60, 52, 53, 44, 61, 62]. Additional studies have shown that anti-

TNFα treated patients were at increased risk for SCC but not BCC[45, 63]. Asgari *et al.* recently reported that NMSC rates were 42% higher among psoriasis patients ever exposed to biologics (HR 1.42, 95% CI 1.12–1.80), largely driven by SCC risk (HR 1.81, 95% CI, 1.23–2.67) and not BCC[56]. A comparison of NMSC risk in anti-TNFα exposed psoriasis versus RA patients showed a significantly higher risk in psoriasis patients (HR 6.0, 95% CI 1.6–22.4)[64] highlighting contributory roles of prior psoriasis therapies such as phototherapy. Prior or concurrent MTX treatment was reported to increase the risk of NMSC in RA [65, 66].

3.3.3 Melanoma—A meta-analysis investigating the risk of malignant melanoma and TNFα inhibitors found a non-significantly elevated risk (RR 1.79, 95% CI 0.92–2.67)[58]. A recent pooled-analysis of 11 European registries that included over 48,000 anti-TNFα treated RA patients did not reveal any elevated risk[67]. However, a meta-analysis of four studies found an increased risk of melanoma in RA patients treated with anti-TNFα compared to non-biologics (pooled effect estimate 1.60, 95% CI 1.16–2.19)[68]. Raaschou *et al.* found an increased risk of invasive melanoma in RA patients treated with anti-TNFα therapy (HR 1.5, 95% CI 1.0 to 2.2), but not melanoma in-situ[69]. Elevated risk of melanoma was also reported in IBD patients treated with TNFα inhibitors (OR 1.88, 95% CI 1.08–3.29)[70]. A retrospective single center study on anti-TNFα treated patients for any indication reported an increased risk of developing melanoma (RR 1.75, 95% CI 1.25–2.43) [71]. Safety data from clinical studies showed increased melanoma incidence in adalimumab treated psoriasis patients compared to the overall population (SIR 3.67[72]–4.37[47], 95% CI 1.47–7.57; 1.89–8.61), however in a large cohort, melanoma risk was similar for psoriasis patients treated with biologic and non-biologic therapies[56].

In summary, numerous recent meta-analyses, observational and cohort studies found no significantly increased risk of systemic malignancies, including lymphoma for anti-TNFα in psoriasis, providing reassurance regarding the widespread use of these agents. An increased risk of SCC has been confirmed by several studies, but there is conflicting evidence regarding risk for melanoma.

3.4 New biologics and small molecule inhibitors

The emergence of targeted biologics for psoriasis in recent years has greatly expanded the spectrum of therapeutic options. Current biologic targets of interest in psoriasis include IL-12, IL-23, IL-17, Janus Kinase, and Phosphodiesterase-4. IL-12 has demonstrated anti-tumor effects in mouse models via enhancement of both innate resistance and adaptive immunity [73]. IL-23 has predominantly anti-tumor effects in mouse models through IFN gamma and CD8+ T cell dependent pathways[74]. IL-17 is a pro-inflammatory cytokine that produces anti-tumor effects in immune-competent mice, but pro-tumor effects in immune-deficient mice[74]. The JAK-STAT pathway is responsible for the transduction of a myriad of extracellular signals, and dysregulation of this pathway has been linked to a variety of hematological malignancies[75]. Phosphodiesterase-4 has been shown to promote angiogenesis in both lung cancer and lymphoma models through elevation of cyclic-AMP[76, 77].

As with all new drugs, the robustness of safety profiles obtained from clinical trials data should not be broadly extrapolated as they have yet to be validated in a real-world setting. Table 3 summarizes incidence rates of malignancy for these newer treatments including biologics targeting IL 12/23 (ustekinumab)[78–83], IL-23 (guselkumab)[84, 85], IL-17 (ixekizumab, secukinumab)[86–88], and small molecule inhibitors of Janus kinase (tofacitinib)[89] and phosphodiesterase-4 (apremilast)[90–92]. Malignancy incidence rates for these therapies are less than or comparable to those seen in the psoriasis population (1.14 per 100 person-years) and general population (0.95 per 100 person-years) [16], but currently available evidence is not sufficient to draw conclusions on their safety. Long-term studies focused on safety surveillance are still lacking for these agents, especially ixekizumab, secukinumab, and apremilast, as well as data for their use in cancer patients and survivors.

4 Psoriasis treatments and malignancy risk in cancer patients and survivors

Evidence based data on the association between psoriasis systemic treatments and cancer recurrence is limited since patients with history of malignancies are usually excluded from participating in clinical trials and dermatologists are hesitant to initiate immunosuppressive agents in cancer survivors. Moreover, psoriasis flares have been noted with the advent of the new immune checkpoint inhibitors for malignant melanoma, such as ipilimumab[93], nivolumab and pembrolizumab[94], making treatment decisions challenging (Figure 1).

4.1 Systemic malignancies

A recent meta-analysis of cohort, case-control and case-series studies including 11,702 cancer survivors with RA, IBD and psoriasis treated with anti-TNFα agents, immunomodulator therapies (MTX or thiopurines) or no immunosuppression therapy, aimed to investigate cancer incidences[95]. Follow-up was 21–102 months with a median of 6 years between the index cancer and immunosuppression initiation. Cancer recurrence incidences were similar for anti-TNFs, immunosuppression therapy and no immunosuppression (33.8, 36.2 and 37.5 cancer recurrences or new primary cancer cases per 1000 patient years, PY). A non-significant higher incidence rate was revealed for combination immunosuppression therapy (54.5/1000 PY, P=0.47). Similar non-significant differences were identified when excluding skin cancers. Additional sub-analyses were performed: new cancer and recurrent cancer incidences, analyses by inflammatory disease and comparing thiopurines versus MTX, and none showed statistically significant differences between the groups[95]. A recent study of the British RA registry confirmed no increased risk of malignancy in cancer survivors with RA treated with TNFα inhibitors compared to non-biologics after a median follow-up of 6.8 years[96].

4.2 Cutaneous malignancies

A retrospective study of RA and IBD patients with NMSC history showed MTX use was associated with an increased risk of a second NMSC in RA (HR 1.60, 95% CI 1.08–2.37). The addition of an anti-TNFα agent increased the risk, as did longer MTX exposure[66]. No increased risk for a consecutive primary melanoma was found in patients with MTX-exposure[97]. A non-significant increased rate of a second melanoma was reported in RA

patients treated with anti-TNFα agents compared to non-biologics (HR 3.2, 95% CI 0.8–13.1)[69],[98]. Notably, use of infliximab and adalimumab for ipilimumab-induced colitis in advanced staged melanoma patients has been reported to have no effect on worsening prognosis and survival[99].

In the PSOLAR study, 3.8% of the psoriasis patients had history of systemic malignancy while 6.2% had skin cancer history. History of malignancy was reported to be associated with higher cancer rates in this cohort (HR 2.64, 95% CI 1.88–3.69)[83], however, malignancy recurrence rates were comparable in patients who were treated with biologic (anti–TNFα agents or ustekinumab) or non-biologic therapies (2.48 versus 3.78 per 100 PY, respectively)[100].

In summary, risk of new or recurrent systemic malignancies is similar between biologics and non-biologic treatments. Risk of additional NMSC in patients with history of NMSC may be increased; however data regarding additional primary melanomas and melanoma recurrence is inconclusive in melanoma survivors.

5 Conclusion

Based on the recent studies with a high level of evidence, we conclude that there is little evidence of an association between non-cutaneous malignancies and the reviewed psoriasis treatments, regardless of a history of prior cancer. There is conflicting data regarding risk of melanoma in patients treated with anti-TNFα agents. There is an elevated risk of SCC for both anti–TNFα agents and non-biologic therapies that increased with PUVA exposure and/or immunosuppressive treatments. Our conclusions are based on meta-analyses from the rheumatology, gastroenterology and dermatology literature that compared treated patients to control patients rather than general population, thereby eliminating possible confounding from baseline malignancy risk of the inflammatory disease[101]. Results from meta-analyses are limited by relatively short exposure and follow-up periods, but large observational and cohort studies confirm these findings. New or recurrent cancer incidence rates are modest and should be weighed against the advantage of controlling disease in psoriasis patients. The newer biologic and non-biologic agents seem promising and effective, however, additional studies are needed to evaluate malignancy risk in these agents.

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Key points

- Psoriasis and some of its treatments have been associated with increased malignancy risk.
- Summarizing the most recent studies with highest available level of evidence on malignancy risk from psoriasis and its treatments in patients and cancer survivors, we found little evidence suggesting increased risk of non-cutaneous solid tumors with psoriasis treatments or lymphoma from TNF inhibitors.
- Based on high-level evidence, psoriasis therapies appear safe. Additional long-term data is warranted for newer treatments and for their use in cancer survivors.

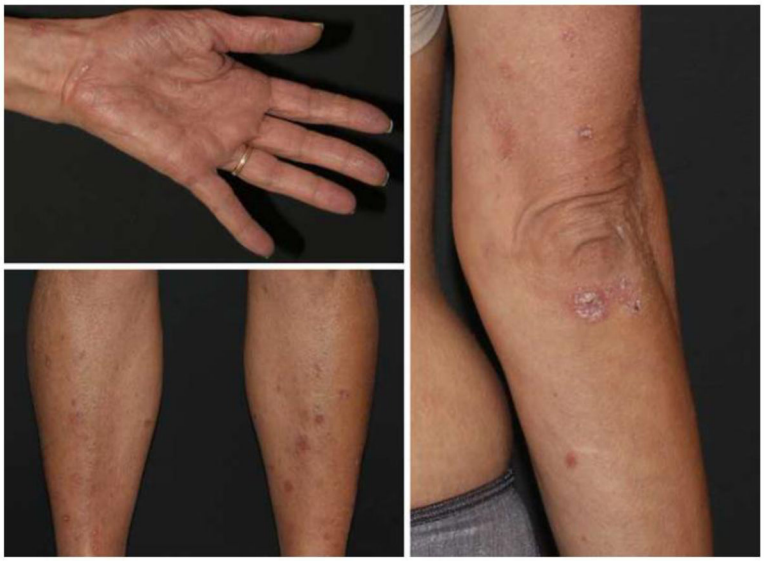

Figure 1. Immunotherapy induced psoriasis

54 year-old female with no prior history of psoriasis, developed numerous scaly erythematous papules and plaques on her limbs including the palms and the trunk. The rash appeared after starting therapy with nivolumab (anti-PD-1) and varlilumab (anti-CD27) therapy for recurrent glioblostoma. Histology of the scaly plaque on the elbow confirmed the diagnosis of psoriasis.

Table 1

Baseline risk of systemic malignancies stratified by organ systems

Type of cancer	Study design	Malignancy risk (95% CI)	Comments
Any lymphoma	Population-based retrospective cohort study[10]	aHR 1.34 (1.16–1.54)	Mild psoriasis
	Observational study with nested case-control analysis[11]	IRR 1.76 (1.19–2.58)	Moderate to severe psoriasis
	Population-based prospective cohort study[12]	aHR 1.86 (1.23–2.80)	
	Retrospective cohort study[14]	SIR 5.42 (1.62–12.94)	biologic-naïve pediatric patients
Any lymphoma excluding CTCL	Observational study with nested case-control analysis[11]	IRR 1.55 (1.03–2.31)	Moderate to severe psoriasis
	Population-based prospective cohort study[12]	aHR 1.62 (1.16–2.28)	
Non Hodgkin's lymphoma	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.40 (1.06–1.86)	
	Population-based retrospective cohort study[10]	HR 1.14 (0.96–1.35)	Excluding CTCL, moderate to severe psoriasis
	Population-based cohort study[15]	HR 1.03 (0.59–1.75)	Mild to severe psoriasis
Leukemia	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.84 (0.78–4.34)	High heterogeneity of included studies
	Observational study with nested case-control analysis[11]	IRR 1.89 (1.21–2.94)	
	Population based prospective cohort study[12]	aHR 1.05 (0.67–1.65)	Moderate to severe Psoriasis
Hodgkins Lymphoma	Population-based retrospective cohort study[10]	HR 1.42 (1.00–2.02)	Patient cohort without systemic treatments
	Retrospective cohort study[102]	SIR 3.3 (1.4–6.4)	Hospitalized patients, did not control for systemic medications
CTCL	Population based retrospective cohort study[10]	aHR 4.34 (2.89–6.52)	Moderate to severe psoriasis group
	Population based prospective cohort study[12]	aHR 9.25 (3.69–23.22)	Possibly secondary to misclassification
Lung	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.52 (1.35–1.71)	No adjustment for smoking
	Population based prospective cohort study[12]	aHR 1.60 (1.14–2.24)	Persistent after adjustment for smoking
	Observational study with nested case-control analysis[11]	IRR 0.79 (0.6–1.06)	
	Population-based cohort study[15]	HR 1.05 (0.61–1.79)	Mild to severe psoriasis
Upper aerodigestive Tract	Systematic review and meta-analysis of epidemiological studies[13]	SIR 3.05 (1.74–5.32)	No adjustment for smoking
	Observational study with nested case-control analysis[11]	IRR 1.36 (0.72–2.54)	Mean follow up of 4.6 years, young age at diagnosis, adjusted for smoking
Pancreas	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.46 (1.10–1.95)	
	Observational study with nested case-control analysis[11]	IRR 2.20 (1.18–4.09)	Trend to increase with longer duration of disease

Type of cancer	Study design	Malignancy risk (95% CI)	Comments
	Population based prospective cohort study[12]	aHR 1.29 (0.64–2.61)	Moderate to severe Psoriasis
Liver	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.90 (1.48–2.44)	
Digestive tract	Population based retrospective cohort study[103]	RR 1.57 (1.41–1.74)	Taiwanese population
	Population based retrospective cohort study[104]	HR 2.02 (1.33–3.07)	Taiwanese population
Kidney/Uri nary Tract	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.31 (1.11–1.55)	
	Population based retrospective cohort study[104]	HR 3.18 (1.54–6.57)	Taiwanese population
	Observational study with nested case-control analysis[11]	IRR 1.25 (0.84–1.85)	Trend to increase with longer duration of disease
	Population-based cohort study[15]	HR 2.5 (1.27–4.92)	Mild to severe psoriasis
Breast	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.15 (1.02–1.29)	
	Observational study with nested case-control analysis[11]	IRR 1.04 (0.83–1.31)	Cohort with minimal systemic treatment
	Population based prospective cohort study[12]	aHR 0.96 (0.71–1.28)	Moderate to severe Psoriasis
	Population-based cohort study[15]	HR 0.89 (0.71–1.10)	Mild to severe psoriasis
Colorectal	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.12 (0.95–1.32)	
	Population based prospective cohort study[12]	aHR 1.20 (0.82–1.74)	Moderate to severe Psoriasis
	Observational study with nested case-control analysis[11]	IRR 1.35 (0.97–1.90)	Trend to increase with longer duration of disease
	Population-based cohort study[15]	HR 1.11 (0.71–1.73)	Mild to severe psoriasis
CNS	Systematic review and meta-analysis of epidemiological studies[13]	SIR 1.24 (CI 0.98–1.59)	
	Observational study with nested case-control analysis[11]	IRR 1.30 (0.69–2.45)	Cohort with minimal systemic treatment
Prostate	Observational study with nested case-control analysis[11]	IRR 0.84 (0.63–1.12)	
	Population based prospective cohort study[12]	aHR 1.16 (0.90–1.50)[12]	Moderate to severe Psoriasis
Female genital organs	Observational study with nested case-control analysis[11]	IRR 1.38 (0.91–2.11)[11]	
	Population-based cohort study [15]	HR 0.54 (0.26–1.15) endometrial; HR 1.28 (0.56–2.88) ovarian	Mild to severe psoriasis
Melanoma	Systematic review and meta-analysis of epidemiological studies[13]	aHR 1.07 (0.85–1.35)	
	Observational study with nested case-control analysis[11]	IRR 0.83 (0.50–1.36)	
	Population based prospective cohort study[12]	aHR 1.28 (0.82–1.99)	Moderate to severe Psoriasis
	Population based retrospective cohort study[17]	IRR 1.19 (1.03–1.37);	Significant in mild psoriasis and not in severe psoriasis

Type of cancer	Study design	Malignancy risk (95% CI)	Comments
		IRR 1.09 (0.75–1.58)	
	Population-based cohort study[15]	HR 1.95 (1.21–3.13)	Mild-to-severe psoriasis

aHR = adjusted hazard ratio; CI = confidence interval; CNS = central nervous system; CTCL = cutaneous T-cell lymphoma; IRR = incidence rate ratio; HR = hazard ratio; SIR = standard incidence ratio.

Table 2

Meta-analyses studies reporting on the malignancy risk of anti-TNFα therapy

Studied agents and population	All malignancy risk (95% CI)	Malignancy risk excluding NMSC (95% CI)	Specific malignancy risk (95% CI)
Adalimumab infliximab in RA[43]	OR 3.3 (1.20–9.10)	OR 3.7 (1.00–13.20)	
Adalimumab infliximab etanercept in RA[105]	RR 1.5 (0.80–3.00)		
Adalimumab infliximab etanercept in RA[60]	OR 1.34 (0.75–2.39)	OR 1.31 (0.69–2.48)	NMSC OR 1.27 (0.67–2.42) Lymphoma OR 1.26 (0.52–3.06)
Etanercept in RA[106]	HR 1.84 (0.79–4.28)	HR 1.86 (0.62–5.59)	
Adalimumab infliximab etanercept in RA[107]	Adalimumab risk ratio 0.55 (0.14–2.11) Etanercept risk ratio 0.98 (0.32–3.02) Infliximab risk ratio 1.64 (0.30–8.89)		
Adalimumab certolizumab etanercept golimumab infliximab in Pso, PsoA[52]	OR 1.48 (0.71–3.09)	OR 1.26 (0.39–4.15)	NMSC OR 1.33 (0.58–3.04)
TNF inhibitors in AS, PsoA, RA[58]	RR 0.95 (0.85–1.05)		NMSC RR 1.45 (1.15–1.76) Melanoma RR 1.79 (0.92–2.67) Lymphoma RR 1.11 (0.70–1.51)
Adalimumab infliximab etanercept in AS, CD, Pso, PsoA, RA[59]	RR 1.30 (0.89–1.95)	RR 0.99 (0.61–1.68)	NMSC RR 2.02 (1.11–3.95)
Adalimumab certolizumab etanercept golimumab infliximab in RA[108]	OR 1.08 (0.50–2.32)		
Adalimumab infliximab etanercept in RA[109]			Lymphoma adjusted rate difference 1.29/1,000 person-years (−0.21–2.79)
Adalimumab certolizumab etanercept golimumab infliximab in RA[44]	OR 0.98 (0.51–1.90)		NMSC OR 1.37 (0.59–3.19) Melanoma OR 1.08 (0.11–10.21) Solid tumors OR 1.31 (0.78–2.20) Lymphoma OR 2.14 (0.55–8.38) Other hematologic malignancies OR 5.30 (0.80–34.99) Unspecified malignancies OR 0.39 (0.07–2.16)
Adalimumab certolizumab etanercept golimumab infliximab in RA[61]	OR 0.93 (0.59–1.44)		NMSC OR 1.37 (0.71–2.66) Solid tumors OR 0.90 (0.57–1.42) Hematologic malignancies OR 0.62 (0.31–1.24)
Certolizumab golimumab in RA[62]		OR 1.06 (0.39–2.85)	NMSC OR 0.69 (0.23–2.11)
Adalimumab certolizumab golimumab infliximab in IBD[110]	RR 0.77 (0.37–1.59)	RR 0.90 (0.40–2.02)	
Adalimumab certolizumab etanercept golimumab infliximab in AS, PsA, AR[111]	OR 1.31 (0.89 – 1.95)		

Studied agents and population	All malignancy risk (95% CI)	Malignancy risk excluding NMSC (95% CI)	Specific malignancy risk (95% CI)
TNF inhibitors in RA[68]			Melanoma Pooled effect estimate 1.60 (1.16–2.19)

CD = Crohn's disease; CI = confidence interval; AS = ankylosis spondylitis; IBD = inflammatory bowel disease; NMSC = non-melanoma skin cancer; OR = odds ratio; Pso = psoriasis; RA = rheumatoid arthritis; PsA = psoriatic arthritis; RR = risk ratio.

Table 3

Malignancy incidence rates of new biologics and small molecule inhibitors

Study agent (mechanism of action)	Study design	Number of patients receiving drug of interest	Follow up time	Malignancy Risk (excluding NMSC) IR per 100 PY (95% CI)	NMSC Risk IR per 100 PY (95% CI)	Pro-tumor or anti-tumor effects of agent target in preclinical studies
Ustekinumab (IL-12/23 inhibitor)	Pooled analyses of clinical trials and LTEs[82]	3117	Up to 5 years	0.60 (0.45–0.78)	0.52 (0.39–0.70)	IL-12 has anti-tumorigenic functions[73] IL-23 has mostly anti-tumorigenic functions[74]
	Postmarketing cohort study[83]	4364	Up to 7 years	0.48 (95% CI not given)	Not given	
Guselkumab (IL 23 inhibitor)	Pooled Phase 3 trial[84, 85]	825	Up to 48 weeks	Not given (3 cases of malignancy)	Not given (3 cases of NMSC)	
Ixekizumab (IL-17 inhibitor)	Pooled analyses of phase 3 trials[86]	3736	Up to 60 weeks	0.40 (0.20–0.70)	0.60 (0.40–0.90)	IL-17 has both anti- and pro-tumorigenic effects[74]
	Pooled analyses of clinical trials[88]	4209	Up to 264 weeks	0.50 (95% CI not given)	0.40 (95% CI not given)	
Secukinumab (IL-17 inhibitor)	Pooled analyses of phase 2 and phase 3 trials[87]	3430	Up to 52 weeks	0.48 (0.25–0.82)	0.48 (0.25–0.82)	
Tofacitinib (JAK 1/3 inhibitor)	Pooled analyses of phase 3 trials and LTEs[89]	1861	Up to 33 months	1.15 (0.78–1.63)	0.71 (0.43–1.10)	Dysregulation of JAK pathway is associated with hematologic malignancies [75]
Apremilast (PDE-4 inhibitor)	Pooled analyses of phase 3 trials[92, 91]	1184	Up to 52 weeks	Not given (0 cases of malignancy)	Not given (2 cases of NMSC)	Mostly pro-tumorigenic effects [76, 77]
	Single phase 3 trial[90]	83	Up to 52 weeks	Not given (0 cases of malignancy)	Not given (0 cases of NMSC)	

CI = confidence interval; IL = interluken; IR = incidence rates; JAK = Janus kinase; LTEs = long-term extension studies; NMSC = non-melanoma skin cancer; PDE-4 = phosphodiesterase-4; PY = patient years