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Current Biological Therapies and Malignancy Risk

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Abstract

Background. The landscape of treatment for chronic inflammatory diseases has been fundamentally transformed by biological therapies and small-molecule inhibitors, yet concerns regarding their long-term safety and malignancy risk remain a focal point of clinical discussion. This review evaluates the oncogenic risk associated with major therapeutic classes, including TNF-α inhibitors, interleukin inhibitors, B-cell depleting agents and Janus kinase inhibitors. Evidence suggests that while some agents, like TNF-α inhibitors and JAK inhibitors, may be associated with an increased incidence of certain skin cancers or lymphomas in specific populations, other classes such as IL-17 and IL-23 inhibitors maintain a favorable safety profile. Furthermore, the paper highlights that effective control of chronic inflammation can paradoxically reduce the risk of inflammation-driven malignancies like colorectal cancer. The review concludes with updated screening recommendations, emphasizing the necessity of routine dermatological and gynecological surveillance to balance therapeutic efficacy with oncological safety.

Aim. The aim of this review is to evaluate the malignancy risks of major therapeutic classes, including TNF-α, interleukin and JAK inhibitors. The focus is placed on clinically significant cancers like HSTCL and skin malignancies, while assessing modifying factors such as age and cumulative exposure.

Material and methods. This work was conducted as a narrative review of literature. The search included clinical trials, meta-analyses and observational data from databases like PubMed and the Cochrane Library. Results were synthesized narratively due to study heterogeneity and methodological constraints like selection bias and short follow-up periods.

Results. TNF-α and JAK inhibitors are associated with an increased risk of NMSC and certain lymphomas. In contrast, IL-17 and IL-23 inhibitors show a safety profile consistent with baseline population rates. HSTCL is almost exclusively linked to combination therapy with thiopurines. Effectively neutralizing chronic inflammation can paradoxically reduce the risk of certain cancers, such as colorectal cancer.

Conclusions. Biological therapies generally do not increase the risk of solid tumors above baseline levels. Aggressive risks are often driven by concomitant therapies or underlying disease rather than biologics alone. Regular dermatological and gynecological screening is essential for maintaining oncological safety during treatment.

Key words: Biological therapy, Malignancy risk, TNF-alpha inhibitors, Interleukin inhibitors.

1. Introduction

The landscape of treatment for chronic inflammatory diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and psoriasis, has been fundamentally transformed by the advent of biological therapies and small-molecule inhibitors (Imam, 2024). By targeting specific cytokines and signaling pathways, such as Tumor Necrosis Factor-alpha (TNF-α), various interleukins (IL-12, IL-17, IL-23) and the Janus kinase (JAK) family, these agents provide significant clinical remission where conventional therapies often fail (Fragoulis et al., 2023; Imam, 2024). However, because these therapies modulate the immune mechanisms responsible for immunosurveillance, concerns regarding their long-term safety, particularly the risk of malignancy, remain a focal point of clinical discussion (Russell et al., 2023).

The relationship between biologic agents and cancer is multifaceted. On one hand, chronic systemic inflammation is a well-established driver of genomic instability and tumorigenesis; thus, effective control of inflammation may theoretically reduce the baseline risk of certain malignancies (Imam, 2024). On the other hand, inhibition of key cytokines, such as TNF-α, which plays a central role in antitumor immune surveillance, may create conditions that favor lymphomagenesis or the progression of solid tumors (Imam, 2024; Phillips, 2020). Recent data from large-scale trials, such as ORAL Surveillance, have further intensified this debate by indicating a higher incidence of malignancies in certain high-risk populations treated with JAK inhibitors (JAKi) compared to those on TNF-inhibitors (TNFi) (Russell et al., 2023).

This review aims to provide a comprehensive review of the current evidence surrounding malignancy risks of major therapeutic classes, including TNF-α inhibitors, interleukin (IL) inhibitors, B-cell depleting agents and JAKi. Specific focus is placed on malignancies of high clinical significance, such as Hepatosplenic T-cell Lymphoma (HSTCL), a rare but often fatal complication predominantly associated with combination therapy in younger male patients (Shah et al., 2020), as well as melanoma and non-melanoma skin cancers (NMSCs). Furthermore, this paper evaluates the influence of modifying factors such as age, sex and cumulative exposure time, while addressing the inherent limitations of available longitudinal data. Finally, we provide updated screening and monitoring recommendations to assist clinicians in balancing therapeutic efficacy with oncological safety.

2. Research materials and methods

This work was conducted as a narrative review of literature. The aim of the review was to provide a comprehensive evaluation of the current evidence surrounding malignancy risks of major therapeutic classes, including TNF-alpha inhibitors, interleukin inhibitors, B-cell depleting agents and Janus kinase inhibitors. The literature search was performed in medical databases including PubMed and the Cochrane Library, utilizing a wide range of studies and systematic reviews. The search strategy focused on identifying clinical trials, large-scale observational studies and meta-analyses exploring the association between biological therapies as well as oncogenesis.

The search covered publications including recent data from 2024 to early 2026 to ensure the inclusion of the latest clinical findings and meta-analyses. In addition, global safety

databases and FDA registry analyses were examined. Publications in English were included. Owing to the methodological constraints and inherent heterogeneity across available studies, such as varying inclusion criteria, selection bias in randomized controlled trials and abbreviated follow-up periods, findings were synthesized narratively to balance therapeutic efficacy with long-term oncological safety.

3. Molecular Mechanisms of Immunomodulation and Oncogenesis

3.1 The Role of TNF-alpha in Tumor Suppression

Tumor necrosis factor-alpha is a pleiotropic cytokine composed of 157 amino acids that forms a biologically active homotrimer (Horiuchi et al., 2010). TNF-α is primarily produced by immune cells, such as monocytes and macrophages, but other cell types, including acinar cells, can also secrete this cytokine. Engagement of TNF-α with its receptors activates multiple downstream pathways, leading to cytokine production, upregulation of adhesion molecules and release of procoagulant mediators (Leone et al., 2023). The production of TNF-α and other inflammatory cytokines, such as IL-1β and IL-6 by malignant cells is a downstream consequence of multiple oncogenic alterations. This suggests that inflammatory processes are embedded in tumor development and progression (Mantovani et al., 2008).

The concentration of serum TNF-α serves as a significant prognostic indicator, where elevated levels typically signal a more aggressive disease course and a higher risk of complications. In a wide array of malignant conditions, researchers have observed that as the cytokine’s presence in the bloodstream increases, the likelihood of a positive clinical response or long-term survival diminishes. Consequently, this inverse relationship suggests that monitoring TNF-α levels can provide critical insights into a patient's overall trajectory and the potential severity of the malignancy (Balkwill, 2009).

A range of therapeutic strategies has been developed to neutralize TNF-α, spanning from targeted biologics, such as monoclonal antibodies, soluble receptors and receptor fusion proteins, to genetic interventions like adenoviral-mediated blockade and small interfering RNA (siRNA). Additionally, small-molecule inhibitors and non-specific agents, including pentoxifylline, thalidomide and metalloproteinase inhibitors offer alternative pathways for TNF-α suppression (Esposito & Cuzzocrea, 2009).

TNF-α plays a dual role in modulating the tumor microenvironment, it not only drives the expansion of effector regulatory T cells via tumor necrosis factor receptor 2 (TNFR2) signaling, but also significantly bolsters their ability to suppress the antitumor activity of CD8+ T cells. By leveraging this pathway, researchers have found that targeting TNFR2 with a TNF-α inhibitor can selectively prevent the rapid rebound of suppressive regulatory T cells following cyclophosphamide-induced lymphodepletion (Chang et al., 2015). Blockade of TNF-α signaling benefits cancer therapy by suppressing effector regulatory T cell expansion. This targeted inhibition effectively breaks the cycle of immune evasion, leading to a marked reduction in the growth of established tumors and shifting the balance back toward a robust immune response. However, while phase I and phase II clinical trials have explored the therapeutic potential of TNF-α antagonists as monotherapies, the objective results across various patient cohorts have remained relatively modest. Despite the strategic attempt to neutralize this cytokine's pro-tumor effects, the majority of participants failed to achieve significant tumor regression, with only a limited subset of individuals reaching a state of stable disease (Woyach et al., 2009). Moreover, TNF-α inhibitors were also associated with several adverse effects, including neurological disorders, drug-induced lupus and an increased risk of infections, particularly the reactivation of latent tuberculosis (Iannone et al., 2014).

3.2 Interleukin-12/23 and Interleukin-17 Pathways

The IL-17 and IL-23 cytokine groups are vital components of the body's immune system, serving as essential bridges between our immediate defenses and our immunity. These cytokines function as powerful signaling molecules that coordinate how the body recognizes and reacts to threats (Iwakura, 2006). IL-12 exerts a profound influence on immune regulation by orchestrating the differentiation of naive CD4+ T cells into IFNγ-producing Th1 cells. This critical lineage commitment is fundamentally driven by the activation of specific intracellular pathways, primarily governed by the transcription factors STAT4 and T-bet. By directing this process, IL-12 acts as a primary catalyst for cell-mediated immunity, ensuring the body produces the specialized effector cells necessary to combat intracellular pathogens and tumors (Szabo et al., 2000). A study employing IL-12–producing B16 melanomas demonstrated that innate lymphoid tissue-inducer cells mediated tumor suppression, highlighting the pleiotropic capacity of IL-12 to engage multiple arms of antitumor immunity (Eisenring et al., 2010).

Chan et al. demonstrated that the expression of IL-23 alone was sufficient to trigger the rapid *de novo* formation of intestinal adenomas in murine models, reaching an incidence rate of 100% within just three to four weeks. Remarkably, this tumorigenic process was driven by type 3 innate lymphoid cells and occurred entirely independently of external factors, such as exogenous carcinogens, *Helicobacter* colonization or pre-existing mutations in tumor suppressor genes. These findings highlight IL-23 as a potent, autonomous driver of colorectal oncogenesis, capable of bypassing the traditional requirements for environmental or genetic triggers (Chan et al., 2014). Research has demonstrated that the neutralization of IL-23 significantly suppresses the formation of experimental lung metastases in multiple cancer models, including B16F10 melanoma, RM-1 prostate carcinoma and 3LL lung carcinoma. Interestingly, the anti-metastatic effect in these models is primarily mediated by host NK cells rather than CD8+ T cells. This suggests that IL-23 acts as a key negative regulator of innate surveillance and its inhibition can empower the innate immune system to effectively intercept and eliminate circulating tumor cells before they establish metastatic niches (Teng et al., 2011).

IL-17 is recognized as a central orchestrator of the immune response, largely due to its ability to drive the production of potent inflammatory mediators. These signals specifically stimulate the expansion and tissue infiltration of myeloid cells, most notably neutrophils, which are essential for mounting an effective defense against pathogens. By mobilizing these innate immune effectors to the site of injury or infection, IL-17 effectively bridges the gap between initial recognition and a robust, systemic inflammatory response (Veldhoen, 2017). IL-17 mobilizes myeloid cells through a two-step process. Specifically, IL-17 induces granulocyte colony-stimulating factor (G-CSF) expression, thereby promoting the expansion of granulocytes (Chung et al., 2013).

4. Risk Assessment

4.1 TNF-Alpha Inhibitors

Since the introduction of anti-TNF agents, an increasing number of reports have documented malignancies arising after treatment initiation, raising concerns that, despite their therapeutic benefits, these agents may be associated with an increased risk of malignancy.

The administration of etanercept has been linked to an increased risk of solid organ malignancies in patients undergoing treatment for granulomatosis with polyangiitis. Specifically, clinical data revealed that 6 out of 89 patients receiving etanercept in combination with standard cyclophosphamide therapy developed solid tumors over a median follow-up of 27 months. In stark contrast, no malignancies were observed in the control group receiving cyclophosphamide alone ($P = 0.01$). The observed cases were diverse in pathology, including two instances of colon adenocarcinoma, as well as individual cases of cholangiocarcinoma, renal cell carcinoma, breast cancer and liposarcoma. These findings suggest that the adjunctive use of TNF inhibitors in this specific clinical context may significantly elevate oncogenic risk ("Etanercept plus Standard Therapy for Wegener's Granulomatosis," 2005).

A meta-analysis encompassing nine clinical trials of anti-TNF-α therapy in patients with RA also identified a significant elevation in the risk of malignancy. The study reported that patients treated with infliximab or adalimumab faced an increased odds ratio (OR) of 3.3 for developing cancer, a risk that was particularly pronounced in those receiving higher therapeutic doses (Bongartz et al., 2006).

Anti-TNF-α therapy has also been linked to an increased incidence of melanoma and nonmelanoma skin cancers. A large-scale observational study involving 13,001 patients identified a specific association between anti-TNF-α therapy and an increased risk of NMSC with the OR of 1.5 (Wolfe & Michaud, 2007).

4.2 Interleukin Inhibitors

Biologic agents targeting the IL-17 and IL-23 pathways significantly enhance the quality of life for patients with psoriasis and other autoimmune disorders. These therapies offer high clinical efficacy alongside a favorable safety profile.

Strober et al. determined that in patients treated with ixekizumab, a IL-17A inhibitor, the incidence of malignancies excluding NMSC was consistent with the expected baseline rates for the psoriasis population. Furthermore, these rates were found to be comparable to those observed in patients receiving etanercept during the induction phase. These findings suggest that ixekizumab maintains a safety profile regarding oncogenic risk (Strober et al., 2017).

In a systematic review conducted by Peleva et al., the compiled data from multiple studies and reviews indicated that the long-term administration of IL-23 inhibitors, such as ustekinumab, was not associated with an elevated risk of malignancy (Peleva et al., 2018).

According to Hasan et al., ustekinumab, a IL-12/23 inhibitor, does not significantly elevate the risk of developing new or recurrent malignancies in patients with IBD who have a history of cancer (Hasan et al., 2022).

4.3 B-Cell Depleting Agents

Rituximab and ocrelizumab are the anti-CD20 monoclonal antibodies. The potent efficacy of these agents in depleting B-cell compartments has led to their widespread use in managing a diverse array of autoimmune diseases. By targeting and removing pathogenic B cells, these therapies effectively interrupt the chronic inflammatory cycle across multiple clinical conditions. The protective synergy between CD20+ B cells and cytotoxic T cells is fundamental to antitumor immunity. Research indicates that the timing of anti-CD20 therapy is a decisive factor in oncogenic outcomes. In murine models, initiating treatment prior to tumor formation appeared to reduce metastatic potential, whereas administering therapy after tumor establishment paradoxically accelerated tumor growth and decreased survival by facilitating metastasis (Melamed & Lee, 2020).

Malignancy rates of the rituximab were analyzed using the global safety database and data from the RA clinical trial program, which included eight randomized trials, two long-term extensions and one prospective study. No evidence of an increased risk for any organ-specific malignancy was shown. The observed malignancy rate of 7.4 per 1,000 patient-years remains within the expected range for this population, with no significant escalation in risk over time or repeated treatment courses. These findings support the long-term oncogenic safety profile of rituximab in the management of RA (Emery et al., 2020).

Despite its generally favorable safety profile, some data suggests a potential association between ocrelizumab and a heightened risk of breast cancer. Clinical trial and open-label extension data through January 2020 recorded a malignancy rate of 0.46 events per 100 patient-years, an incidence that remains within baseline epidemiological expectations (Hauser et al., 2021). Nevertheless, due to these concerns, ocrelizumab is contraindicated in the European

Union for patients with known active malignancies, reflecting a targeted regulatory caution regarding its impact on existing oncogenic processes.

4.4 Janus kinase inhibitors

Janus kinase molecules are essential mediators in cellular activation pathways. The mechanism of action for JAK inhibitors centers on their ability to precisely modulate the JAK-STAT (Signal Transducer and Activator of Transcription) signaling pathway. Over the last decade, JAKi have emerged as highly promising targeted therapies, playing a pivotal role in the modern treatment of various inflammatory and autoimmune diseases.

Evidence regarding the oncogenic risk of JAKi relative to other therapies remains nuanced. According to Russell et al., network meta-analyses indicate that the incidence of all malignancies, including NMSCs, does not differ significantly when comparing JAKi to either a placebo (incidence rate ratio (IRR) 0.71; 95% confidence interval (CI) 0.44-1.15) or methotrexate (IRR 0.77; 95% CI 0.35-1.68). However, when evaluated against TNFi, JAKi were associated with a statistically significant increase in malignancy incidence, with an IRR of 1.50 (95% CI 1.16-1.94) (Russell et al., 2023). Conversely, Yang et al. reported that JAKi did not significantly elevate the risk of overall cancers compared to TNFi (pooled HR: 1.06; 95% CI 0.81-1.37), though the certainty of evidence was rated as very low. Their secondary outcome analysis did, however, identify a specific increase in the risk of NMSC (HR: 1.21; 95% CI 1.03-1.41), suggesting that while the broad systemic cancer risk may be comparable to biologics, a localized vulnerability to skin malignancies may persist (Yang et al., 2026).

5. Specific Malignancies of Concern

5.1 Hepatosplenic T-cell Lymphoma

A rare but often fatal malignancy is associated with the combination of anti-TNF drugs and thiopurine, particularly in young male patients with Crohn’s disease. This has led to a clinical shift toward monotherapy or alternative biological treatment.

The risk of lymphoma in patients with IBD is significantly modulated by the choice of therapeutic regimen, as evidenced by a nationwide cohort study of approximately 190,000 patients. Lemaitre et al. demonstrated that while thiopurine and anti-tumor necrosis factor monotherapies present statistically significant increase in lymphoma risk (adjusted hazard ratios (HR) of 2.60 and 2.41, respectively), this risk is substantially amplified during combination therapy, reaching an adjusted HR of 6.11 (Lemaitre et al., 2017). This elevation in risk is a critical factor in clinical decision-making, particularly regarding the prevention of HSTCL, a rare but highly aggressive malignancy.

The pathogenesis of HSTCL in the context of IBD appears inextricably linked to thiopurine exposure rather than biological treatment in monotherapy. Systematic reviews and FDA database analyses by Kotlyar et al. and Shah et al. have confirmed that HSTCL develops almost exclusively in patients undergoing chronic thiopurine monotherapy or combination therapy involving thiopurines and TNFi (Kotlyar et al., 2011; Shah et al., 2020). There are no documented cases of HSTCL in patients treated exclusively with anti-TNF agents (Kotlyar et al., 2011; Shah et al., 2020). Furthermore, newer generations of biologics, including vedolizumab and ustekinumab, maintain a high safety profile. Only rare lymphoma cases were reported during their use and have been limited to patients with prior histories of classic immunosuppressant and anti-TNF exposure (Shah et al., 2020).

HSTCL mostly affects young males under 35 years old, with a reported median age of 28 years (Kotlyar et al., 2011; Shah et al., 2020). Schwartz et al. highlighted that this demographic profile requires additional caution when prescribing immune-modifying therapies to young males, as they represent a susceptible group (Schwartz et al., 2025).

The clinical prognosis for HSTCL remains extremely poor, with a five-year survival rate. The management of this malignancy is further complicated by the frequent onset of hemophagocytic syndrome, a potentially fatal complication that drastically shortens survival. While Chen et al. noted that combined systemic chemotherapy following splenectomy may offer improved outcomes compared to chemotherapy alone, the disease remains refractory to current treatment modalities (Mingyue-Chen et al., 2024).

5.2 Malignant Melanoma

While the link between biological therapies and malignant melanoma is considered less definitive than other skin cancers, its potential severity warrants clinical caution (Budiasih &

Handrean, 2025; Johnson et al., 2017; Kerbleski & Gottlieb, 2009). Epidemiological data from a comprehensive cohort study indicates that while RA itself does not intrinsically raise melanoma risk compared to the general population, patients treated with TNFi demonstrate a 50% increased relative risk of developing invasive melanoma (J. Wolfe, 2013). This is further supported by clinical case reports detailing the onset of melanoma and potential melanocytic proliferation following prolonged exposure to anti-TNF drugs, such as adalimumab and infliximab (J. Wolfe, 2013).

The pathophysiology of this increased melanoma risk is complex and heavily influenced by ultraviolet (UV) radiation exposure. Systemic TNF inhibition fundamentally alters the native cutaneous response to UV radiation (Budiasih & Handrean, 2025). Endogenous TNF-α normally serves as an early mediator in the UV-induced inflammatory cascade, activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways that upregulate microphthalmia-associated transcription factor (MITF) and drive protective melanin synthesis (Budiasih & Handrean, 2025). Because naturally occurring TNF-α drives this cycle of protective pigment production, using medications to block this protein can fundamentally change how the skin reacts to UV radiation, potentially leading to irregular pigmentation and atypical melanocyte activity (Budiasih & Handrean, 2025).

Despite these concerns, a comprehensive review of current biological therapies indicates no statistically significant correlation with an increased risk of malignant melanoma compared to standard treatments of chronic inflammatory diseases (Esse et al., 2020). Although patients receiving biologics for conditions such as psoriasis, RA and IBD occasionally demonstrate a slightly higher estimated risk, robust statistical data do not support a definitive clinical connection (Esse et al., 2020). Recent meta-analyses focusing specifically on TNFi demonstrate that long-term immunosuppression does not significantly elevate malignancy rates, with RR reported at 1.04 (95% CI: 0.71-1.51) in interventional studies and 1.42 (95% CI: 0.72-2.79) in observational cohorts (Driscoll et al., 2025). Furthermore, contemporary systematic reviews confirm that the incidence of malignant melanoma remains consistently low and stable across newer therapeutic classes. Modern alternatives, including JAKi and IL-12/23, IL-23 and IL-17 inhibitors, do not carry oncologic risk, demonstrating an overall melanoma incidence rate of just 0.08 events per 100 patient-years (95% CI: 0.05-0.15) (Krzysztofik et al., 2023).

However, investigators raise awareness that a latent increase in melanoma risk cannot be definitively excluded (Esse et al., 2020). A significant limitation of current literature is that many existing studies fail to control for crucial confounding variables, such as a patient's natural skin phototype and history of ultraviolet radiation exposure (Esse et al., 2020). Consequently, researchers emphasize the critical necessity for high-quality, long-term prospective cohort studies to adequately track these genetic and environmental factors and to properly monitor for delayed adverse events (Driscoll et al., 2025; Esse et al., 2020; Krzysztofik et al., 2023).

5.3 Non-melanoma skin cancers

TNFi are highly effective biological therapies that have revolutionized the management of chronic inflammatory conditions (Kerbleski & Gottlieb, 2009; J. Wolfe, 2013). However, their use is frequently accompanied by dermatological side effects, including injection site reactions, local and systemic infections or allergic rashes (Kerbleski & Gottlieb, 2009). Beyond these inflammatory complications, the immunosuppressive nature of biological therapies requires patient screening due to an associated risk of cutaneous malignancies (Johnson et al., 2017; J. Wolfe, 2013).

Unlike melanoma, TNFi have a clearly linked and well-established association with an increased ratio of NMSC, specifically basal cell and squamous cell carcinomas (Budiasih & Handrean, 2025; J. Wolfe, 2013). The pathophysiology of this increased malignancy risk is heavily driven by environmental UV exposure combined with pharmacologic immunosuppression. Systemically suppressing the immune system can impair the skin's native immune surveillance, exacerbating the DNA-damaging effects of UV rays and influencing the presentation of malignant transformations (Johnson et al., 2017; Kerbleski & Gottlieb, 2009).

Given the coincidence of systemic immunosuppression, altered physiological cutaneous responses and environmental UV risks, strict patient compliance as well as preventive measures are essential for patients at risk of NMSC. Current clinical guidelines advise that patients receiving TNFi therapies should practice photoprotection and undergo routine dermatologic surveillance (Budiasih & Handrean, 2025; Johnson et al., 2017; Kerbleski & Gottlieb, 2009). Specifically, annual total-body skin examinations are highly recommended

to ensure the early detection of basal cell carcinomas, squamous cell carcinomas and any other suspicious lesions (Johnson et al., 2017; Kerbleski & Gottlieb, 2009).

5.4 Breast, Lung and Colorectal tumors

Epidemiological evidence supports the oncologic safety of TNFi regarding the development of malignancies. A comprehensive 2025 meta-analysis encompassing over 57,000 patients demonstrated a remarkably low incidence of breast, lung and colorectal cancers, revealing no statistically significant increase in malignancy ratio (Hellgren et al., 2021). These findings are strongly corroborated by a large Nordic cohort study involving patients with psoriatic arthritis, which found that the overall rate of solid tumors remained unchanged during TNFi therapy, yielding a standardized incidence ratio (SIR) of 1.0 (95% CI: 0.9-1.1) (Kalliolias et al., 2023). Ultimately, these data suggest that the level of immunosuppression required to manage chronic inflammatory conditions does not inherently elevate major malignancy risks above baseline population levels (Kalliolias et al., 2023).

While certain site-specific risk variations exist, these are primarily driven by underlying disease pathogenesis, shared environmental exposures, rather than the biological therapies themselves (Kalliolias et al., 2023). For example, the increased incidence of lung cancer is largely attributed to shared etiologic factors such as smoking and chronic interstitial lung disease (Kalliolias et al., 2023).

Moreover, patients often exhibit a decreased risk of colorectal and breast cancers relative to the general population. This reduction is linked to the chemopreventive effects of routine non-steroidal anti-inflammatory drug use and cumulative glucocorticoid exposure (Kalliolias et al., 2023). It suggests that biologic immunomodulation is not the primary driver of altered malignancy rates for these common solid tumors, supporting a favorable oncologic safety profile for these therapies (Driscoll et al., 2025; Hellgren et al., 2021; Kalliolias et al., 2023).

6. Modifying Factors

6.1 Combined therapies

Malignancy risks in autoimmune treatments vary significantly based on the drug class, underlying condition and specific cancer type. In IBD, combinations of thiopurines and anti-TNF drugs are heavily implicated in driving HSTCL (Shah et al., 2020). However, prolonged use of these therapies in IBD cohorts does not significantly elevate the risk of recurrent NMSC (Scott et al., 2016).

In contrast, methotrexate presents a distinct NMSC risk profile for patients with RA. Using methotrexate alongside other medications significantly increases the risk of a second NMSC (HR, 1.60; 95% CI, 1.08-2.37). Furthermore, adding anti-TNF agents to a methotrexate regimen raises the recurrence hazard compared to methotrexate monotherapy (HR, 1.49; 95% CI, 1.03-2.16) (Scott et al., 2016).

Ultimately, these contrasting profiles demand highly individualized patient monitoring. Thiopurine combinations in IBD require strict vigilance for lymphoproliferative disorders like HSTCL, while methotrexate-based regimens in RA necessitate heightened dermatologic surveillance for recurrent NMSC.

6.2 Age and sex of patient

Age is a primary modifier of malignancy risk in patients receiving biological therapies, whereas patient sex does not significantly alter this risk (B. Singh et al., 2026). The clinical paradigms for oncogenesis differ fundamentally between geriatric and pediatric populations.

In geriatric population patients over 65, baseline cancer risk is doubled due to physiological aging and accumulated exposures (B. Singh et al., 2026). However, meta-analyses demonstrate that biological therapy itself does not significantly increase incident cancer risk in this cohort (RR: 0.90), though it raises infection risk (Piovani et al., 2019). The elevated oncogenic risk often attributed to these treatments is primarily driven by concomitant immunomodulators, such as thiopurines. Newer biologic classes, including vedolizumab and ustekinumab, demonstrate high safety profiles (B. Singh et al., 2026).

Pediatric risk profiles are heavily influenced by the underlying autoimmune pathology. A retrospective study of children with juvenile idiopathic arthritis (JIA) found that the disease itself independently triples the baseline cancer incidence compared to matched controls (SIR: 4.0) (Nordstrom et al., 2012). This elevated inherent risk must be accounted for when evaluating the oncogenic potential of biologic disease-modifying antirheumatic drugs (bDMARDs).

While the absolute occurrence of malignancies in children treated with bDMARDs is rare, registry data and cohort studies suggest a potentially elevated rate of incident hematologic malignancies over long-term follow-up (Koker et al., 2020; Zimmer & Horneff, 2025). The primary challenge in pediatric pharmacovigilance is the prolonged latency period of oncogenesis. Because malignancies associated with early biologic intervention may not clinically manifest until adulthood, continuous, longitudinal surveillance extending well beyond the pediatric years is strictly required to define life-long risk (Koker et al., 2020; Zimmer & Horneff, 2025).

6.3 Exposure time

Current evidence indicates that prolonged administration of biological therapies does not result in a cumulative, dose-dependent increase in malignancy risk (Driscoll et al., 2025; Mercer et al., 2015; B. Singh et al., 2026). While malignancies may occur in patients with extended treatment durations, these are primarily driven by independent variables such as advancing age, genetic predisposition, chronic systemic inflammation and cumulative exposure to conventional immunomodulators (e.g., thiopurines or methotrexate), rather than the biologic agents themselves (Mercer et al., 2015; B. Singh et al., 2026; Takamura et al., 2025).

Continuous biological therapy has consistently demonstrated a long-term safety profile and even some protective benefits. In psoriasis cohorts, prolonged biologic exposure significantly reduced the cumulative cancer rate compared to topical treatments alone (4.4% versus 18.2%), likely due to the continuous suppression of oncogenic chronic inflammation (Takamura et al., 2025). Similarly, in IBD, newer targeted therapies, such as TNFi, ustekinumab and vedolizumab do not exhibit accumulating cancer risk over time (B. Singh et al., 2026).

7. Clinical Guidelines and Screening

7.1 Inflammation control

Chronic inflammation is a well-established driver of carcinogenesis, demonstrated by the heightened risk of colorectal cancer (CRC) in patients with IBD (Poullenot & Laharie, 2023). Because the progression is heavily dependent on the duration, anatomical extent and severity of active chronic colitis, effectively neutralizing the pro-neoplastic inflammatory microenvironment provides a critical intervention point (Poullenot & Laharie, 2023). While immunosuppressive therapies historically raise concerns, suppressing inflammation with targeted biologic drugs can paradoxically reduce the risk of certain inflammation-driven malignancies (Chen et al., 2022; Poullenot & Laharie, 2023).

Clinical evidence strongly supports this chemopreventive effect. Achieving disease control with anti-inflammatory medications, specifically anti-TNF drugs and thiopurines is associated with a markedly decreased risk of CRC in patients with longstanding colitis (Poullenot & Laharie, 2023). By extinguishing chronic inflammation these therapies protect against inflammation-associated carcinogenesis, effectively overriding the theoretical oncologic risks of immunosuppression (Poullenot & Laharie, 2023).

Recent genetic studies provide robust mechanistic support for these clinical observations. A drug-target Mendelian randomization study evaluated the genetically proxied inhibition of TNFR1, which mimics the pharmacological action of anti-TNF treatment (Chen et al., 2022). The study demonstrated that this TNF inhibition successfully suppressed systemic inflammation, marked by decreased C-reactive protein levels and was associated with a statistically significant reduction in colorectal cancer risk (Chen et al., 2022). Together, these clinical and genetic findings highlight that anti-TNF drugs not only manage autoimmune pathologies but also hold significant potential as targeted chemopreventive agents against CRC (Chen et al., 2022; Poullenot & Laharie, 2023).

7.2 Limitations of the available studies

The assessment of long-term oncological safety and potential side effects associated with advanced biological therapies is hindered by the methodological constraints (Bonovas et al.,

2016; Zimmer & Horneff, 2025). A primary confounding variable across the literature is the pervasive selection bias inherent to randomized controlled trials (RCTs) (Bonovas et al., 2016; J. A. Singh et al., 2017; Zimmer & Horneff, 2025). Phase III trials typically employ strict inclusion and exclusion criteria, which omit older patients, those with significant comorbidities and individuals with a history of malignancy (Bonovas et al., 2016; Zimmer & Horneff, 2025). A Cochrane systematic review of biological treatments for RA underscored this vulnerability, demonstrating the routine exclusion of high-risk demographics (J. A. Singh et al., 2017). As a result, the highly curated cohorts within these trials fail to mirror the baseline oncological risk of real-world populations, potentially distorting safety evaluations (Bonovas et al., 2016; J. A. Singh et al., 2017; Zimmer & Horneff, 2025).

Moreover, a fundamental temporal mismatch exists between standard clinical trial durations and the natural pathogenesis of cancer (Bonovas et al., 2016; J. A. Singh et al., 2017). RCTs designed to evaluate the safety and efficacy of biologics are generally characterized by abbreviated follow-up intervals, typically spanning from six months to a few years (Bonovas et al., 2016; J. A. Singh et al., 2017). Given that the biological latency required for carcinogenesis often extends beyond a decade, these brief observational windows are fundamentally ill-equipped to detect incident malignancies (Bonovas et al., 2016). Zimmer and Horneff recently highlighted this discrepancy, noting that the protracted biological progression of cancer far exceeds the observational capacity of standard trials (Zimmer & Horneff, 2025).

Consequently, the absence of elevated cancer incidence within short-term trial datasets does not preclude the possibility of long-term neoplastic risk (Bonovas et al., 2016; J. A. Singh et al., 2017). Depending exclusively on RCT data is, therefore, insufficient for determining definitive oncological outcomes (Zimmer & Horneff, 2025). To mitigate trial-induced selection bias and accurately document longitudinal cancer incidence, it is imperative to augment RCT data with rigorous post-marketing surveillance and comprehensive patient registries. Monitoring expansive cohorts across a lifelong trajectory is critical to ensure that follow-up durations adequately encompass the delayed latency periods characteristic of oncogenesis (Bonovas et al., 2016; J. A. Singh et al., 2017; Zimmer & Horneff, 2025).

7.3 Dermatological and Gynaecological screening recommendations

The introduction of systemic therapies for the management of psoriasis necessitates rigorous evaluation of associated oncologic risks, particularly regarding NMSC. The Psoriasis Longitudinal Assessment and Registry (PSOLAR) observational study evaluated the incidence of (BCC and SCC among approximately 12,000 psoriasis patients receiving systemic treatments (deShazo et al., 2019). Utilizing Cox proportional-hazards regression, researchers compared the first-incident risk of NMSC in patients exposed to TNFi, ustekinumab and MTX against an unexposed control group. The findings revealed significant variance in malignancy risk depending on the therapeutic agent. Notably, exposure to MTX (HR: 8.58) and TNFi (HR: 2.54) was associated with a significantly elevated risk of developing BCC (deShazo et al., 2019). Ustekinumab exposure did not increase BCC risk and demonstrated a statistically significant association with a decreased incidence of SCC (deShazo et al., 2019).

Given these established epidemiological associations, the initiation of biological and systemic therapies mandates a comprehensive baseline oncological risk assessment. This evaluation must incorporate the patient's personal and familial malignancy history, environmental exposures and prior use of immunosuppressive agents. In dermatologic practice, surveillance protocols are heavily oriented toward the early detection of NMSC.

Standard of care dictates that a full-body skin examination be performed prior to the initiation of treatment and annually thereafter (Barbieri et al., 2021). Such vigilant dermatologic monitoring is strictly recommended for patients with a history of prolonged phototherapy or conventional immunosuppressant use, particularly in light of the documented correlations between TNFi therapy and localized cutaneous malignancies (Barbieri et al., 2021; deShazo et al., 2019).

In addition to routine skin examinations, patients receiving systemic immunosuppression require careful gynecological monitoring. Because immunosuppressive therapies can theoretically impair the immune system's ability to clear viruses, there is a potential risk for viral-driven oncogenic progression. Therefore, before initiating biological therapies, female patients must be up-to-date with routine Papanicolaou smears and primary human papillomavirus screenings (Barbieri et al., 2021).

While current clinical guidelines do not require accelerated or more frequent gynecological screening simply because a patient is on biologics, strict adherence to standard,

population-based screening schedules is critical (Barbieri et al., 2021). If active dysplastic or malignant lesions are discovered, multidisciplinary coordination between dermatologists and gynecologists is essential. This collaborative management ensures the patient receives appropriate intervention for the lesion while avoiding unnecessary interruptions to their biological treatment regimen (Barbieri et al., 2021).

8. Conclusion

The relationship between biological therapies and malignancy is multifaceted, as these agents both modulate immune surveillance and suppress the chronic inflammation that drives tumorigenesis. While TNF-α inhibitors and JAKi are associated with an increased risk of non-melanoma skin cancers and certain lymphomas, newer interleukin inhibitors targeting IL-17 and IL-23 pathways demonstrate an oncogenic safety profile consistent with baseline population rates. Crucially, the risk of rare but fatal complications like Hepatosplenic T-cell Lymphoma appears almost exclusively linked to combination therapy involving thiopurines rather than biological monotherapy. Furthermore, the overall incidence of major solid tumors, such as breast, lung and colorectal cancers, does not appear to be significantly elevated by biological treatment; in fact, the suppression of systemic inflammation may offer protective chemopreventive effects against colorectal cancer.

Despite these reassuring findings, the assessment of long-term risk remains limited by the abbreviated follow-up periods and selection biases inherent in clinical trials. Continuous longitudinal surveillance is essential, particularly for pediatric populations where oncogenic latency may extend into adulthood. Clinicians must remain vigilant by implementing standardized screening protocols, including annual total-body skin examinations and regular gynecological monitoring, to ensure early detection of potential malignancies. Ultimately, the current evidence supports a favorable benefit-risk ratio for most biologic therapies, provided that treatment is accompanied by individualized risk assessment and rigorous patient monitoring. Future research should focus on genetic biomarkers to identify the small subset of patients who may be predisposed to therapy-induced malignancies.

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