

Methotrexate and malignancy in rheumatoid arthritis: Evidence, risks, and clinical considerations

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Abstract

In this review, we summarized the current evidence on the risks of incident malignancy and cancer recurrence in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX). Before considering the effect of MTX, it is important to recognize the malignancy risk associated with RA itself. The overall risk of malignancy in patients with RA modestly increased, as per two meta-analyses, although Japanese studies report inconsistent findings, with one showing a slight decrease and another a slight increase. The risk of malignant lymphoma is increased, whereas the risk of colorectal cancer appears to be reduced. Additionally, there are concerns regarding the increased risk of lung and skin cancers. However, there is limited evidence specific to patients with RA treated with MTX. According to an Australian report, these patients have a higher risk of overall malignancy, along with an increased risk of malignant lymphoma, lung cancer, and melanoma. Studies comparing MTX with tumour necrosis factor inhibitors have reported no significant difference in the overall malignancy risk or increased malignancy risk. In White patients, MTX has been associated with an increased risk of recurrence in patients with RA and a history of non-melanoma skin cancer. There is insufficient evidence regarding the risks of MTX use in patients with RA and malignancy. Therefore, decisions regarding MTX use should be made individually based on shared decision-making, and careful follow-up is necessary.

Keywords rheumatoid arthritis, methotrexate, malignant tumours, cancer recurrence

Introduction

In this review, we summarize the current knowledge on the risk of incident malignancy and recurrence in methotrexate (MTX)-treated patients with rheumatoid arthritis (RA), with the aim of informing discussions on these clinical challenges.

MTX is the most widely used conventional synthetic disease-modifying antirheumatic drug (csDMARD) worldwide for the treatment of RA and is regarded as an anchor drug [1–3]. In routine clinical practice, MTX is not merely one option among others; it forms the foundation of long-term RA management [4]. Because patients with RA and the general population have an increased incidence of malignancies [5], the question of whether MTX use is appropriate when RA coexists with a malignancy arises. In addition, it is unclear whether MTX is appropriate for intensifying RA treatment in patients with a history of malignancy.

The relationship among RA, MTX, and malignancy is extremely complex. When a malignancy develops in patients with MTX-treated RA, it is often inappropriate to attribute the cause solely to MTX therapy. Factors such as RA disease activity, concomitant glucocorticoid use, other immunomodulators, smoking, frailty, and other patient backgrounds may interact and influence this risk. Moreover, several important questions remain unsolved, including whether MTX increases the risk of new malignant tumours, whether this risk varies by tumour type, whether MTX affects cancer recurrence after treatment, whether it can be continued during active cancer therapy, and how RA disease activity should be managed if MTX is discontinued.

Therefore, the clinical question extends beyond whether MTX is simply safe in patients with malignancy and instead requires an individualized assessment. Decisions should consider which patients are most appropriate for MTX therapy, under what

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clinical conditions, for which cancer types, and to what extent treatment should be continued. However, addressing these questions through clinical studies is challenging due to ethical and study design considerations.

Literature search

This narrative review aims to provide evidence, assess risks, and offer clinical insights into MTX and malignancies in patients with RA. Relevant literature published between January 2000 and April 2026 (last search date: 30 April 2026) was identified through a non-systematic PubMed search using keywords related to MTX, RA, and malignancies. As this was a narrative review, formal inclusion and exclusion criteria were not established *a priori*. Studies were selected based on their relevance to MTX and malignancies, as well as key clinical themes, such as malignant lymphoma (ML), lymphoproliferative disorders (LPDs), lung cancer (LC), skin cancer, and malignancy recurrence. Given the heterogeneity of study designs and outcomes, as well as the predominance of observational evidence, no quantitative synthesis was attempted. Instead, the findings were summarized narratively to provide clinically meaningful insights.

Relative risk of malignancy in patients with rheumatoid arthritis

Before discussing the impact of MTX on malignancy risk, it is important to understand the inherent malignancy risk associated with RA. Failure to do this may lead to an overestimation or underestimation of treatment-specific risks. We reviewed two meta-analyses that compared patients with RA to the general population, noting that Reference [6] builds upon Reference [7] by including reports published after 2008. The overall risk of malignancy was shown to be broadly similar, with small increases reported as the standardized incidence ratio (SIR) 1.05 [95% confidence interval (CI), 1.01–1.09] [7] and an SIR 1.09 (95% CI, 1.06–1.13) [6].

RA exhibited a characteristic distribution among cancer types. Specifically, the risk of ML was elevated (SIR 2.08, 95% CI, 1.80–2.39 [7]; SIR 2.46, 95% CI, 2.05–2.96 [6]), as was the risk of LC was increased (SIR 1.63, 95% CI, 1.43–1.87 [7]; SIR 1.64, 95% CI, 1.51–1.79 [6]). Melanoma risk was also reported to be increased (SIR 1.23, 95% CI, 1.01–1.49) [6], but with variability across studies. In contrast, the risks of colorectal cancer (SIR 0.77, 95% CI, 0.65–0.90 [7]; SIR 0.78, 95% CI, 0.71–0.86 [6]) and breast cancer were reduced (SIR 0.84, 95% CI, 0.79–0.90 [7]; SIR 0.86, 95% CI, 0.73–1.01 [6]). These results suggest that RA is not associated with a uniform increase in the overall risk of malignancy, but rather with a cancer-specific profile.

Data from the Japanese population are particularly important when considering regional and ethnic differences. The overall malignancy risk among Japanese patients with RA was reported by Hashimoto *et al.* [8] to be slightly lower than that in the general population (SIR 0.89, 95% CI, 0.82–0.97). By cancer type, ML risk was increased (SIR 3.43, 95% CI, 2.59–4.28), while the risk of colorectal cancer was decreased (SIR 0.71, 95% CI, 0.51–0.91); rectal cancer showed an SIR of 0.59 (95% CI, 0.32–0.86); and liver cancer showed an SIR of 0.33 (95% CI, 0.15–0.51) [8]. The Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort showed a slightly elevated overall cancer risk (SIR 1.18, 95% CI, 1.02–1.37).

For cancer types, ML (SIR 6.07, 95% CI, 3.71–9.37) and LC (SIR 2.29, 95% CI, 1.57–3.21) risks were significantly higher, while colorectal cancer risk (SIR 0.49, 95% CI, 0.26–0.83) was lower [9].

From these data, it appears that the RA-associated malignancy risk profiles may differ by race; however, there are consistent shared patterns, including an increase in ML and LC risks and a decrease in colorectal cancer risk.

Overall risk of malignancy in patients with rheumatoid arthritis treated with methotrexate

The evaluation of the association between MTX and malignancy is difficult for several reasons. In addition to the small number of studies, there are fundamental issues with the study design and causal inference. For example, MTX exposure has been inconsistently defined in different studies. Some studies used ‘ever use’, while others analysed current use, cumulative dose, duration, or time-dependent exposure. These distinctions reflect biologically different exposure scenarios despite the same labels for ‘MTX’ use. For instance, short-term prior users and long-term users may have markedly different exposure characteristics until the time of cancer diagnosis; however, they are sometimes grouped together. The choice of comparator also greatly affects the interpretation. Comparisons with the general population did not adequately adjust for the background malignancy risk inherent to RA. In contrast, comparisons with tumour necrosis factor (TNF) inhibitors or other DMARDs are complicated by non-random drug selection and prescription biases. Patients with kidney disease, pulmonary involvement, frailty, advanced age, or prior malignancy may be less likely to receive MTX, potentially creating apparent risk differences. Moreover, many studies have not adequately adjusted for key confounders such as smoking, disease activity, cumulative inflammatory burden, interstitial lung disease (ILD), glucocorticoid exposure, or prior malignancy. Even when adjustments are made, residual confounding is likely, and the observed associations cannot be considered causal.

Compared with the literature on malignancy risk in RA, MTX-focused studies are limited but clinically important. A representative Australian study by Buchbinder *et al.* [10] matched RA patients receiving MTX with the general population. They identified all malignancies [excluding non-melanoma skin cancer (NMSC)] from 1983 to 1998 using the State Cancer Registry and all deaths up to the end of 1999 using the National Death Index. Follow-up began at the time of MTX initiation and ended on the last date of rheumatology consultation or death. In 4145 person-years (mean 9.3 years) of data, 87 malignancies were identified. The overall cancer risk was elevated (SIR 1.5, 95% CI, 1.2–1.9), with increased risks for non-Hodgkin lymphoma (SIR 5.1, 95% CI, 2.2–10.0), LC (SIR 2.9, 95% CI, 1.6–4.8), and malignant melanoma (SIR 3.0, 95% CI, 1.6–4.8) occurring more frequently during MTX use [10]. These results raise concerns about MTX-cancer-type relationships; however, interpretation requires caution because the comparator was the general population and not an RA-specific background risk.

Some studies have compared patients treated with MTX with those treated with alternative antirheumatic therapies. For example, a Taiwanese retrospective cohort included patients with RA ($n = 21,699$), new MTX users ($n = 10,352$), and non-users

($n = 11,347$). MTX users had a cancer risk hazard ratio (HR) of 0.87 (95% CI, 0.74–1.02) compared with the non-users, and cumulative-dose analyses showed a lower risk with moderate (1125–2250 mg) and high (>2250 mg) doses, but there was no accounting for smoking and disease activity [11]. Askling *et al.* [12] linked Swedish Biologics Register data with RA registers and the Swedish Cancer Register to analyse cancer incidence among patients with RA who first started TNF inhibitors ($n = 6366$) between 1999 and 2006 and those who newly started MTX ($n = 5989$). Among MTX initiators, 260 developed cancers as opposed to 240 among patients who initiated TNF inhibitors, with a relative risk (RR) of 0.99 (95% CI, 0.79–1.24) [12]. Setoguchi *et al.* [13] conducted a cohort study using US and Canadian administrative databases from the two countries to examine cancer risk. The cohort included 1152 biological DMARDs (bDMARDs) and 7306 MTX users. Patients receiving both MTX and bDMARDs were classified into the bDMARDs group, and MTX users without bDMARD exposure were classified into the MTX group. Within 2940 person-years, 11 events of hematologic malignancies and 46 events of solid tumours were identified in the bDMARD group, while within 30,300 person-years, 88 events of hematologic malignancies and 558 events of solid tumours were identified in the MTX group. Overall cancer risk did not significantly differ between TNF inhibitors and MTX, with a HR of 0.98 (95% CI, 0.73–1.31) [13]. Using the CORRONA registry, Solomon *et al.* [14] evaluated the cancer risk associated with DMARDs between 2001 and 2010 and compared MTX with other DMARDs. Across the cancer cases, the non-MTX csDMARDs group (1900 person-years, four events) and TNF inhibitors (10,293 person-years, 46 events) showed a lower risk of cancer than the MTX group (2866 person-years, 30 events), with HR 0.17 (95% CI, 0.05–0.65) and HR 0.29 (95% CI, 0.14–0.60), respectively [14].

Focused review by cancer type

At a high level, two meta-analyses repeatedly showed an increase in ML, LC, and skin cancer when examining the RRs of malignancy in patients with RA versus the general population. In Japanese data, there is also evidence suggesting an increase in ML and LC risks. In MTX-focused analyses, especially data from outside Japan, there is an increased risk of non-Hodgkin's lymphoma, LC, and skin cancer. Based on these findings, we conducted a more detailed literature search for the three cancer types: ML, LC, and skin cancer.

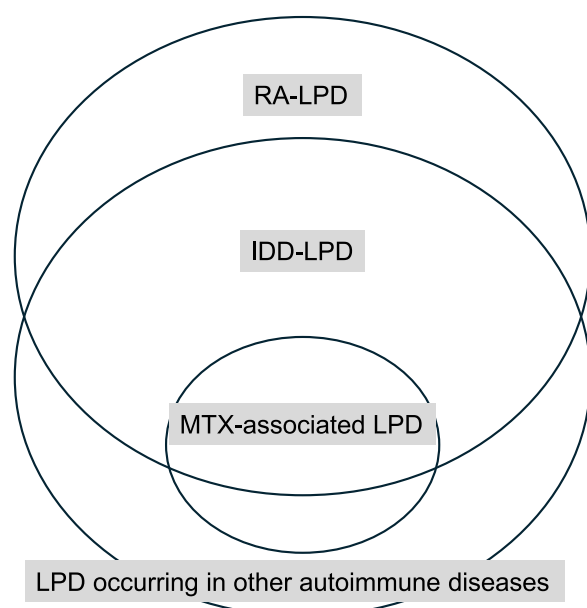
Malignant lymphoma and lymphoproliferative disorders

ML is one of the most common malignancies associated with RA. RA is associated with an increased risk of ML [6–8]. Consequently, it is extremely challenging to determine whether MTX independently contributes to ML risk or whether the observed risk mainly reflects RA activity.

In the third edition of the World Health Organization (WHO) classification (2001), LPDs occurring during MTX therapy were classified as immunodeficiency-associated LPDs under the designation 'MTX-associated LPD' (MTX–LPD). Notably, they were recognized for their high rate of spontaneous regression (SR) following the discontinuation of MTX [15]. Subsequently, in

international classifications and overseas literature, 'MTX–LPD' was not treated as an independent disease entity; instead, these conditions were categorized within a broader framework, specifically iatrogenic or treatment-related LPDs occurring in the context of immunodeficiency or immune dysregulation. Specifically, the WHO Classification (fourth edition, 2008) renamed the condition 'other iatrogenic immunodeficiency-associated LPD; Other Iatrogenic Immunodeficiency-Associated (OIIA)–LPD' [16]. Around that time, cases of LPDs occurring during MTX-based treatment for RA began to attract attention in Japan. However, the term 'MTX–LPD' continues to be widely used in clinical practice and rheumatology literature, leading to confusion. Issues regarding adverse event compensation and litigation concerning the diagnosis and management of RA-associated LPD have arisen in clinical settings. Consequently, a joint working group comprising the Japan College of Rheumatology, Japanese Society of Hematology (JSH), and Japanese Society of Pathology was established to develop clinical guidelines and recommendations [17]. Guidelines have established that LPDs that develop during RA treatment are collectively classified as RA-associated LPD (RA–LPD). In 2022, the fifth edition of the WHO Classification of haematolymphoid tumours introduced a three-component nomenclature system for LPDs based on a combination of pathological findings, viral associations, and immunodeficiency or dysregulation (IDD) [18]. Regarding RA–LPD, there are slight differences in the understanding of its pathogenesis and significance between Japan and other countries; indeed, the vast majority of recent case reports and case series have originated in Japan [19–24]. Discrepancies between the terminology used in Japanese clinical practice and international standards can lead to confusion – as previously noted – particularly when LPDs occurring during MTX therapy are labelled 'iatrogenic' without adequately considering factors such as chronic inflammation associated with RA, Epstein–Barr virus (EBV) infection, ageing, disease activity, and concomitant immunosuppressive therapy. In fact, because MTX is sometimes perceived as prone to inducing iatrogenic LPD, some physicians avoid using it even when it is clinically indicated. In Japan, these are collectively referred to as RA–LPD. Furthermore, LPDs arising during immunosuppressive therapy including MTX should be classified in accordance with the latest WHO classification as 'iatrogenic/treatment-related in the setting of immune deficiency or dysregulation; IDD–LPD'. In addition, the specific notation '(Drug: MTX)' can be added in cases where MTX involvement is suspected (Figure 1).

The following studies from Japan have examined MTX-associated LPD. Large-scale studies in Japanese patients with RA linking MTX exposure to LPD have suggested an association between MTX and its dose [25]. Conversely, analyses that matched disease activity and compared patients with RA who developed LPD with those who did not found that MTX dose was not a risk factor [26], indicating no clear relationship with MTX dose, cumulative dose, and duration were not risk factors. Among reports from countries other than Japan that have examined MTX and ML risk, most have reported no increase in incidence, SIR, or odds ratio (OR) [27–31]. Clinically, lymphadenopathy, persistent fever, weight loss, elevated lactate dehydrogenase (LDH) levels, or extranodal lesions should be suspected during MTX therapy. EBV-related mechanisms have also been proposed [32]. In Japan, the SIRs of ML in RA have been reported to be 3–6 [8, 9]. Mizushima *et al.* [33] examined background factors



Key points

- There is a discrepancy between the terminology used in clinical practice in Japan and international terminology.
- In particular, there is a risk of confusion when LPDs occurring during MTX therapy are interpreted as "iatrogenic" without adequately considering factors such as chronic inflammation associated with RA, EBV infection, aging, disease activity, and concomitant immunosuppressive therapy.
- In fact, because MTX is perceived as a drug prone to inducing iatrogenic LPD, some physicians may avoid using it even in situations where it is indicated.
- LPD developing during the course of RA treatment should be collectively termed "RA-associated LPD" (RA-LPD); specifically, LPD occurring during treatment with immunosuppressive drugs, including MTX, should be uniformly classified as "iatrogenic/treatment-related in the setting of immune deficiency/dysregulation (IDD-LPD)".
- Importantly, reducing the MTX dosage to prevent LPD is not advisable if disease activity is not adequately controlled.
- If LPD develops during MTX use, the drug should be discontinued promptly.

Figure 1 Schematic diagram of disease concept and key points of management of LPDs associated with RA.

distinguishing ML from other malignancies in patients with RA registered in the NinJa (National Database of Rheumatic Diseases in Japan) registry from 2012 to 2018 (110,571 person-years). They identified 935 patients with RA who developed new malignancies. In the ML and other malignancy groups, the rates of MTX use were 74.4% and 56.8%, respectively, while those of nonsteroidal anti-inflammatory drugs use were 56.7% and 35.3%, respectively. Both univariate and multivariate analyses consistently showed that MTX use and nonsteroidal anti-inflammatory drugs were significantly associated with ML compared to other malignancies [33]. Hashimoto *et al.* [8] reported that advanced age and MTX and tacrolimus use were potentially associated with lymphoma in the NinJa cohort. However, the results must be interpreted with caution as statistical models cannot fully adjust for the cumulative disease activity of RA, and the timing of medication data collection for patients with RA who do not develop lymphoma is not clearly specified. Notable recent clinical characteristics in Japanese patients include an age at onset frequently ranging from 60 to 70 years, and an interval of > 10 years between the onset of RA and the development of LPD. Extranodal lesions are observed in 40–70% of cases, affecting multiple sites such as the oral cavity, pharynx, and lungs. The pathological diagnosis predominantly reveals B-cell non-Hodgkin lymphoma, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype (approximately 50–60%), followed by Hodgkin lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Furthermore, even within the category of RA-LPD, clinical presentation, primary site, histological subtype, and degree of EBV association vary among cases, suggesting heterogeneity driven by factors such as the intensity of immunosuppressive therapy and differences in concomitant medications. Although there are no specific laboratory tests for LPD, elevated serum levels of acute-phase reactants, LDH, and soluble interleukin-2 receptor (sIL-2R) can sometimes serve as clues for the early diagnosis of LPD [34]. One study showed that sIL-2R levels in LPD occurring in RA patients treated with MTX are significantly lower than those in patients

with LPD occurring in RA patients not treated with MTX and in EBV-negative DLBCL in non-RA patients [35].

The response to MTX discontinuation is a critical turning point. SR is observed in 20–70% of cases following MTX withdrawal, and it has been shown to be potentially associated with the recovery of peripheral lymphocyte counts [36]. However, in some cases where SR was achieved, regrowth or recurrence occurred subsequently, and in some instances, this was accompanied by a change in the histological subtype over time [34]. The treatment approach was selected based on the patient's pathology, disease stage, and immune status. Although the discontinuation of MTX is generally accepted as the initial course of action, chemotherapy is frequently administered if regrowth, recurrence, or progressive disease is suspected. Although rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) are the most frequently reported regimens, other regimens, such as CHOP, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), R-THP-COP (rituximab, pirarubicin, cyclophosphamide, oncovin, and prednisolone), rituximab monotherapy, and combinations of rituximab with other chemotherapy agents, have also been reported [35, 37]. Nakano *et al.* [38] reported a high drug retention rate with tocilizumab (TCZ) demonstrated a high maintenance rate in patients with RA-LPD treated with a TCZ regimen. TCZ has also been identified as an independent factor capable of suppressing tumour regrowth following SR [39]. Importantly, reducing MTX alone to prevent LPD is not advisable if disease activity cannot be adequately controlled [4] (Figure 1).

Immunosuppression with tacrolimus or cyclosporine, which is used to prevent rejection following organ or haematopoietic stem cell transplantation, carries the risk of abnormal proliferation of EBV-positive lymphocytes. This condition is known as post-transplant LPD (PTLD) and is particularly likely to develop in children or individuals who have not been previously infected with EBV when exposed to potent immunosuppressive agents. One study examined the effect of tacrolimus on time to development of PTLD [40, 41].

Table 1 Major studies evaluating malignancy risk in RA- and MTX-treated patients.

Target group	Control group	Outcome	Abstract	Adjusted (model/covariate) confounding factors	Ref.
RA patients (meta-analysis)	Common man	Overall risk of developing cancer	The overall risk of malignant tumours in patients with RA was approximately the same as that in the general population (SIR 1.05). The risk of ML and LC was increased, whereas the risk of colorectal and breast cancer decreased	NA	Smitten <i>et al.</i> [7]
RA patients (meta-analysis)	Common man	Overall risk of developing cancer	The overall cancer risk in patients with RA was approximately equivalent to that in the general population (SIR, 1.09). An increased risk of ML and LC and a decreased risk of colorectal and breast cancer were reported	NA	Simon <i>et al.</i> [6]
Japanese RA patients	Common man	Overall risk of developing cancer	The overall cancer risk was slightly lower than that in the general population (SIR 0.89). The risk of ML was increased, while the risks of colorectal and liver cancers were lower	Age, sex, NSAID use, glucocorticoid use, MTX use, tacrolimus	Hashimoto <i>et al.</i> [8]
Japanese RA patients	Common man	Overall risk of developing cancer	The overall cancer risk was SIR 1.18, with an increased risk for ML (SIR 6.07) and LC (SIR 2.29) and a decreased risk for colorectal cancer (SIR 0.49)	Disease activity	Yamada Laboratory <i>et al.</i> [9]
Australian RA patient continuing MTX treatment	Common man	Overall cancer risk and site-specific cancer risk	The overall risk of cancer increased (SIR 1.5). The risks of non-Hodgkin lymphoma (SIR 5.1), LC (SIR 2.9), and malignant melanoma (SIR 3.0) have also increased	Age, sex, RF, history of immunosuppressants such as cyclophosphamide (CV), azathioprine (AZ)	Buchbinder <i>et al.</i> [10]
Taiwanese RA patient	MTX new users vs non-users	Overall risk of cancer	MTX users had a lower risk of cancer, 0.87 (95% CI, 0.74–1.02) compared to non-users, and the cumulative incidence of cancer was significantly lower in the MTX group. The risk was lower with medium- and high-dose cumulative exposure	Glucocorticoids	Perng <i>et al.</i> [11]
RA patients being treated with MTX or TNF inhibitors	RA patients receiving MTX treatment	Overall risk of cancer	There was no significant difference in overall cancer risk between the TNF inhibitor and MTX groups (HR 0.99)	Gender, place of residence, year of birth, comorbidities, hospitalization, duration of illness	Asking <i>et al.</i> [12]
/Canadian RA patients being treated with MTX or TNF inhibitors	RA patients treated with MTX vs other csDMARDs or TNF inhibitors RA patients on RA treatment	Overall risk of cancer	There was no significant difference in overall cancer risk between the TNF inhibitor and MTX groups (HR 0.98)	Age, gender, history of DMARDs/glucocorticoid use	Setoguchi <i>et al.</i> [13]
North American RA patients (CORONA)	RA patients receiving other csDMARDs or TNF inhibitors	Risk of MTX for cancer	Compared to MTX use including the risk of cancer was lower in the csDMARDs other than MTX (HR 0.17) and the TNF inhibitor group (HR 0.90.29)	Smoking, alcohol consumption, disease activity, glucocorticoids	Solomon <i>et al.</i> [14]
Japanese RA patients	MTX non-user	Risk of LPD	Age and MTX used (including the amount used) were associated with LPD	Age, sex, bDMARDs, duration of illness, MTX dose, CRP, Sjögren's syndrome	Honda <i>et al.</i> [25]
Japanese IORRA Cohort	LPD vs non-LPD	Risk factors for LPD	MTX dosage was not identified as a risk factor; however, disease activity was identified as a risk factor	Disease activity, glucocorticoids	Shimizu <i>et al.</i> [26]
RA patients who developed ML		Risk of developing ML	The increased risk of ML is more strongly associated with high disease activity than with treatments	Disease activity	Backlund <i>et al.</i> [27]
RA patients		Risk of ML	While the risk of lymphoma was increased in patients with RA, no clear additional risks attributable to MTX or anti-TNF therapy were observed	Age, gender, years of education, comorbidities	Wolfe <i>et al.</i> [29]
Patients with inflammatory polyarthritis listed in the Norfolk Arthritis Register	Common man	Risk of ML	The MTX treatment group had a higher risk of lymphoma	Age, gender	Franklin <i>et al.</i> [30]
US RA patients	Other treatments	Risk of ML	It had odds of 1.3 compared to other csDMARDs	HAQ, DMARDs, glucocorticoids, age, sex, education, smoking	Wolfe <i>et al.</i> [31]
RA patients suffering from malignant tumours	ML vs other malignant tumour patients	Differences in background factors	In ML, MTX and NSAIDs were used more frequently	Age, sex, duration of illness, smoking, MTX, TNF inhibitors, IL-6 inhibitors, abatacept, NSAIDs, disease activity, glucocorticoids	Mizushima <i>et al.</i> [33]
Japanese RA patients	Risk of LPD	The effects of antirheumatic drugs on LPD	Antirheumatic drugs administered before LPD onset may influence the clinicopathological characteristics of LPD. After the onset of LPD, a regimen of TCZ alone is recommended for treatment	NA	Hoshida <i>et al.</i> [39]
US Medicare (95–100% White)	RA patients with NMSC	MTX use vs other treatments	Compared to the SASP/HQC users, MTX-exposed patients had an increased risk of developing a second NMSC	Age, sex, glucocorticoids, dermatology visit	Scott <i>et al.</i> [41]

NA, not applicable.

Lung cancer

LC is another important malignancy associated with RA [6, 7]. The background behind LC involves multiple factors, such as smoking, chronic lung inflammation, ILD, and immune regulatory abnormalities, which can also be prevalent among MTX users. Therefore, disentangling the MTX-specific effects is challenging. Solomon *et al.* [14] reported that the HR for LC was lower in the TNF inhibitor group than in the MTX group (HR 0.05, 95% CI, 0.01–0.58). However, in that analysis, the MTX group had two events in 2866 person-years, the non-MTX csDMARD group had no events in 1900 person-years, and the TNF inhibitor group had three events in 10,293 person-years. Smoking history is a strong confounding factor that was not been adequately considered. Moreover, RA-associated ILD can influence the malignancy risk and treatment choices; therefore, interpretations should be made with caution [14].

The recurrence risk after cancer treatment in patients with rheumatoid arthritis

Scott *et al.* [42] used US Medicare data (predominantly White, 95–100%) to examine the RR of NMSC recurrence after the first NMSC episode in patients with RA or inflammatory bowel disease (IBD) who started MTX, TNF inhibitors, or azathioprine. Compared with salazosulfapyridine (SASP)/hydroxychloroquine (HCQ) users, MTX-exposed cases showed an increased risk of a second NMSC (HR 1.81, 95% CI, 0.94–3.52) [42]. However, the incidence of skin cancer varies by race, and the recurrence risk of MTX-associated cancers in the Japanese population remains a challenge.

The management of rheumatic immune-related adverse events (irAEs) arising from immune checkpoint inhibitors has recently gained prominence. csDMARDs are considered when glucocorticoids are insufficient or cannot be tapered. MTX is the most commonly administered drug. Long-term safety data are not well documented; however, the median follow-up reportedly exceeds 1 year [43]. Major studies evaluating malignancy risk in RA- and MTX-treated patients were shown in Table 1.

Limitations and future challenges

There are limitations to studying MTX use, specifically in patients with RA and malignancies. First, few studies have focused on patients with RA treated with MTX. Second, substantial heterogeneity was observed in study design, comparators, exposure definitions, follow-up definitions, and outcome definitions. Third, distinguishing the effects of RA from those of MTX is inherently difficult, particularly for ML and LC. Additionally, there are substantial racial differences in the incidence of cancers, such as skin cancer, and findings from other countries may not be generalizable to the Japanese or other Asian populations. Many studies inadequately adjust for key confounders, leading to residual confounding. Recurrence risk data were limited to specific types of cancer. Prospective data on recurrence risk in patients with active cancer or those undergoing cancer treatment are particularly scarce. Although randomized trials are ethically challenging, large observational cohorts or prospective registries are still considered feasible and present future challenges.

Conclusion

Current evidence does not clearly define the oncological risk of MTX in patients with RA with current or prior malignancies. Further high-quality studies are required to determine the conditions under which MTX can be safely administered to patients with RA. Shared decision-making is especially important along with careful follow-up.

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Conflicts of interest

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