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Effects of Abatacept in Patients with Rheumatoid Arthritis and Cancer Risk: A Systematic Review

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ABSTRACT

Introduction: As a chronic autoimmune disease, Rheumatoid arthritis (RA) affects the joints. Studies have shown a complex and challenging link between cancer and RA. However, articles claim a significant relationship between cancer and treatment with DMARDs and biological DMARDs (e.g., Abatacept); however, the results are contradictory. Accordingly, this systematic review investigates the prevalence of cancer in RA patients taking Abatacept.

Methods: We searched for articles published in four databases, namely Web of Science, Medline, PubMed, and Scopus up to September 29, 2023. The methodology followed recommendations from the Cochrane Handbook. During the search process, we selected articles using keywords such as "rheumatoid arthritis", "malignancy", and "cancer" with the Boolean operators "AND" and "OR"."

Results: A total of 12 studies were considered, the majority highlighted the effectiveness of Abatacept as an anti-RA medicine in the risk of cancer prevalence. Most of the patients investigated in the trials were female. Lung cancer was the greatest malignancy in those suffering from RA diseases. However, these investigations found no significant link between Abatacept use and cancer risk.

Conclusion: There is speculation regarding the potential use of rheumatoid arthritis drugs in treating RA and its potential association with cancer incidence. According to the findings presented in this review article, there was no statistically significant association between the utilization of Abatacept and the prevalence of cancer in patients who were administered Abatacept either as a standalone treatment or in combination with other anti-rheumatoid medications. However, it is advised that further clinical trials be conducted to thoroughly investigate this association.

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Introduction

As an inflammatory autoimmune condition, Rheumatoid arthritis (RA) initially targets hands and feet joints and in later stages affects larger joints (1). RA prevalence and incidence rates are increasing worldwide, with almost 20 million people affected globally (2). Patients with RA manifest a vast spectrum of symptoms, such as extra-articular complications, chronic joint deformities, joint stiffness, pain, and swelling. A fundamental part of RA management is medications. They can be categorized into three groups: 1) symptomatic drugs, such as

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acetaminophen and opioid analgesics, which alleviate symptoms and pain; 2) disease-modifying antirheumatic drugs (DMARDs) including biologic and nonbiologic types that treat inflammation and damage to joints; and 3) glucocorticoids, which promote symptom relief and reduce the progression of the disease (3).

There appears to be some association between RA drug treatments and an increased risk of cancer; however, such hypotheses need to be proven (4). Additionally, studies showed an association between an increased risk of malignancy and RA, especially non-melanoma skin cancer (NMSC), malignant lymphomas, and lung cancer (5-9). RA is now treated with a variety of medications, including tumor necrosis factor (TNF) antagonists, androgen deprivation therapy (ADT), Tofacitinib, Abatacept, and other biological DMARDs (bDMARDs) (10-12).

Since the introduction of bDMARDs to treat chronic rheumatoid disease, one of the critical focuses has been on a greater prevalence of cancers (13). Recently, there have been some concerns regarding the potential risk of cancer associated with the administration of bDMARDs, in particular, Abatacept, a fusion protein of CTLA-4 (T-lymphocyte-associated protein 4) (14). However, there is a dearth of data on Abatacept safety, especially from first-line studies (12). Some research indicated the probable association of Abatacept with a higher NMSC risk compared to bDMARDs (15, 16). Evidence, however, showed that physicians were prescribing Abatacept more often to older patients with more comorbid conditions and long-term diseases (3).

In general, prescribers perceive Abatacept as a first-line treatment that has a better safety profile, which may encourage their use in cancer-affected populations (12). Some of these agents are suspected to carry a cancer risk that has led researchers to require warnings (17). Patients and providers are concerned about these warnings because RA is a chronic condition requiring long-term treatment (16). The present study reviews the effect of Abatacept, an anti-rheumatoid medication, on the risk of cancer prevalence in this study.

Materials and Method

Abatacept, a class of bDMARD medications, was used to treat RA, and its effect on cancer risk was investigated in this systematic review. The research process followed the seven stages of the Cochrane Handbook for Systematic Reviews. These stages included considering the inclusion and exclusion criteria, conducting a thorough search for collecting data from the database, excluding unrelated studies, assessing the quality evaluation, retrieving data, and investigating the extracted data (18).

Inclusion and Exclusion Criteria

The eligibility criteria were determined for this study through Participants, Intervention, Comparison, and Outcome Study research. The primary inclusion criteria were RA and treatment programs, cancer incidence, sample size greater than 10, human clinical trials, and publication in English. All studies that did not use Abatacept as medicine were excluded, followed by case reports or case series, nonclinical studies, editorial letters, review articles, short communications, qualitative investigations, and meta-analyses. On the other hand, all case controls, as well as retrospective and prospective investigations on human samples evaluating RA and cancer risk, were included in the current review due to the observational purpose of the topic.

Literature search

All articles published in Web of Sciences, Medline, PubMed, and Scopus from 5 February 2022 to 29 September 2023, were searched using such keywords as “cancer,” “malignancy,” and “rheumatoid arthritis.”

Data extraction and study design

Based on a systematic review, researchers examined the effect of Abatacept therapy on cancer risk among cases with RA. In the initial phase, four selected databases (Web of Sciences, Medline, PubMed, and Scopus) were researched up until September 29th, 2023. Afterward, the number of relevant articles was determined. Following that, the relevance of titles and abstracts was assessed. The screening process considered eligibility criteria. According to the study’s purpose, full-text articles were obtained for final screening. As part of the process, articles that were duplicates, irrelevant, non-English, or lacking enough data were excluded from the research process. Two researchers carried out all of the research in the same way and independently reviewed the study titles and abstracts. Information was constantly exchanged among researchers. After agreeing on the goals, they collected the necessary information. Finally, the collected information was entered into a checklist. The PRISMA flow chart depicts all of the steps involved in selecting articles (Figure 1).

Bias risk and assessment of quality

Based on the Cochrane risk of bias tool, the bias risk in the submitted studies was determined

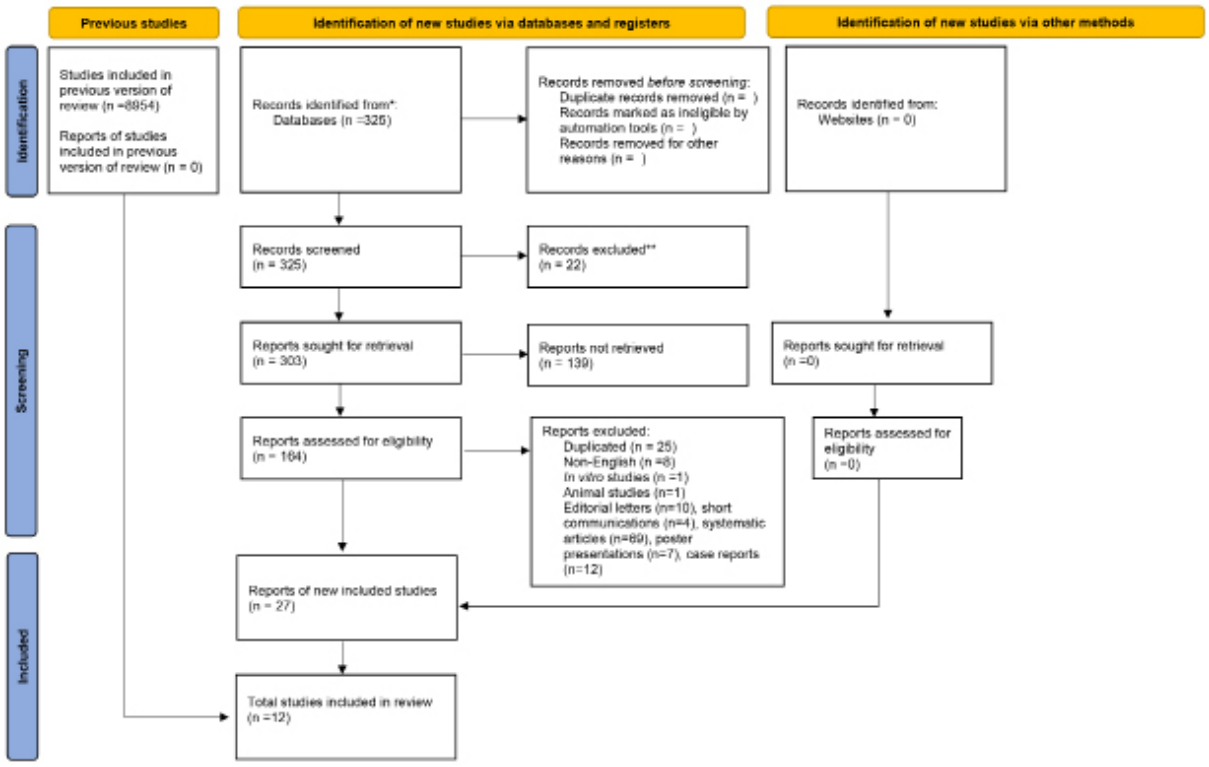

Figure 1. PRISMA flowchart showing the selection process in the study

through consideration of eight factors (18) .

A summary of results and outcomes

In total, 325 articles were found in the databases. After removing irrelevant titles and abstracts (n=139) and 25 duplicated articles, we excluded the articles written in languages other than English (n=8), followed by articles describing experimental or *in vitro* studies (n=1), animal research (n=1), editorial letters (n=10), short communications (n=4), reviews of narrative and systematic articles (n=69), poster presentations (n=7), articles with unavailable full texts (n=7), and case reports or series (n=29). Furthermore, irrelevant papers (n=28) and articles not focusing on Abatacept as an RA medication (n=134) were removed from the research process. In the end, 12 articles were included in this study, comprising retrospective observational studies [n=6; 50%] and prospective observational studies [n=6; 50%]. These studies were conducted in various regions, with the majority taking place in European countries such as France, the United Kingdom, Sweden, Germany, the Czech Republic, Denmark, Italy, and Britain. It is worth mentioning that 3 studies were conducted in the US and 1 study was conducted in Canada. Additionally, one of the submitted articles was conducted in Japan; however, no research was found to be conducted in Africa.

These studies were conducted on a total of 86,894 patients with RA who took Abatacept. All participants were over the age of 18 and the majority were female. and. The studies were conducted over a period of 9.45 years on average. The included studies investigated various types of cancer, including breast cancer (n=7; 58.33%), lymphoma (n=8; 66.66%), lung cancer (n=10; 83.33%), melanoma (n=4; 33.33%), NMSC (n=3; 25%), cervical cancer (n=2; 16.66%), central nervous system (n=2; 16.66%), ovarian (n=2; 16.66%), colon cancer (n=4; 33.33%). Additionally, one of the submitted articles investigated the prevalence of various types of cancer, including renal, hematopoietic, urinary, uterus, digestive, pancreas, liver, prostate, duodenal, thyroid, and testicular cancers. The prevalence of various cancers was investigated in two studies.

Table 1 summarizes the information obtained from each study, including the study's initiation and termination dates, number of participants, age, gender ratio, study type, cancer type, and medicine type. Table 2 shows the concomitant disease and drug prescribed for the risk of cancer in monotherapy or combination therapy. Monotherapy with Abatacept was used in all studies except for Hashimoto's study, in which patients received Abatacept in combination with tocilizumab.

Table 1. Data extracted from the included studies

Author/year	Type of study	Sample size	Age	Ratio f/m	Type of cancer	Medicine	Concomitant disease	Follow-up	Outcome	Period of patient collection
Kyung Min Ko (2023) (33)	prospective, observational cohort study,	5,023 (on Abatacept: 5)	Mean 46(37-55)	3,544 (85.5) (f)/ 599 (14.5)	Stomach, colon, lung, brain and central nervous system		Cardiovascular disease: 2226, Interstitial lung disease: 68, Pulmonary tuberculosis: 424, COPD: 168, Diabetes mellitus: 652, Liver disease: 164, Gastric ulcer: 450, Thyroid disease:588	--	Patients with RA have a lower overall risk of cancer than people in the general population. Patients who had thyroid disease and had had their RA for a longer time were more likely to get cancer than those who took hydroxychloroquine.	8 years
Teresa A Simon (2023) (34)	prospective observational	abatacept (*n* = 5182), csDMARDs (*n* = 73,755), and other b/tsDMARDs (*n* = 37,195)	≥18	—	Lung, Breast, Lymphoma	Abatacept, csDMARDs, b/tsDMARDs	Hypertension, Diabetes, Heart failure, Myocardial infarction, COPD, CKD	3.1 years for abatacept	A few incidences of lymphoma were found in a few of the registries; ARTIS (Sweden) found that abatacept had a rate ratio (RRs) of 2.8 (95% CI 1.1-6.8) compared to csDMARDs in these cases. When compared to csDMARDs and b/tsDMARDs, the abatacept pooled RRs (95% CIs) for total cancer were 1.1 (0.8-1.5) and 1.0 (0.8-1.3), respectively.	10 years
Yosuke Kunishita (2023) (35)	multicenter, retrospective study	312	70.85±11.65	263 (f)/ 49 (m)	Duodenal, Thyroid, Colon, Lung, Malignant, lymphoma, Ovarian	abatacept, anti-cyclic citrullinated peptide antibody, b/tsDMARDs, methotrexate, prednisolone, alazosulfapyridine, tacrolimus	Interstitial lung disease (n=70)	3.55 years	Patients with a history of cancer received Abatacept just as effectively and safely as those without.	12 years
Sibylle de Germay(2020) (20)	Original article	15846	≥18	3830 (24.2) (f)	Breast, lymphoma, melanoma, lung, and NMSC	Abatacept and those exposed to other bDMARDs	--	--	There was a significant association between Abatacept and increased risk of reporting melanoma in patients with RA, compared to those with other bDMARDs	10 years
Franc¸ois Montastruc (2019) (12)	Original article	64 188 patients (4328 on Abatacept vs 59 860 on other bDMARDs)	≥18	49428 (f)/ 14760 (m)	Breast, lung, lymphoma, melanoma, and NMSC	Abatacept and bDMARDs	Hypertension: 1405 (32.5%), Type 2 diabetes: 587 (13.6%), Asthma: 279 (6.4%), Chronic obstructive pulmonary disease: 294 (6.8%), Chronic kidney disease: 97 (2.2%), Leukopaenia: 30 (0.7%), Neutropaenia: 18 (0.4%), Peripheral arterial disease: 54 (1.2%), Hyperlipidaemia: 891 (20.6%), Cardiovascular disease: 1076 (24.9%), Autoimmune disease (excluding RA): 771 (17.8%)	6 m	When compared to other bDMARDs, the utilization of the Abatacept as the first bDMARDs regarding the RA treatment was correlated with a slight increase in the overall risk of cancer, specifically, non-melanoma skin cancer.	7 years

Teresa A. Simon (2019) (22)	Retrospective	n = 17,517+12,120+3354= 32991//OTHERS: 59026	≥18		Lung, lymphoma, breast, and NMSC	Abatacept versus other b/tsDMARDs	Cardiovascular disease: 64, Autoimmune diseases: 54		The specific cancers and infection risks showed no significant difference between patients in the Abatacept and other b/tsDMARDs groups in this real-world multi-database study.	8 years
T A Simon (2009) (30)	Extended report	4134	<20 - ≥75	3323 (80)	All malignancies (excluding NMSC)	Abatacept	--	2.1 year	The Abatacept CDP's IR for total malignancy (excluding NMSC), colorectal, breast, lymphoma, and lung cancers were comparable to those in a comparable RA population. The results indicate that there are no new safety signals for malignancies, which will be closely monitored.	5 years
Hjalmar Wadström (2017) (19)	Original investigation	2021	mean 61 (51-68)	20 m	Breast, colorectal, lung, and lymphoma	Abatacept	COPD: 6 %, Diabetes: 10%, IHD: 11%	--	With one exception that requires replication treatment with TNFi (as a first or second bDMARDs), it does not appear that Tocilizumab, Abatacept, or Rituximab increase the overall occurrence of malignant neoplasms; moreover, there were no signals of increased risks for specific cancer types.	3 years
Seoyoung C. Kim (2016) (21)	A cohort Study	14729	≥ 18	f	Cervical	DMARDs	Diabetes: 21%, Chronic kidney disease: 3 %, Liver disease: 8%,	--	When compared to nonbiologic DMARDs, initiation of the biologic DMARD therapy showed a correlation with a numerically significant but not statistically significant increase in the risk of high-grade cervical dysplasia or cervical cancer among women with RA.	12 years
Atsushi Hashimoto (2015) (29)	Prospective cohort	66953	mean 62.7	81.6% female and 18.4% male	Lung, gastric, breast, lymphoma, and colon, as well as overall malignancies	Non-anti-TNF biologics (including Tocilizumab and Abatacept)	--	--	Although patients with RA revealed no higher overall rate of cancer, lymphoma was significantly more common in them, compared to the general population.	9 years
Louise K Mercer (2016) (31)	Clinical and epidemiological research	1563	mean 57.4 (56-58.2)	78.4 (77-79.2) f/	Melanoma	Abatacept	--	4399 (pyr)	No evidence of an increased risk of melanoma was indicated in this large European collaborative study as a result of TNFi exposure.	9 years

Viking Huss (2021) (32)	Original article	3306	(50-68) 60	male 19%	Prostate, testicular, breast, hematopoietic, renal, lung, colorectal, ovarian, cervical, urinary, CNS, uterus, digestive, pancreas, and liver	Abatacept	Diabetes mellitus: 10%, Hypertension: 25%, IHD: 10%, CHD: 5%, COPD: 6%, Renal insufficiency: 2%, Joint replacement: 19%	years 3.8	Findings are generally reassuring for other b/tsDMARDs and site-specific risks, but they contain signals that require further investigation.	years 17

COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease

Table 2. Shows the concomitant disease, and drug prescribe the risk of cancer in the in monotherapy or combination therapy

Auther/year	Concomitant disease	Drug prescribe	Monotherapy (abatacept) OR combination (abatacept + X)	Risk of cancer in Monotherapy or combination
Kyung Min Ko (2023) (33)	Cardiovascular disease: 2226, Interstitial lung disease: 68, Pulmonary tuberculosis: 424, COPD: 168, Diabetes mellitus: 652, Liver disease: 164, Gastric ulcer: 450, Thyroid disease:588	Hydroxychloroquine (n= 1,409), Sulfasalazine (n=681), Leflunomide (n=1288), NSAIDs (n=3336), Corticosteroids (n=3063), Bisphosphonate (n=1009), Abatacept (n=2), Adalimumab (n=35), Etanercept (n=61), IL-17 inhibitors (n=1), Infliximab (n=53), Rituximab (n=13),	Monotherapy	Incidence of malignancies in people on Abatacept =0
Teresa A Simon (2023) (34)	Hypertension, Diabetes, Heart failure, Myocardial infarction, COPD, CKD	infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, tocilizumab, rituximab, tofacitinib, anakinra, methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, tacrolimus, gold sodium thiomalate, leflunomide, aurothioglucose, auranofin, cyclosporine, penicillamine, and cyclophosphamide	Monotherapy	Crude incidence rates (IRs) per 1000 patient-years of overall malignancy ranged from 7.6–11.4 (abatacept)
Yosuke Kunishita (2023) (35)	Interstitial lung disease (n=70)	b/tsDMARDs (n=223), methotrexate (n=134), prednisolone (n=96), salazosulfapyridine (n=35), tacrolimus (n=17)	Monotherapy	Following the use of Abatacept, the incidence of cancer was 1080.3 per 100,000 person-years.
Sibylle de Germay(2020) (20)	—	Carcinogenic drugs (n=208 patient): ethinylestradiol, estradiol, estriol, estrone, estrogen, tibolone, diethylstilbestrol, tamoxifen, busulfan, chlorambucil, mephalan, semustine, thiotepa, treosulfan, chlormethine, vincristine, procarbazine, etoposide, chlornaphazine, methoxsalen and phenacetin	Monotherapy	Mono: [ROR 0.98 (95% CI 0.91, 1.05)].
Franc¸ois Montastruc (2019) (12)	Hypertension: 1405 (32.5%), Type 2 diabetes: 587 (13.6%), Asthma: 279 (6.4%), Chronic obstructive pulmonary disease: 294 (6.8%), Chronic kidney disease: 97 (2.2%), Leukopaenia: 30 (0.7%), Neutropaenia: 18 (0.4%), Peripheral arterial disease: 54 (1.2%), Hyperlipidaemia: 891 (20.6%), Cardiovascular disease: 1076 (24.9%), Autoimmune disease (excluding RA): 771 (17.8%)	MTX: 2116 (48.9) Other csDMARDs: 1709 (39.5), Parenteral antibiotics : 208 (4.8), Oral corticosteroids: 2506 (57.9), Other corticosteroids : 1167 (27.0) NSAIDs : 1767 (40.8) , Cholesterol-lowering medication: 954 (22.0)	monotherapy	Hazard ratioadjusted (HR) 1.17; 95% CI 1.06, 1.30)
Teresa A. Simon (2019) (22)	Cardiovascular disease: 64, Autoimmune diseases: 54	csDMARDs:184, b/tsDMARDs: 150, Glucocorticoids: 186	monotherapy	(HR [95% CI] 1.09 [1.02–1.16])
T A Simon (2009) (30)	—	Oral corticosteroids: 2657 (64%), NSAID: 3113 (75%)	monotherapy	Incidence of malignancies per 100 person-years (95% CI) in the abatacept clinical trial experience: SIR 0.61, 95% CI 0.45 to 0.80)

Hjalmar Wadström (2017) (19)	COPD: 6 %, Diabetes: 10%, IHD: 11%	csDMARD: 56%, Prednisolone: 58%, NSAID: 43%	monotherapy	crude incidence per 100 000 person-years: 61 (1026)
Seoyoung C. Kim (2016) (21)	Diabetes: 21%, Chronic kidney disease: 3 %, Liver disease: 8%,			Risk of high-grade cervical dysplasia or cervical cancer : Hazard ratio (95% CI) : 1.25 (0.78–2.01), Incidence rate per 1,000 person-years (95% CI): 1.59 (1.20–2.11)// Rate ratio of any gynecologic procedures: Incidence rate per 1,000 person-years (95% CI): 135.8 (129.1–142.8), Rate ratio (95% CI): 0.99 (0.90–1.09)
Atsushi Hashimoto (2015) (29)	_	_	Combination: tocilizumab and abatacept	Overall incidence of malignancies: (standardized incidence rates) 0.89, 95% CI 0.82–0.97)
Louise K Mercer (2016) (31)	_	_	monotherapy	SIR : 1.6 (95% CI)
Viking Huss (2021) (32)	Diabetes mellitus: 10%, Hypertension: 25%, IHD: 10%, CHD: 5%, COPD: 6%, Renal insufficiency: 2%, Joint replacement: 19%	_	monotherapy	1.2, 95% CI: 1.0, 1.3

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, b/tsDMARDs : targeted synthetic disease-modifying antirheumatic drugs, NSAID: non-steroidal anti-inflammatory drugs, COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease

The risk of bias identification

A total of 12 articles were investigated in this study. The quality of these articles was evaluated using the Cochrane guidelines, which consist of seven domains. 'Yes' and 'No' options were employed to mark the low and high risks of bias, respectively, in the evaluation of bias risk. The term 'unclear' was used to describe a risk of bias that was unclear or unknown. Table 3 summarizes these factors related to confounders, participants' selection, the intervention measurement, missing data, selective reporting, measurement outcome, a departure from the intended intervention, and other factors. Disease activity and duration of

Table 3. Risk of bias in the included studies (risk of bias tool by Cochrane)

Auther/year	Random sequence generation	Allocation Concealment	Blinding of participant, personal	Blinding of outcome assessment	Attrition bias	Incomplete outcome data	Selective reporting	Free of other biases	Risk of bias
Kyung Min Ko (2023) (33)	No	Unclear	No	Yes	No	No	No	No	Intermediate
Teresa A Simon (2023) (34)	No	Unclear	No	Yes	No	No	No	No	Intermediate
Yosuke Kunishita (2023) (35)	No	Unclear	No	Yes	No	No	No	No	Intermediate
Sibylle de Germay(2020) (20)	Yes	Yes	No	Yes	No	No	No	No	Low
Franc¸ois Montastruc (2019) (12)	Yes	Yes	No	Yes	No	No	No	Yes	Intermediate
Teresa A. Simon (2019) (22)	Yes	Yes	No	Yes	No	No	No	Yes	Intermediate
T A Simon (2009) (30)	No	No	No	No	No	Yes	No	Yes	Intermediate
Hjalmar Wadström (2017) (19)	Yes	Yes	No	unclear	No	No	No	Yes	Intermediate
Seoyoung C. Kim (2016) (21)	Yes	Yes	No	Yes	No	No	No	Yes	Intermediate
Atsushi Hashimoto (2015) (29)	Yes	Yes	No	Yes	No	No	No	Yes	Intermediate
Louise K Mercer (2016) (31)	No	Yes	No	Yes	No	Yes	No	Yes	Intermediate
Viking Huss (2021) (32)	Yes	Yes	No	Yes	No	No	No	Yes	Intermediate

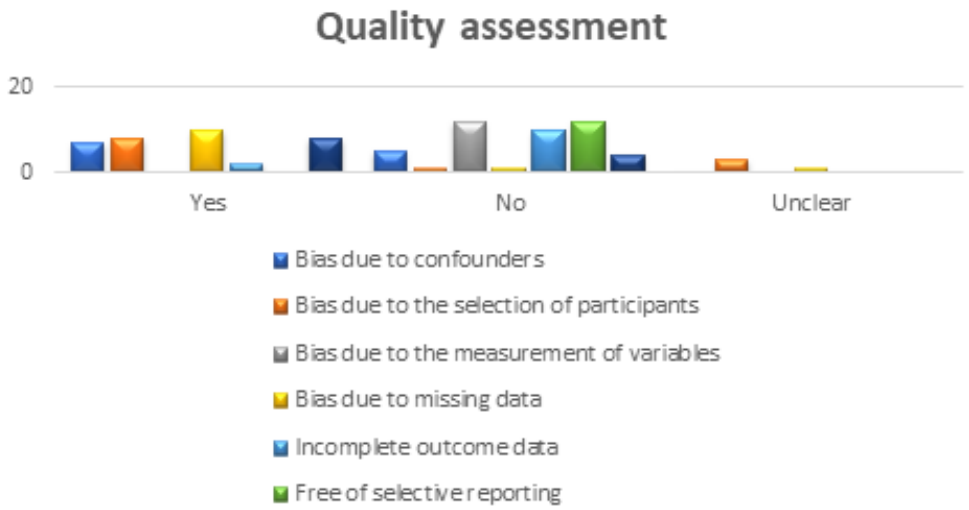

Figure 2. Quality assessment of the articles in the review process

disease were not recorded in the studies. The assessment of the selected articles' quality is presented in Figure 2.

Discussion

Several previous observational cohort studies have investigated the effect of Abatacept and other bDMARDs as first- or second-line treatments for RA on specific cancer patients. One study found no link between Abatacept use and the development of the first invasive solid or hematologic malignant neoplasm (not including NMSC). However, patients who received Abatacept revealed a higher risk of developing the first invasive squamous cell skin cancer compared to those who received TNF-α inhibitors (19). According to a study by Germay, the utilization of Abatacept is linked to higher melanoma risk in RA cases than other bDMARDs. They suggested that it was reasonable to closely monitor patients who had been exposed to Abatacept for melanoma; however, adverse reactions to this drug may occur rarely (20). Montastruc et al. demonstrated a statistically significant increase in overall cancer risk (17%) in comparison with patients who received other bDMARDs as treatment and those initiating treatment with Abatacept. Except for NMSC, the cancers under concern (lymphoma, breast, lung, and melanoma) showed no statistically significant differences. In sensitivity analyses, the results obtained from Abatacept and cancer risk stayed unchanged (12).

Molecular Mechanism of Abatacept

Inhibitory molecules, such as CTLA-4, have a key role in preventing T cells from becoming activated. According to a cohort study in the US, the overall prevalence of high cervical dysplasia or cervical cancers in the entire research cohort was estimated at 1.30 per 1,000 people/year. Furthermore, the high-grade cervical dysplasia and cervical cancer risk was 1.3 times more significant with an expansive 95% confidence level interleaved the negative value in female RA patients who started treatment with a biologic DMARD with or without a nonbiologic DMARD in comparison with patients who began their treatment with a nonbiologic DMARD only (21).

A slight improvement in total cancer risk can be attributed to Abatacept vs. other b/tsDMARD treatment that was discovered in a report by Simon et al. They utilized three large healthcare databases in the US to extract data and show safety outcomes in RA patients. However, the differences did not reach statistical significance (22).

Moreover, it is noteworthy that Abatacept has been shown to have a similar malignancy risk in some interventional trials and real-world analyses when compared to placebo or other comparators (23-25). There are several possible explanations for the modest but significant increase in average malignancy danger observed following Abatacept treatment, including Abatacept's distinctive upstream molecular mechanism and variations in patient characteristics. Abatacept is a CTLA-4 analogue. Inhibitory molecules, such as CTLA-4, can effectively prevent T cells from becoming activated. Therefore, this explains why Abatacept is being used to treat autoimmune and inflammatory diseases. Regarding the biology of cancer, the CTLA-4's role is more complicated involving tumor progression and a weakened anti-tumor response ;(26) however, there are controversies concerning this issue, and the clinical significance remains unknown (27). Furthermore, Abatacept prevents the

CD80/CD86:CD28 costimulatory signal, which is considered necessary for the activation of full T cell. As a result, this could affect immune responses to tumors while also reducing pathogenic autoimmunity (28).

Rheumatoid arthritis, cancer, and the role of race, age, and gender

The total incidence of malignancies differs in different studies, as does the incidence of each malignancy type based on racial or regional characteristics. In comparison with an age- and gender-matched Japanese population, the study of Japanese RA patients showed a slightly, however, significantly lower total incidence of all types of malignancies other than an excess of lymphoma. They also reported reduced rates of some cancer types, such as liver and colorectal, resulting in fewer malignancies overall. Hashimoto et al. suggest that it is critical to distinguish between RA characteristics (particularly long-term disease activity) and the effect of environmental or therapeutic factors, as well as comorbidities when studying the malignancy risk among RA patients. Additionally, these factors need to be looked into further. More research is needed to figure out what causes an increase in lymphoma but a decrease in the incidence of some other cancers in RA patients (29). Simon's research revealed that breast, colorectal, lung, and lymphoma incidence malignancy rates (except for NMSC) in the Abatacept clinical development program were the same as those in a comparable RA population (30).

Rheumatoid arthritis and cancer incidence: the effect of the treatment period

The findings of the study conducted by Wadström et al. were also in agreement with the preceding results. They discovered that RA patients who started therapy with TNFi or non-TNFi had the same overall cancer risk as patients with bDMARD-naive RA (19). Nonetheless, the last signal of **an** incremented **risk** of melanoma after TNFi highlighted by previous studies was not replicated across the registries in this study despite the European collaborative project of 11 registers from nine countries (31). Moreover, they found no evidence of a notable rise in both age and gender standardized incidence ratios. In terms of melanoma incidence, there was no notable difference between biologic-naive patients and those who had received TNFi, RTX, or Abatacept, or TOC.

The longest average cancer risk follow-up in RA cases treated with a b/tsDMARD (17 years) was performed by Huss et al. (32). The study found no significant increase in cancer incidence with TNF inhibitors and observed no trends with time since treatment start, time on active treatment, or age attained, in comparison with b/tsDMARD-naive cases. Even when estimates of some relative risk were (statistically significantly) higher than 1, they found no steady signal of incremented total cancer risks with other bDMARDs. Regarding the relative risk for 16 cancer sites, they found some statistically notable relationships with the TNFis Rituximab and Abatacept for urinary tract cancer.

Limitations and suggestions

According to the studies, we found no statistically notable link between the risk of Abatacept use and the prevalence of malignancy. However, studies suggest that this medicine and other effective RA prescriptions be used with greater caution. Furthermore, one of the significant flaws in the studies reported in this review article is no mention of medicine doses among patients, even when they are of different ages and genders. This could be one of the essential factors confounding the outcomes. Moreover, the use of biologics in combination with other immunosuppressive drugs can raise malignancy risk in these patients. This issue may have distorted the findings of the reviewed studies. Finally, it is recommended that clinical trials focus on the dose and duration of Abatacept and compare them to the control groups in the future.

Conclusion

In comparison to other biologic antirheumatic drugs (bDMARDs), the administration of Abatacept as the initial bDMARD in rheumatoid arthritis has shown a rise in the overall cancer risk, specifically in relation to non-melanoma skin cancer (NMSC). Nonetheless, the rate of malignancies in RA patients was not significantly greater in comparison with the general population. The obtained results indicate that there is no additional indication of safety concerns related to the development of malignancies. However, it is important to note that ongoing surveillance will be conducted to closely monitor this matter. Further studies are required to substantiate the use of Abatacept in those suffering from RA.

Conflict of interest

The authors declare no competing interests.

Authors' contributions

Drafting of the manuscript and screening the article was done by (Homapoor S, Sahebari M). Conception and design was done by (Khodashahi M, Homapoor S). Critical revision of the manuscript

for important intellectual content and double review to minimize bias was conducted by authors (Khodashahi M, Sahebari M, Homapoor S).

Ethics approval and consent to participate

This is a systematic review article and all ethics approval and consent of used articles was checked. No aspect of this article was related to laboratory animals, special human illnesses, and/or the use of people's information.

Consent for publication

"Not applicable."

Availability of data and materials

All data from this study are included in the published article and its supplementary files.

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