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Association between rheumatoid arthritis and lung neoplasm; a systematic review and meta-analysis

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Abstract

Introduction: Lung cancer is one of the most common malignancies in patients with rheumatoid arthritis (RA). Therefore, this study aimed to determine the association between RA and lung neoplasm using a systematic review and meta-analysis.

Materials and Methods: This research was conducted according to the PRISMA guidelines. The databases ProQuest, PubMed, Embase, Web of Science, Cochrane, Scopus, and the search engine Google Scholar were searched up to October 8, 2024. Data analysis was performed using STATA 14 software, and $P<0.05$ was considered statistically significant.

Results: A total of 24 cohort studies, comprising 792,699 participants, were evaluated. The results indicated that RA increased the risk of lung neoplasm. Specifically, the hazard ratio (HR) was 1.54 (95% CI: 1.33–1.77), the standardized incidence ratio (SIR) was 1.30 (95% CI: 1.19–1.41), and the risk ratio (RR) was 1.50 (95% CI: 1.31–1.71). RA increased the risk of lung neoplasm in both women (SIR: 1.24; 95% CI: 1.12, 1.39) and men (SIR: 1.71; 95% CI: 1.37, 2.15). No significant statistical association was found between RA and lung neoplasm in patients aged 30-39 years (SIR: 1.40; 95% CI: 0.64, 3.08) and 40-49 years (SIR: 0.64; 95% CI: 0.21, 1.93). However, in patients aged 50-59 years (SIR: 1.31; 95% CI: 1.18, 1.45) and 60-69 years (SIR: 1.63; 95% CI: 1.51, 1.77), RA increased the risk of lung neoplasm.

Conclusion: Rheumatoid arthritis was associated with an increased risk of lung neoplasm, and this risk increased with age. The risk of lung neoplasm was higher in men than in women. Therefore, advanced age and male gender were identified as risk factors for lung neoplasm in RA patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024602266) and Research Registry (UIN: reviewregistry1900) websites.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammatory polyarthritis, extra-articular manifestations, severe disability, and increased mortality (1-4). The most common inflammatory joint disease is RA, affecting 24.5 million people worldwide (5). In 60%-80% of patients with RA, pulmonary involvement is an extra-articular manifestation (6). In addition, RA is associated with an increased risk of comorbidities, including cardiovascular diseases, infections, and cancers, which further increase disease burden and reduce life expectancy (7,8). RA and its treatment disrupt immune regulation and increase susceptibility to infections, which may greatly impact the risk of developing many cancers (1,9).

Rheumatoid arthritis is one of the most common malignancies in patients (10). There have been several proposed risk factors for lung carcinoma in RA, including male gender, smoking, and interstitial lung disease (11-13). This disease may also increase lung carcinoma risk due to chronic inflammation.

Key point

In a comprehensive evaluation of 24 cohort studies involving a total of 792 699 participants, evidence indicates that rheumatoid arthritis significantly elevates the risk of lung cancer. The analysis reveals that as patients age, their likelihood of developing lung cancer increases, with a pronounced risk observed in men compared to women. Consequently, both advanced age and male gender emerge as critical risk factors for lung carcinoma among individuals suffering from rheumatoid arthritis. This correlation underscores the need for heightened surveillance and targeted interventions in these high-risk populations to mitigate lung cancer incidence associated with rheumatoid arthritis.

RA patients have been shown to have a link between pro-inflammatory cytokines and lung carcinoma risk independent of smoking (14,15). Cohort studies of the association between RA and lung carcinoma have yielded conflicting results. RA has been identified as a risk factor for lung carcinoma in some studies (16,17) and not in others (18,19). Even one study suggested that RA might lower the risk of lung carcinoma (20). For this reason, the current study was conducted as a systematic review and meta-analysis to summarize previous findings and present a comprehensive conclusion.

Materials and Methods

Study protocol

The PRISMA protocol (21) was used to design this systematic review and meta-analysis, and the study protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) and Research Registry websites.

PECO elements

Population: Studies evaluating the association between RA and lung cancer risk.
Exposure: Diagnosis of RA.
Comparison: Individuals without RA.
Outcome: Lung cancer risk.

Search strategy

Using relevant keywords and their MeSH equivalents, searches were conducted in databases such as ProQuest, PubMed, Embase, Web of Science, Cochrane, Scopus, and Google Scholar up to October 8, 2024. The keywords included lung neoplasms, lung cancer, pulmonary neoplasm, rheumatic arthritis, rheumatic fever, and inflammatory rheumatism. The search was conducted without time or geographic restrictions. Keywords were combined using logical operators (AND, OR). The reference lists of primary and review studies were manually reviewed. The search strategy used for the Web of Science database is outlined as follows: Rheumatic Arthritis OR Rheumatic Fever OR Inflammatory Rheumatism (All Fields) AND Lung Neoplasms OR Lung Cancer OR Pulmonary Neoplasm (All Fields).

Inclusion and exclusion criteria

Studies that evaluated the association between RA and lung cancer risk were included. However, studies with insufficient data for analysis, duplicate studies, reviews, and meta-analyses, low-quality studies, studies without accessible full texts, studies investigating the impact of RA on overall cancer without separately addressing lung carcinoma, letters to the editor, and studies assessing the combined effect of RA and another condition on lung carcinoma were excluded from the review process.

Qualitative assessment

This stage was conducted independently by two researchers. The quality of studies was assessed using the Newcastle Ottawa Scale (NOS). Each question could receive a maximum of one star, except for the comparison question, which could be awarded up to two stars. The lowest possible score was zero (poorest quality), and the highest was ten (best quality) (22).

Data extraction

Data extracted from the studies included the author's name, study type, country, number of patients, patient age, year, association between RA and lung carcinoma in the overall population as well as in men and women (including upper and lower limits), study duration, and other relevant details. Two researchers carried out this stage.

Statistical analysis

The collected data was analyzed by logarithms of the hazard ratio (HR), relative risk (RR), and standardized incidence ratio (SIR). The studies were then combined. The I^2 index was used to assess the heterogeneity of the studies. A random effects model was used due to high heterogeneity. Subgroup analyses were performed to examine the association between RA and lung carcinoma by age, country, and index. We also performed additional analyses, such as meta-regression and publication bias. Data analysis was done using STATA 14 software, and $P < 0.05$ was taken as statistically significant.

Results

Study selection

A total of 739 studies were identified after the search phase. Of these, 342 were duplicates and were discarded. Of the remaining 397 studies, 38 were excluded because of incomplete abstract information and lack of accessible full texts. We reviewed the full texts of 359 studies and excluded 51 studies that did not report essential data for analysis. Of the remaining 308 studies, 284 were excluded for other exclusion criteria, leaving 24 studies for analysis (Figure 1).

A total of 24 cohort studies with a combined sample size of 792 699 participants were evaluated in this meta-analysis (Table 1).

In Figure 2, RA was shown to increase the risk of lung

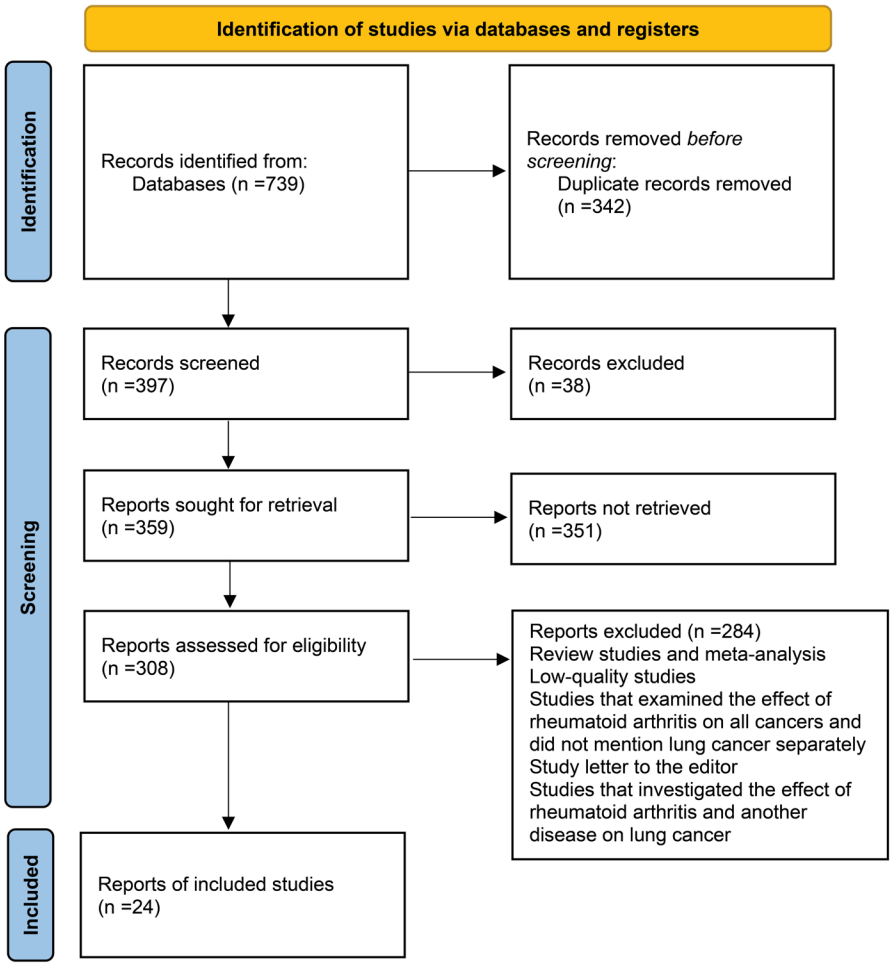

Figure 1. The PRISMA flowchart of the study.

carcinoma. The HR was 1.54 (95% CI: 1.33, 1.77), the SIR was 1.30 (95% CI: 1.19, 1.41), and the RR was 1.50 (95% CI: 1.31, 1.71) (Figure 2).

Subgroup analysis showed that the association between RA and lung carcinoma was not statistically significant in South Korea (SIR: 1.39; 95% CI: 0.83, 2.35), Taiwan (SIR: 1.16; 95% CI: 0.95, 1.43), Japan (SIR: 1.54; 95% CI: 0.72, 3.30), Canada (SIR: 1.08; 95% CI: 0.64, 1.83), and China (SIR: 1.22; 95% CI: 0.45, 3.31). However, in the UK (SIR: 1.21; 95% CI: 1.16, 1.27), Sweden (SIR: 1.55; 95% CI: 1.33, 1.79), the US (SIR: 1.58; 95% CI: 1.53, 1.64), France (SIR: 1.41; 95% CI: 1.36, 1.46), and Denmark (SIR: 1.50; 95% CI: 1.31, 1.72), RA significantly increased the risk of lung carcinoma (Figure 3).

No significant association between RA and lung carcinoma was found in patients aged 30-39 years (SIR: 1.40; 95% CI: 0.64, 3.08) and 40-49 years (SIR: 0.64; 95% CI: 0.21, 1.93). However, RA increased the risk of lung carcinoma in patients aged 50-59 years (SIR: 1.31; 95% CI: 1.18, 1.45) and 60-69 years (SIR: 1.63; 95% CI: 1.51, 1.77) (Figure 4).

As illustrated in Figures 5 and 6, RA increased the risk of lung carcinoma in women (SIR: 1.24; 95% CI: 1.12, 1.39) and men (SIR: 1.71; 95% CI: 1.37, 2.15).

We performed a meta-regression analysis and found no significant association between the "RA and lung carcinoma association" and year of study publication ($P=0.849$) or sample size ($P=0.924$) (Figures 7 and 8).

As shown in Figure 9, the publication bias plot showed no publication bias ($P=0.739$), and the search was not biased ($P=0.739$).

Discussion

The risk of lung carcinoma is significantly increased in RA, and older age and male gender are key risk factors. Moreover, RA patients in the United Kingdom (21%), Sweden (55%), the United States (58%), France (41%) and Denmark (50%) had a higher risk of lung carcinoma.

A meta-analysis by Wu et al, which included 11 cohort studies and 183,888 patients, found that RA is associated with an increased risk of lung carcinoma (RR: 1.44; 95% CI: 1.31, 1.57) (42). The findings of this study are consistent with the current study, which reviewed 24 cohort studies with 792 699 patients. The current analysis also ran the review up to October 2024, whereas Wu's analysis ended in 2019. Therefore, the larger sample size in the present

Table 1. A summary of the information of the reviewed articles

Index	Author, year	Country	Sample size in target group	Mean age in target group	Sample size in compare group	Mean age in compare group	Duration of study
HR	Brooks RT, 2024 (16)	USA	72795	63	633937	61.9	between 2000 and 2019
HR	Yang TO, 2024 (17)	UK	62681	57.9	1251157	56.6	Between 1996 and 2001
HR	Cho MH, 2024 (23)	South Korea	51899	58.6	259495	58.6	between 2010 and 2017
SIR	Ko KM, 2023 (20)	South Korea	5077	46	NR	NR	from July 2009 to December 2011
SIR	Beydon M, 2023 (24)	France	257074	≥20	NR	NR	between January 1, 2010 and December 31, 2020
SIR	Sugimoto N, 2023 (19)	Japan	11299	57.2	NR	NR	from April 2000 to September 2013
HR	Wang F, 2023 (25)	USA	68415	NR	1340538	NR	from April 1, 2008, to December 31, 2019
HR	Chatzidionysiou K, 2022 (26)	Sweden	44101	61	216495	61	from 1 January 1995 to 31 December 2018
HR	Choi HG, 2022 (27)	South Korea	3070	≥40	12280	≥40	between 2002 and 2015
HR	Zhang L, 2020 (18)	China	18	68.83	136	64.35	between January 2015 and December 2017
SIR	Lim XR, 2019 (28)	Singapore	1117	48.1	NR	NR	Between 2001 and 2013
SIR	Lee H, 2019 (29)	South Korea	1885	55.8	NR	NR	between 1996 and 2009
SIR	Yu KH, 2016 (30)	Taiwan	35182	52.56	NR	NR	from 1997 to 2010
HR	Raheel S, 2016 (31)	USA	813	55.9	NR	NR	1980–2007
SIR	Huang WK, 2014 (32)	Taiwan	30504	53.6	NR	NR	between 1996 and 2008
SIR	Chang SH, 2014 (33)	South Korea	2104	51	NR	NR	between January 2000 and April 2012
SIR	Chen YJ, 2011 (34)	Taiwan	23644	53.08	NR	NR	1996 to 2007
SIR	Yamada T, 2011 (35)	Japan	7566	55.9	NR	NR	from April 2001 to April 2005
SIR	Askling J, 2005 (36)	Sweden	53067	≥16	NR	NR	1990-2003
SIR	Thomas E, 2000 (37)	UK	26623	NR	NR	NR	1 January 1981 to 31 December 1996
SIR	Cibere J, 1997 (38)	Canada	862	43	NR	NR	from 1966 to 1974
RR	Mellemkjaer L, 1996 (39)	Denmark	20699	NR	NR	NR	1977-1987
SIR	Gridley G, 1993 (40)	Sweden	11683	NR	NR	NR	from 1965 to 1983
RR	Katusic S, 1985 (41)	USA	521	34.3	NR	NR	from 1950 to 1975

NR, Not reported; HR, hazard ratio; RR, Risk ratio; SIR, Standardized incidence ratio.

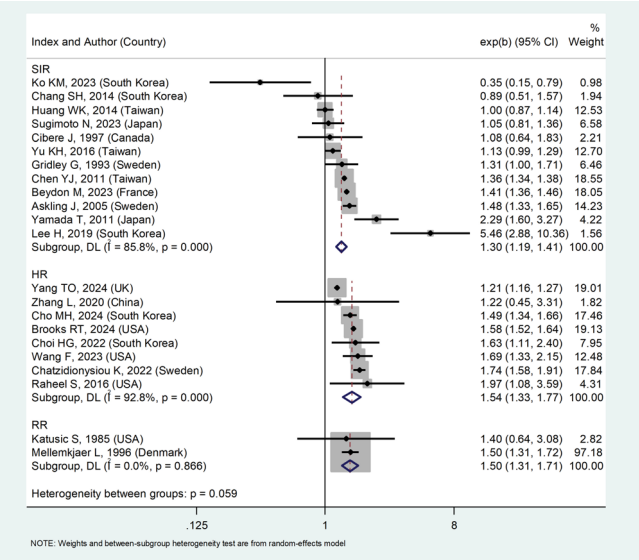

Figure 2. Forest plot showing the association between rheumatoid arthritis and lung neoplasm by index.

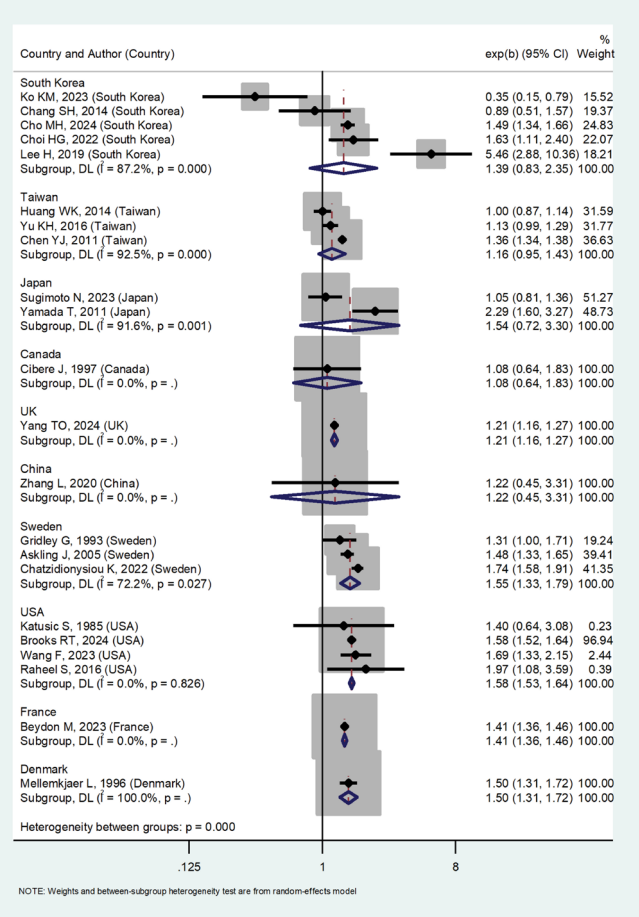

Figure 3. Forest plot showing the association between rheumatoid arthritis and lung neoplasm by country.

meta-analysis increases the generalizability of its results.

Simon and colleagues also conducted another meta-analysis of the incidence of malignancies in RA patients. They found that RA patients have a higher incidence of lymphoma (SIR: 2.46; 95% CI: 2.05, 2.96) and lung carcinoma (SIR: 1.64; 95% CI: 1.51,1.79) than the general population (10). RA is also associated with an increased risk of lung carcinoma, according to the meta-analysis by Smitten et al combined with the present analysis (43), these studies indicate that people with RA have an increased risk

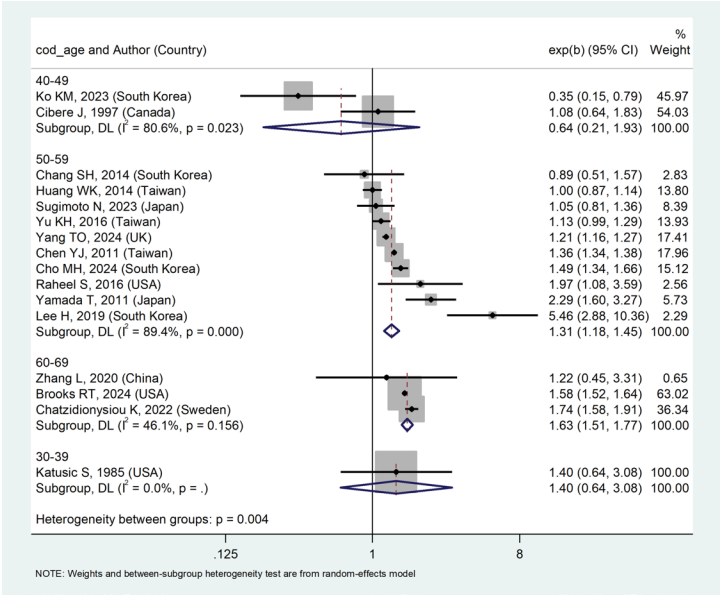

Figure 4. Forest plot showing the association between rheumatoid arthritis and lung neoplasm by age group.

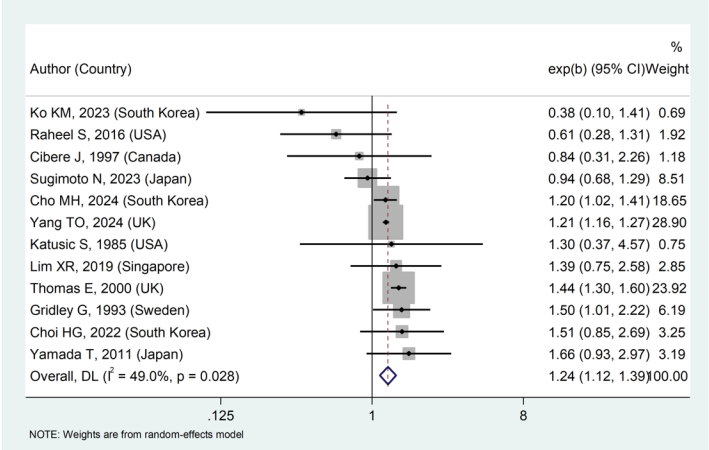

Figure 5. Forest plot showing the association between rheumatoid arthritis and lung neoplasm in females.

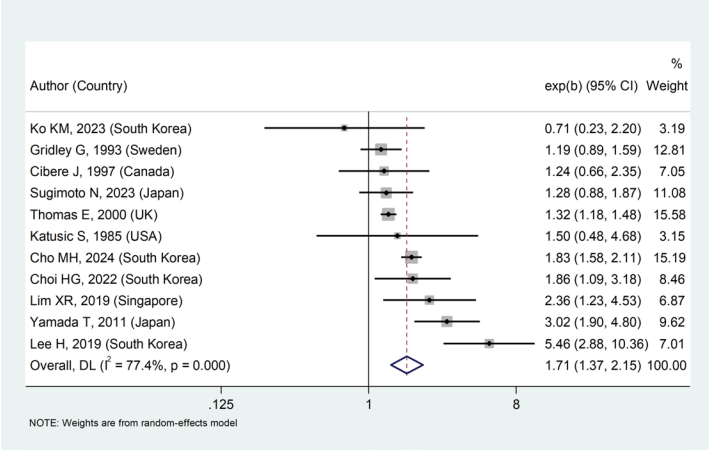

Figure 6. Forest plot showing the association between rheumatoid arthritis and lung neoplasm in males.

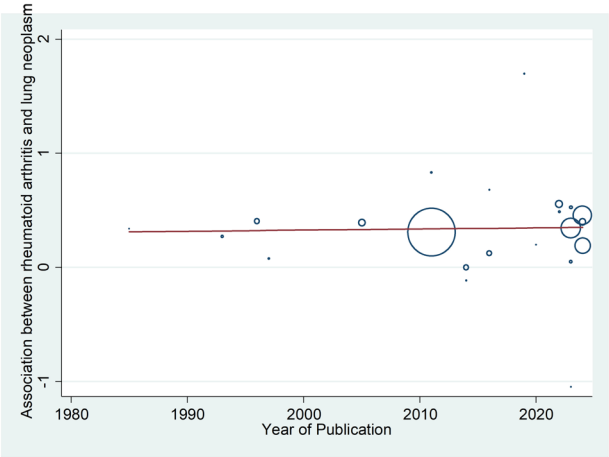

Figure 7. Meta-regression plot of the association between rheumatoid arthritis and lung neoplasm with year of publication.

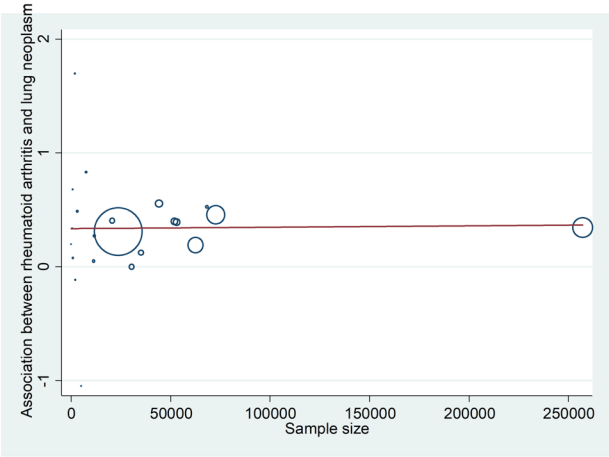

Figure 8. Meta-regression plot of the association between rheumatoid arthritis and lung neoplasm with sample size.

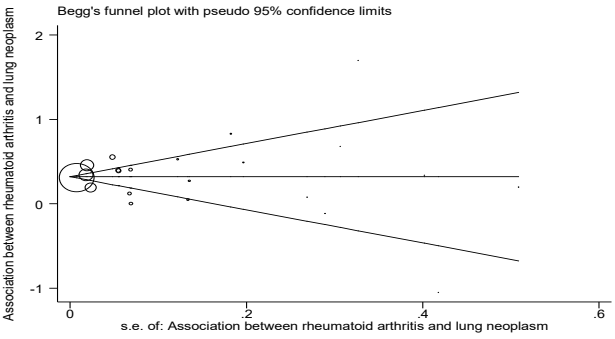

Figure 9. Plot of publication bias.

of lung carcinoma (SIR: 1.63; 95% CI: 1.43,1.87) relative to the general population.

On the contrary, the Tian et al meta-analysis found that RA was not associated with increased breast cancer risk (SIR: 0.86; 95% CI: 0.72,1.02) (44), which is consistent with the current finding, but because a distinction could be made between cancer types (RA and lung cancer) based on their common risk factors, such as smoking.

Wu et al also conducted a meta-analysis to investigate the association between systemic lupus erythematosus (SLE) and lung cancer risk (OR: 1.60; 95% CI: 1.44,1.77) (45), and they found that SLE raises the risk of lung cancer. SLE is found to increase the risk of malignancies such as lung cancer (RR:1.86; 95% CI: 1.21, 2.88) (46), Cao and colleagues found. Song et al also found an association between SLE and lung cancer (SIR: 1.62; 95% CI: 1.40,1.87) (47), and Zhong et al examined the relationship between primary Sjögren's syndrome and cancer risk and found increased lung cancer risk (SIR: 1.55; 95% CI: 1.29,1.85) (48), which further confirms that besides RA, SLE and Sjögren's syndrome are also associated with higher lung cancer risk.

Conclusion

Patients with RA exhibit a significantly elevated risk of developing lung cancer compared to the general population, with advanced age and male gender identified as major risk factors contributing to this increased susceptibility. Notably, American RA patients appear to be at the highest risk for lung carcinoma, highlighting a critical area for public health intervention. Given these findings, it is strongly recommended that targeted lung cancer prevention measures be implemented for this high-risk demographic. Such proactive strategies could potentially mitigate the incidence of lung cancer among RA patients, ultimately improving their overall health outcomes and quality of life.

Limitations of the study

The limitations of the study are significant and multifaceted. Firstly, not all analyzed studies reported a gender breakdown, which restricts the ability to draw comprehensive conclusions regarding gender-specific outcomes. Additionally, the inclusion criteria were limited to cohort studies, potentially overlooking valuable insights from other study designs that could provide a more robust understanding of the topic. Furthermore, there was a notable absence of studies from certain countries, indicating a geographical bias that may affect the generalizability of the findings. Finally, the reviewed studies did not provide an average duration of RA, which is critical for contextualizing the results and understanding how chronicity may influence outcomes in the population studied.

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Authors' contribution

Conceptualization: Amir Behnam Kharazmi and Sajad Ataei Azimi.
Data curation: Hossein Mardanparvar.
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Supervision: Amir Behnam Kharazmi.

Validation: Gülüzar Özbolat.
Visualization: Seyed Amir Sheikholeslami.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest
There are no competing interests.

Ethical issues
This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42024602266) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1900). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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