RMD Open
Rheumatic & Musculoskeletal Diseases

EDITORIAL

Is there room for better screening for lung cancer in rheumatoid arthritis?

Chrysoula G Gialouri,[1] George E Fragoulis [2]

To cite: Gialouri CG, Fragoulis GE. Is there room for better screening for lung cancer in rheumatoid arthritis?. *RMD Open* 2022;**8**:e002774. doi:10.1136/rmdopen-2022-002774

Received 31 October 2022
Accepted 15 November 2022

[1]Joint Academic Rheumatology Program, 2nd Department of Medicine and Laboratory, General Hospital of Athens "Hippokration", National and Kapodistrian University of Athens, Athens, Greece
[2]Joint Academic Rheumatology Program, First Department of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

Correspondence to
Dr George E Fragoulis; geofragoul@yahoo.gr

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis with a high morbidity burden attributed to extra-articular manifestations, comorbidities and disease/treatment-related complications.[1] Comorbidities commonly hamper the control of the disease and contribute to worse disease outcomes.[1 2] Of note, cardiovascular disease and malignancies are the leading causes of death in RA.[3 4]

Lung cancer is one of the most frequent incident malignancies in patients with RA and is estimated as the principal cancer-related cause of death in RA.[3 5 6] Also, compared with the general population, patients with RA have 1.5–3.5 times higher risk of lung cancer, which is more pronounced in older, male patients.[7]

The association of lung malignancies with RA can have at least four not mutually exclusive explanations.

First, lung cancer and RA share common risk factors. Among them, smoking is a well-defined predisposing factor for both entities. Tobacco smoke provokes oxidative stress, which in turn induces pulmonary inflammation, initiation of carcinogenesis and thus immune system activation.[8] Smoking also induces post-translational modifications (eg, citrullination, carbamylation) of proteins in the mucosa of the lungs, leading to the creation of neoepitopes, which can then be recognised by the adaptive immune system, resulting in the production of autoantibodies such as anticitrullinated peptide antibodies (ACPA) (eg, antimutated citrullinated vimentin and anticyclic citrullinated peptide antibodies).[9 10] Interestingly, there is one hypothesis supporting that, in genetically susceptible individuals, the critical events that trigger the autoimmunity and therefore ACPA-positive RA take place initially in the lungs.[11] Beyond smoking, other airway exposures have been found to stimulate the pathways involved in RA and lung cancer pathophysiology.[12 13] Furthermore, interstitial lung disease (ILD) is emerging as another potential shared determinant. Limited available data support that lung cancer is significantly more prevalent among patients with ILD,[14] while in parallel ILD is the most characteristic extra-articular manifestation of RA.[15] Notably, interstitial lung abnormalities have been associated with a greater hazard of subsequent lung cancer diagnosis and mortality in the general population,[16] while a retrospective cohort has demonstrated high incidence of lung cancer in patients with RA-ILD.[17]

Second, since many of patients with RA have some evidence of at least subclinical ILD,[18] this population undergoes a more thorough clinical evaluation and imaging screening, enabling earlier diagnosis of lung cancer.

Third, given the role of immune system in tumour surveillance, the immunosuppressive/immunomodulatory therapies for RA could potentially be implicated in the risk of malignancy. Although more research is warranted to eliminate this concern, studies so far have not shown a clear sign of higher malignancy rates in patients with RA treated with these drugs.[19 20] Besides, in a recent large prospective cohort of Swedish patients with RA, with a median follow-up of more than 3 years, the risk of cancer overall as well as specifically in the lungs was not increased in patients who were treated with tumour necrosis factor inhibitors, anti-CD20 or interleukin-6 inhibitor compared with those who were naïve to biologic disease-modifying antirheumatic drugs.[21]

Fourth, yet importantly, the biological mechanisms in RA could directly mediate the occurrence of lung cancer. Besides, in a large Swedish cohort, the risk of lung cancer increased only after the diagnosis of RA.[22] Chronic immune dysregulation/inflammation is prominent in the course of RA[9] and is also a well-known precursor to neoplastic processes.[23] To elaborate the association between inflammation and cancer, the 'Rotterdam' study examined general population participants aged at least 55

years and found that individuals with C-reactive protein levels >3 mg/L (vs <1 mg/L) had a higher adjusted risk of getting lung cancer, even after a latent period of 5 years.[24] In populations with RA, inflammation has mainly been recognised as a key factor for lymphoma, whereas evidence for lung cancer has been missing thus far.[19]

The study by Chatzidionysiou and colleagues[25] introduces another RA-related feature: the autoantibody status, particularly the ACPA positivity or the double positivity for rheumatoid factor (RF) and ACPA, as a smoking-independent determinant of incident lung cancer in patients with RA.

In brief, the authors aimed to investigate whether the increased risk of lung cancer in RA could be explained by factors other than known confounders such as smoking. They conducted a population-based, prospective, matched-cohort study using three Swedish sources to compose the RA population: the Swedish Rheumatology Quality Register and its adjunct biobank, the National Patient Register, and the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case–control study. In the entire cohort (44 101 patients with RA and 216 495 general population controls, matched 1:5 for age, sex, calendar period and area of residence), 56 and 33 incident lung cancers per 100 000 person-years in the RA and general populations, respectively, were identified, with an adjusted HR (for age, sex, index year, county of residence and comorbidities) of 1.70 (95% CI 1.54 to 1.87). Of note, majority of the cases were observed within the first 5 years of RA diagnosis. Additionally, in the EIRA subcohort (mean follow-up: 9 years; 2060 patients with RA and 2779 controls), the risk of lung cancer in RA (vs controls) increased independently of smoking (HR of 1.77 (95% CI 1.06 to 2.97) in the multivariable model that included ever/never smoking and HR of 1.99 (95% CI 1.16 to 3.41) in the model with pack-years of smoking). When the EIRA participants were divided into (1) ever-smokers/never-smokers and (2) current/past smokers, the adjusted (for comorbidities) HR (with 95% CI) of lung cancer was significantly increased only in ever-smokers and current smokers with (vs without) RA, confirming the strong association between smoking and lung cancer. Interestingly, the risk of lung cancer in ever-smokers with RA (vs never-smokers) increased about ninefold (HR: 8.68, 95% CI 2.09 to 36.14) compared with a fourfold increased risk in the respective general population groups (HR: 3.95, 95% CI 1.36 to 11.52).

To examine whether the observed risk of lung cancer in RA, in addition to smoking, downs to seropositivity, Chatzidionysiou *et al*[25] stratified patients from the EIRA subcohort by autoantibody status and demonstrated that ACPA-positive (vs ACPA-negative) as well as double-positive (RF and ACPA vs double-negative) patients had at least a twofold higher risk of lung cancer. In addition, autoantibody positivity (defined as RF, ACPA, RF and/or ACPA, and RF and ACPA positivity) was significantly associated with increased risk of lung cancer even after controlling for confounders such as smoking (ever/never or intensity) and comorbidities (renal failure, heart failure, ischaemic heart disease, chronic obstructive pulmonary disease, respiratory infections, hospitalisation). Across all models, the risk increased two to six times, with the highest hazard being found in the case of double-positive (vs double-negative) status. In total, at 20 years, the absolute risk of lung cancer was almost 3% in the overall EIRA cohort and over 4% in ever-smoker patients with RA with at least one autoantibody (RF, ACPA).

The study by Chatzidionysiou *et al*[25] has certain strengths. This is a prospective cohort with a long follow-up period and a large sample size, conferring external validity. Also, the methodology used to minimise confounding, most importantly of smoking, and the presence of comparator group increased the internal validity of the cohort. Additionally, this is the first study to examine the relative risk of lung cancer in patients with RA in relation to autoantibody status, taking into account smoking habits.

However, the present study also has some limitations. First, in the EIRA subcohort, at which was studied the role of autoantibody status, information on seropositivity was based mainly on International Classification of Diseases (ICD) codes, whereas data of only 8% (174 out of 2060) of patients were retrieved from a reliable biobank. Notably, serostatus was defined at one timepoint. Furthermore, data on smoking habits were available up until the time of RA diagnosis and so changes were not captured. Importantly, residual confounding from other airway exposures which are able to induce immune responses, RA and lung cancer cannot be excluded,[26] since the respective data were not recorded. Another limitation is that ILD and other coexisting conditions in participants with RA were sourced by ICD codes. Therefore, the rate of ILD in this cohort was about 1%–3%, which is lower than other data sets.[18] Also, subclinical diseases cannot be excluded so as to estimate their effects on the risk of lung cancer.

Yet these findings meaningfully support seropositivity as an independent risk factor for lung cancer in patients with RA, although any causal relationship cannot be confirmed and residual confounding from smoking, ILD and other determinants cannot be totally excluded. Chatzidionysiou *et al*[25] also raised the question of whether selected patients with RA (ie, ever-smokers with seropositive RA) should undergo regular CT lung screening.

To date, several randomised controlled trials of low-dose CT-based lung cancer screening have been conducted, with the most powerful being the US National Lung Screening Trial[27] and the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) trial.[28] Overall, the evidence highlights a significant reduction in mortality associated with implementation of lung screening in asymptomatic high-risk individuals.[29] However, respective studies in patients with RA are lacking. On the other hand, delayed diagnosis is the main cause of death in patients with lung cancer. Hence, screening programmes should be restricted to individuals who are at high risk of lung cancer within the RA population so as to minimise

all potential harms (eg, exposure to radiation) and maximise the benefits from prompt detection and intervention, as well as its cost-effectiveness for diverse healthcare systems.

In summary, mass CT lung screening of all patients with RA cannot be supported with the currently available evidence. Instead, increased awareness of lung cancer is essential in selected patients with RA, such as smokers and those with positive autoantibodies. Definitely, regular clinical evaluation and interventions for smoking cessation are irreplaceable in everyday practice. Further well-designed studies are required for better stratification of lung cancer risk in RA according to clinical, serological and molecular characteristics of patients.

Contributors CGG: drafting of the manuscript. GEF: drafting and approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests GEF has received honoraria/speaker fees from AbbVie, Genesis, Pfizer, Novartis, Lilly, UCB, Janssen, Amgen and Aenorasis.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD

George E Fragoulis http://orcid.org/0000-0003-4932-7023

REFERENCES

1 Dey M, Nagy G, Nikiphorou E. Comorbidities or extra-articular manifestations: time to reconsider the terminology? *Rheumatology* 2022;61:3881–3.
2 Norton S, Koduri G, Nikiphorou E, *et al*. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. *Rheumatology* 2013;52:99–110.
3 Jain K, Laila D, Nandagudi A, *et al*. Long-term outcomes in Rheumatoid Arthritis: Review of data from the 'Basildon Inflammatory Arthritis Cohort'. *Rheumatol Adv Pract* 2022;6:rkac075.
4 Widdifield J, Paterson JM, Huang A, *et al*. Causes of death in rheumatoid arthritis: how do they compare to the general population? *Arthritis Care Res* 2018;70:1748–55.
5 Simon TA, Thompson A, Gandhi KK, *et al*. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015;17:212.
6 Mattey DL, Thomson W, Ollier WER, *et al*. Association of Drb1 shared epitope genotypes with early mortality in rheumatoid arthritis: results of eighteen years of followup from the early rheumatoid arthritis study. *Arthritis Rheum* 2007;56:1408–16.
7 Fragoulis GE, Chatzidionysiou K. Lung cancer in rheumatoid arthritis. is there a need for better risk assessment and screening? *Clin Rheumatol* 2020;39:957–61.
8 Valavanidis A, Vlachogianni T, Fiotakis K, *et al*. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *Int J Environ Res Public Health* 2013;10:3886–907.
9 Smolen JS, Aletaha D, Barton A, *et al*. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
10 van Delft MAM, Huizinga TWJ. An overview of autoantibodies in rheumatoid arthritis. *J Autoimmun* 2020;110:102392.
11 Reynisdottir G, Olsen H, Joshua V, *et al*. Signs of immune activation and local inflammation are present in the bronchial tissue of patients with untreated early rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1722–7.
12 Zhao C-N, Xu Z, Wu G-C, *et al*. Emerging role of air pollution in autoimmune diseases. *Autoimmun Rev* 2019;18:607–14.
13 Xue Y, Wang L, Zhang Y, *et al*. Air pollution: a culprit of lung cancer. *J Hazard Mater* 2022;434:128937.
14 Jung HI, Park JS, Lee M-Y, *et al*. Prevalence of lung cancer in patients with interstitial lung disease is higher than in those with chronic obstructive pulmonary disease. *Medicine* 2018;97:e0071.
15 Conway R, Nikiphorou E. Treating interstitial lung disease in rheumatoid arthritis - the embers of hope. *Rheumatology* 2020;59:3589–90.
16 Axelsson GT, Putman RK, Aspelund T, *et al*. The associations of interstitial lung abnormalities with cancer diagnoses and mortality. *Eur Respir J* 2020;56. doi:10.1183/13993003.02154-2019. [Epub ahead of print: 17 12 2020].
17 Fu Q, Wang L, Li L, *et al*. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clin Rheumatol* 2019;38:1109–16.
18 Fragoulis GE, Nikiphorou E, Larsen J, *et al*. Methotrexate-Associated pneumonitis and rheumatoid Arthritis-Interstitial lung disease: current concepts for the diagnosis and treatment. *Front Med* 2019;6:238.
19 De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. *Best Pract Res Clin Rheumatol* 2018;32:869–86.
20 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386:316–26.
21 Huss V, Bower H, Wadström H, *et al*. Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice. *Rheumatology* 2022;61:1810–8.
22 Hellgren K, Smedby KE, Feltelius N, *et al*. Do rheumatoid arthritis and lymphoma share risk factors?: a comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. *Arthritis Rheum* 2010;62:1252–8.
23 O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer* 2001;85:473–83.
24 Siemes C, Visser LE, Coebergh J-WW, *et al*. C-Reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam study. *J Clin Oncol* 2006;24:5216–22.
25 Chatzidionysiou K, di Giuseppe D, Soderling J, *et al*. Risk of lung cancer in rheumatoid arthritis and in relation to autoantibody positivity and smoking. *RMD Open* 2022;8:e002465.
26 Otsuki T, Maeda M, Murakami S, *et al*. Immunological effects of silica and asbestos. *Cell Mol Immunol* 2007;4:261–8.
27 National Lung Screening Trial Research Team, Aberle DR, Adams AM, *et al*. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
28 de Koning HJ, van der Aalst CM, de Jong PA, *et al*. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020;382:503–13.
29 Oudkerk M, Liu S, Heuvelmans MA, *et al*. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol* 2021;18:135–51.