ΛΑΪΚΟ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

Screening για νεοπλασίες στις φλεγμονώδεις αρθρίτιδες. Τι νεότερο;

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Disclosures

Fellow, *EULAR Recommendations on Malignancy Risk Assessment in Autoimmune Rheumatic Diseases*

Outline

Background

Malignancy risk in inflammatory arthritides (IA)

Risk factors and “screening”

Considerations and Discussion

Background – Introduction

Inflammatory arthritis (IA)

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PsA)
- Axial Spondyloarthritis (AxSpA)

- Accumulating data support that specific malignancies have increased frequency in individuals with IA compared with the general population.

- Whether this prevalence is affected by the pharmacological treatment used in IA remains unclear.

Background – Malignancies entity

- Hematologic malignancies

  [e.g., Hodgkin's lymphoma (HL), non- Hodgkin's lymphoma (non-HL), Diffuse large B-cell lymphoma (DLBCL), etc.]

- Solid organ malignancies

  (e.g., Lung, Liver, Thyroid, Uterine, Breast, Prostate, etc.)

- Skin cancer

  [melanoma and non-melanoma skin cancer (NMSC), etc.)

Background – What about the evidence?

Step 1: Establish the evidence about the elevated risk (either relative or absolute) – Which malignancies in which inflammatory arthritis

Step 2: Recognize potential risk factors

Step 3: Recognize “high risk” individuals and apply “screening” procedures

Step 1: Establish the evidence about the elevated risk

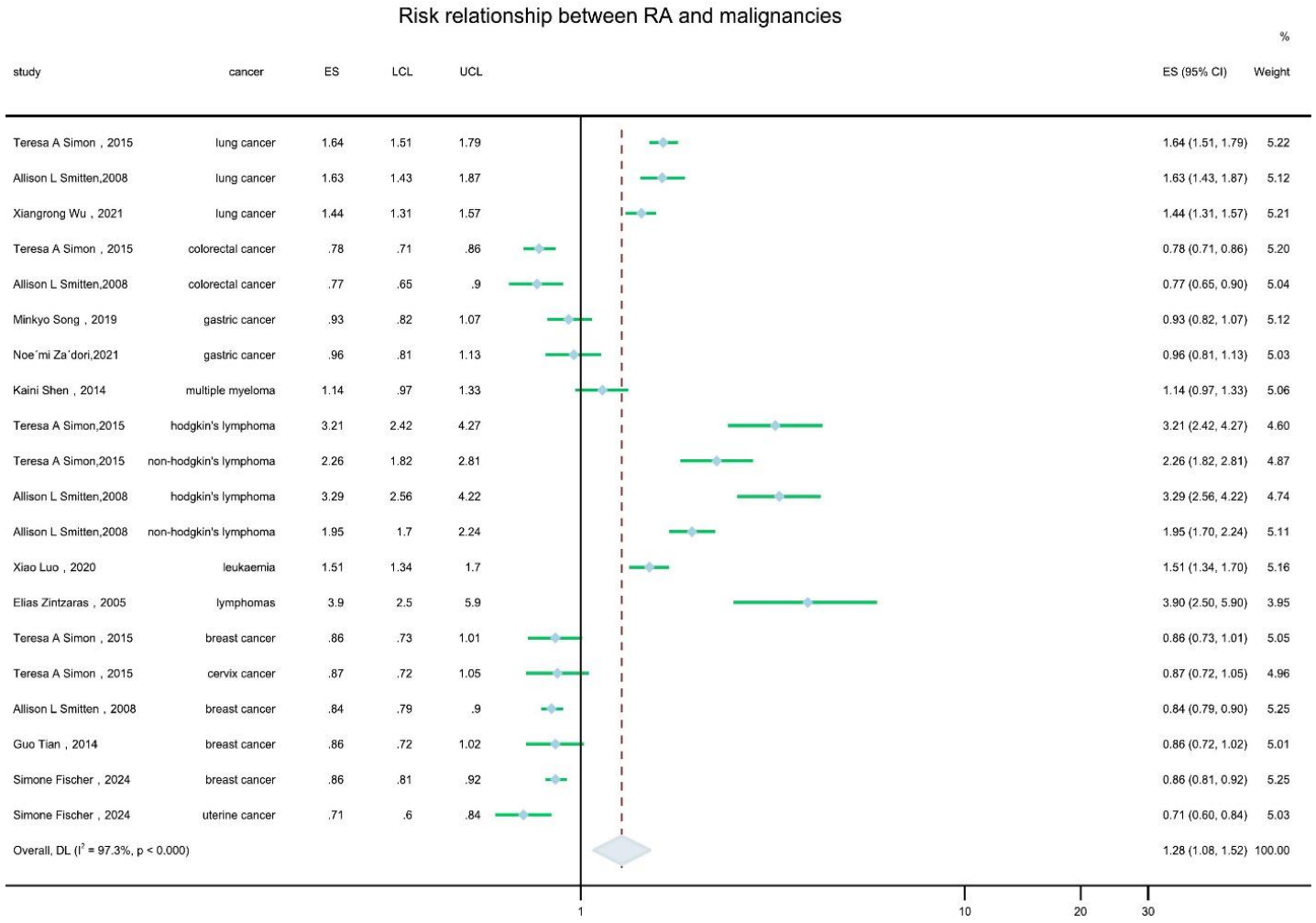
Rheumatoid arthritis

Meta-meta-analysis of 7 other meta-analyses assessing malignancy risk in Rheumatoid arthritis

RA overall malignancy risk: EE: **1.28**, 95% CI: **1.08-1.52**, sig. (I^2 = 97.3 %, p < 0.000)

Subgroup analysis: **increased risk of developing**

- Lung cancer
- Multiple myeloma
- Leukemia
- Lymphoma, including Hodgkin's lymphoma and non-Hodgkin's lymphoma



Yang P, Autoimmun Rev. 2025 Apr 30;24(5):103779. doi: 10.1016/j.autrev.2025.103779.

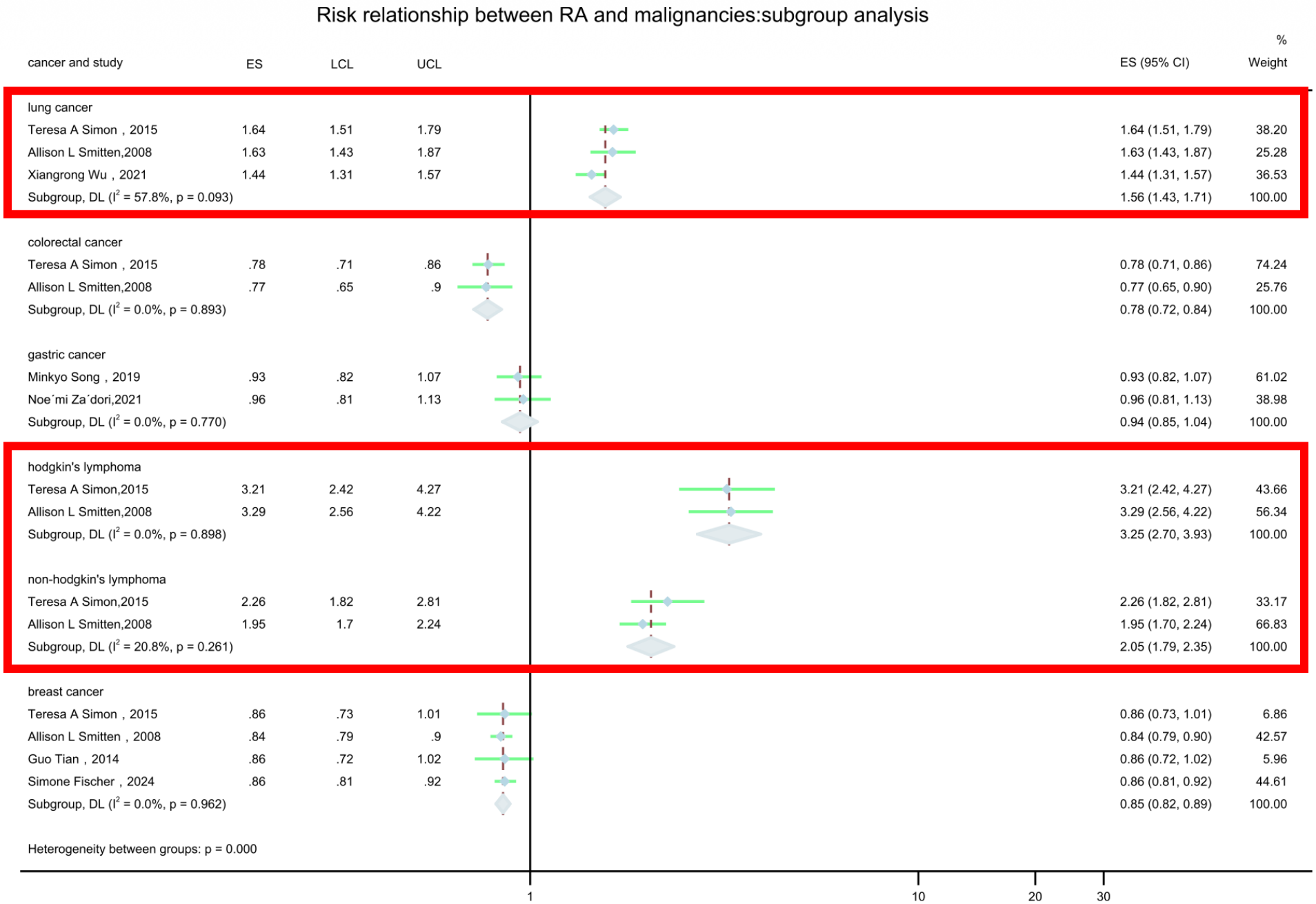
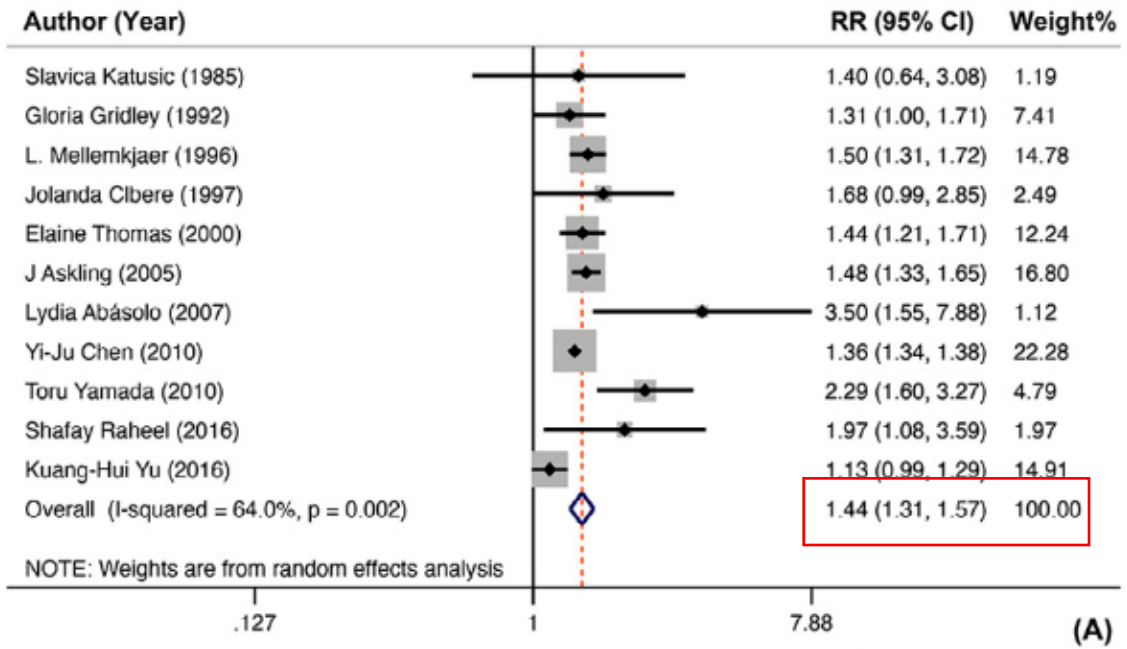


Fig. 5. Risk relationship between RA and malignancies: subgroup analysis.

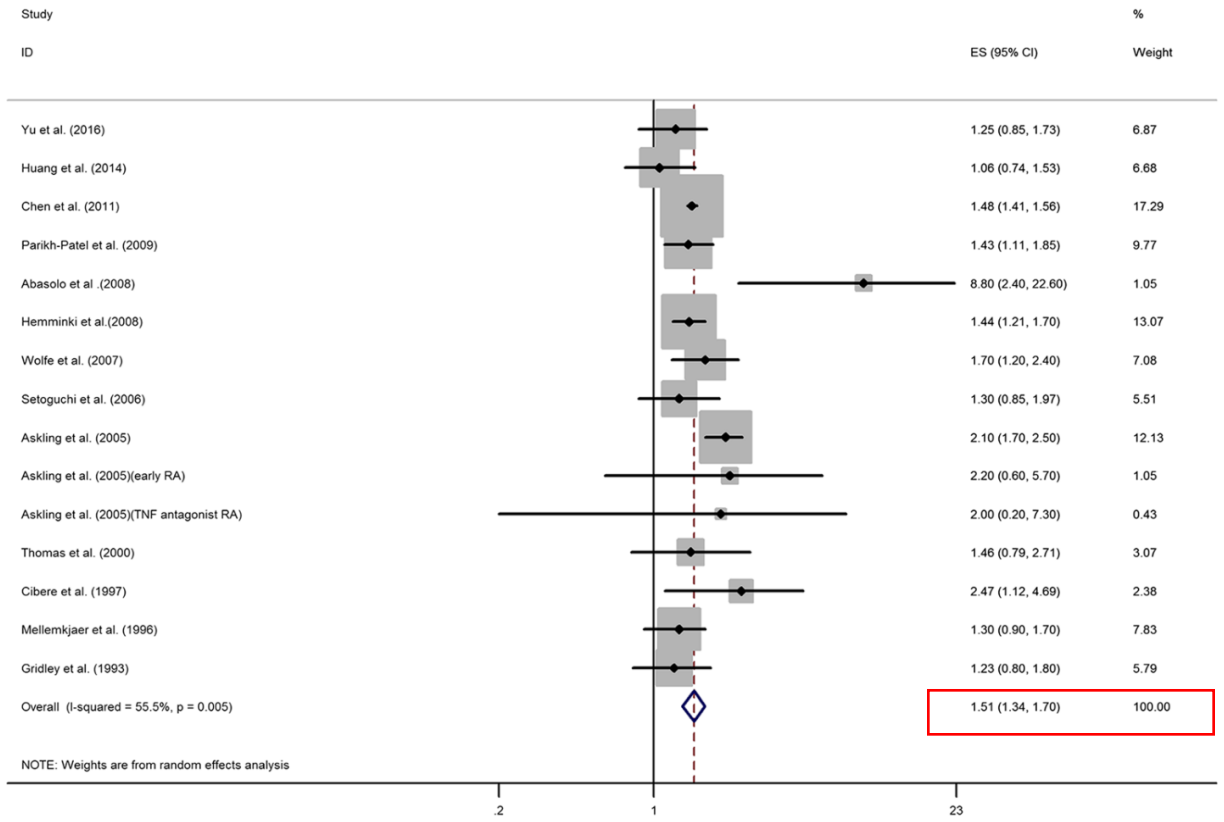
Yang P, Autoimmun Rev. 2025 Apr 30;24(5):103779.
doi: 10.1016/j.autrev.2025.103779.

Rheumatoid arthritis

Meta-analysis evaluating the relative risk of lung cancer in RA (11 studies)



Meta-analysis assessing risk of leukemia in RA compared to general population (15 studies)



X. Wu et al. / Seminars in Arthritis and Rheumatism 51 (2021) 565 575
Luo X et al. Clinical Rheum 2021

Axial Spondyloarthritis

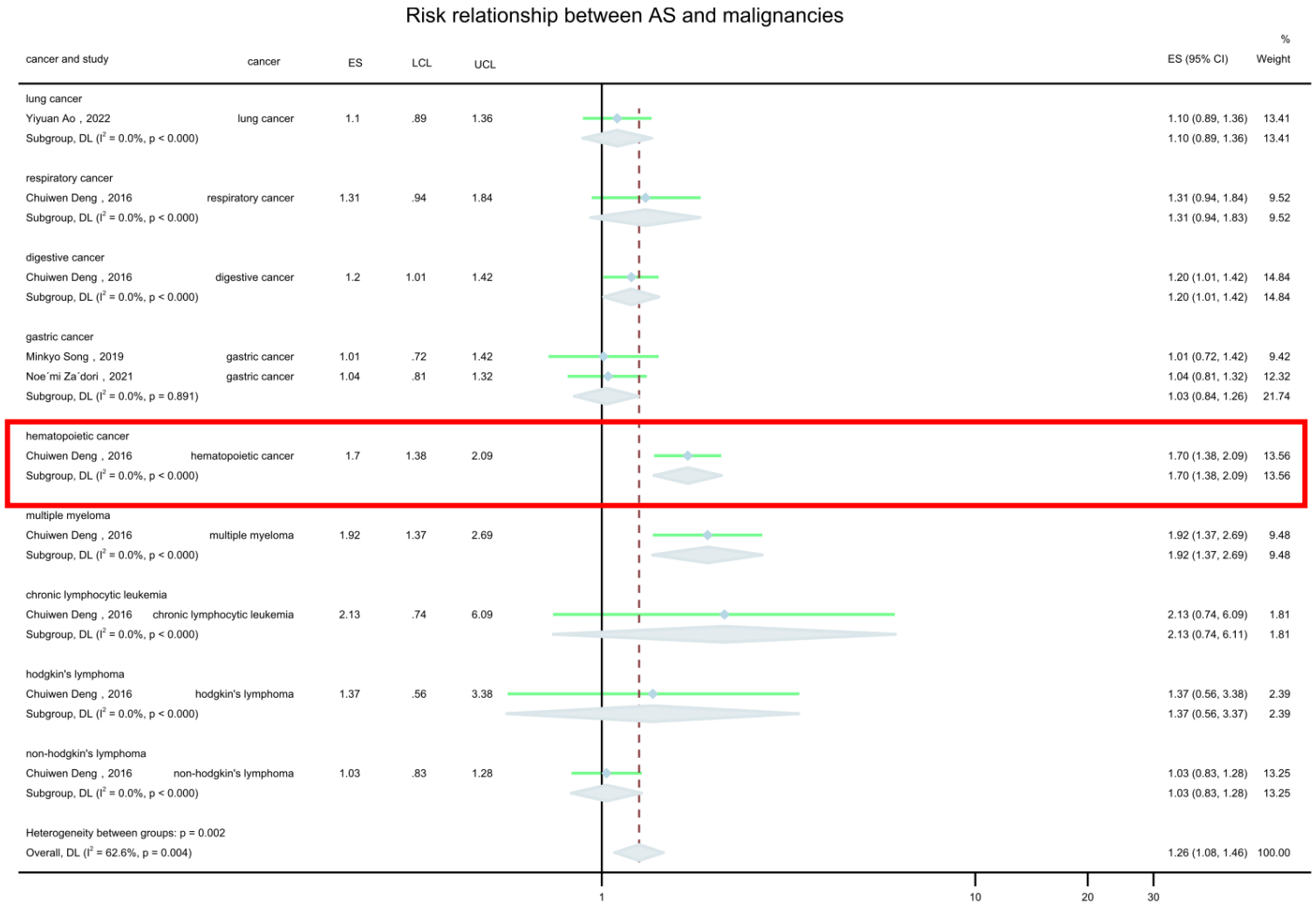


Fig. 8. Risk relationship between AS and malignancies.

Meta-meta-analysis of 2 other meta-analyses assessing malignancy risk in Axial Spondyloarthritis

AxSpA overall malignancy incidence risk: **1.26**, 95% CI: **1.08-1.46**, sig. (I^2 = 62.6 %, p = 0.004)

Subgroup analysis: **increased risk of developing hematological malignancies**

Yang P, Autoimmun Rev. 2025 Apr 30;24(5):103779.
doi: 10.1016/j.autrev.2025.103779.

Axial Spondyloarthritis

Rheumatology, 2025, **64**, 440–454
https://doi.org/10.1093/rheumatology/keae294
Advance access publication 3 June 2024
Systematic Review and Meta Analysis

British Society for Rheumatology RHEUMATOLOGY OXFORD

Basic science

Association of ankylosing spondylitis with the risk of cancer: a meta-analysis of cohort studies

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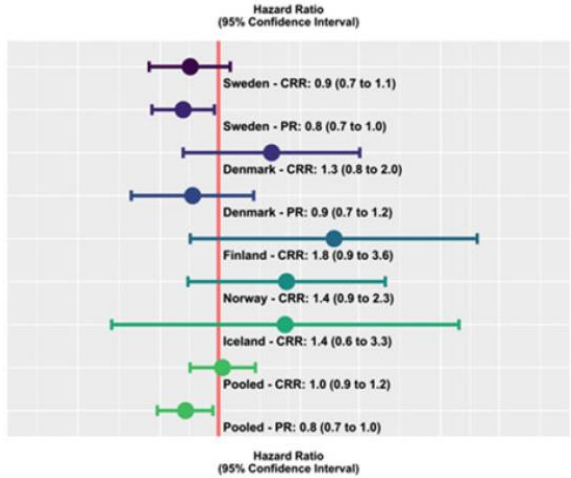
‡L.Y. and Y.Y. contributed equally.

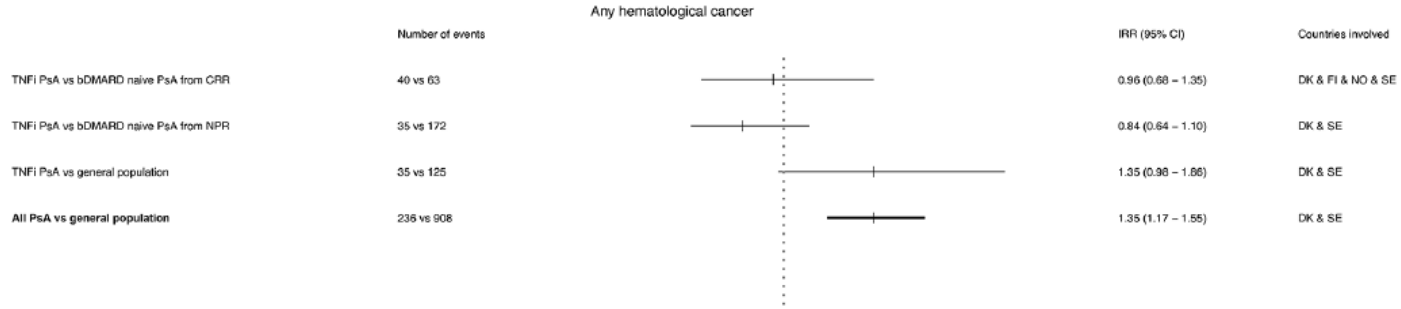
Author/ year	Population	Comparator	Type of malignancy	Outcome (95% CI)
Yu L, 2025	20 studies n >330,000	Non-AxSpA controls	Multiple myeloma	**RR: 1.74 (1.42–2.15)**
			Leukemia	**RR: 1.52 (1.27–1.82)**
			Non-Hodgkin's lymphoma	**RR: 1.42 (1.17–1.73)**

Psoriatic arthritis

- Data from 5 Nordic registries (~60.000py)
  - TNF-treated patients
    - No increased risk for solid malignancies
      - Of any type
    - No increased risk for Hematological malignancies
  - PsA patients
    - Higher risk for Hematological malignancies Vs General population

Haematological malignancies In PsA > Gen population





Hellgren, et al. Rheumatology. 2022 Jun 20;keac358

Psoriatic arthritis - MGUS

Toronto PsA cohort (2008-2011)

361pts: 9.7% had Monoclonal gammopathy of undetermined significance (MGUS) vs 1.5-3% in the general population

- Older (mean Age 61 years old)
- Higher disease duration of PsA

Eder, et al. J Rheum 2012

Comparative Study > J Eur Acad Dermatol Venereol. 2015 Nov;29(11):2262-3.
doi: 10.1111/jdv.12565. Epub 2014 Jun 9.

Frequency of monoclonal gammopathy in psoriatic patients receiving anti-TNF therapy compared with patients taking conventional drugs: a cross-sectional study

V Di Lernia [1], E Ficarelli [1], A Lallas [1], N Possemato [2], I Chiarolanza [2], C Salvarani [2]

Affiliations + expand

PMID: 24911670 DOI: 10.1111/jdv.12565

Table 2 Characteristics of patients with MGUS

Characteristics	TNF-alpha blockers treated patients (*n* = 180)		Conventional drugs treated patients (*n* = 492)		*P*
MGUS *n* (%)	8 (4.44%)	5 non IgM MGUS 1 IgM MGUS 2 LC-MGUS.	26 (5.28%)	22 non IgM MGUS 4 LC-MGUS	0.65
Sex M/F	4/4		14/12		–
Age, y (± SD)	54.5 (± 9.9)		69.1 (± 7.43)		0.001
Psoriasis duration	29.25 (± 15.95)		11.23 (±7.41)		0.07
PsA *n* (%)	4 (50%)		8 (30.76%)		0.05

Skin cancer risk in Inflammatory arthritides

	Rheumatoid arthritis		Psoriatic arthritis		Axial spondyloarthritis	
Inherent risk of skin cancer	Melanoma*	NMSC*	Melanoma†	NMSC†	Melanoma‡	NMSC‡
Conventional synthetic DMARDs§						
TNF inhibitors¶						
IL-17 inhibitors¶						
IL-23 inhibitors¶						
IL-6 inhibitors¶						
IL-1 inhibitors¶						
Abatacept¶						
Rituximab¶						
JAK inhibitors¶						

- **Figure: Inherent and treatment-associated risk for skin cancer in inflammatory arthritides**
- Red: caution—positive association. Green: no signal recognized. Light blue: limited or conflicting data to draw reliable conclusions. Grey: not an approved treatment for the disease evaluated. DMARDs=disease-modifying antirheumatic drugs. IL=interleukin. JAK=Janus kinase. NMSC=non-melanoma skin cancer. TNF=tumor necrosis factor.
- *Inherent risk of skin cancer based on studies assessing this specific type of skin cancer in rheumatoid arthritis (irrespective of treatment) compared with the general population.
- †Inherent risk of skin cancer based on studies assessing this specific type of skin cancer in psoriatic arthritis (irrespective of treatment) compared with the
- general population.
- ‡Inherent risk of skin cancer based on studies assessing this specific type of skin cancer in axial spondyloarthritis (irrespective of treatment) compared with the general population. §Based on studies assessing for skin cancer risk in biologic-naïve individuals with inflammatory arthritides (treated with conventional synthetic
- DMARDs) compared with the general population.
- ¶Based on studies assessing for skin cancer risk in individuals with inflammatory arthritides treated with this drug compared with biologic-naïve individuals with the same type of inflammatory arthritides or individuals with inflammatory arthritides treated with other biological DMARDs or the general population.

Vassilakis et al. 2025, The Lancet Rheumatol

Wrapping up

Rheumatoid arthritis - elevated risk for

- Lung cancer
- Hematologic malignancies
- Skin cancer

Axial Spondyloarthritis – elevated risk for hematological malignancies

Psoriatic arthritis – elevated risk for NMSC and a positive signal for hematological malignancies

Step 2: Recognize potential risk factors

RA and risk factors for lung cancer development

Population-based cohort study

RA (n=44 101) and individually matched general population reference individuals (n=216 495) identified in Swedish registers and from the Epidemiological Investigation of RA early RA study

- Compared with general population subjects who were never smokers, **patients with RA who were ever smokers had almost 7-fold risk of lung cancer**
- **Seropositivity was a significant lung cancer risk factor**, even when adjusted for smoking, **increasing the incidence 2 to 6 times**

Table 3 Number of events, person-years of follow-up, number of events per 100 000 person-years and relative risk of lung cancer according to autoantibody status in the EIRA subcohort

	No of events (person years of follow-up; no of events per 100 000 person years)						
	Positive	Negative	Crude HR (95% CI)	Model A HR (95% CI)	Model B HR (95% CI)	Model C HR (95% CI)	Model D with smoking as pack-years instead of ever/never
RF (n=2060)	30 (49 440; 60.7)	6 (49 440; 12.1)	2.78 (1.16 to 6.69)	3.01 (1.25 to 7.26)	2.82 (1.17 to 6.82)	2.44 (1.01 to 5.89)	2.16 (0.88–5.28)
ACPA (n=2060)	30 (49 440; 60.7)	6 (49 440; 12.1)	3.13 (1.30 to 7.51)	3.43 (1.42 to 8.25)	3.22 (1.33 to 7.77)	2.88 (1.19 to 6.95)	3.29 (1.26–8.58)
RF and/or ACPA (n=2060)	34 (49 440; 68.8)	2 (49 440; 4.0)	6.38 (1.53 to 26.56)	7.62 (1.83 to 31.83)	7.20 (1.72 to 30.11)	6.29 (1.51 to 26.30)	5.76 (1.37–24.21)
RF and ACPA (positive vs double negative) (n=1608)	26 (38 592; 67.4)	2 (38 592; 5.2)	6.67 (1.58 to 28.08)	7.92 (1.87 to 33.50)	7.08 (1.67 to 29.98)	6.21 (1.47 to 26.33)	5.86 (1.37–25.01)

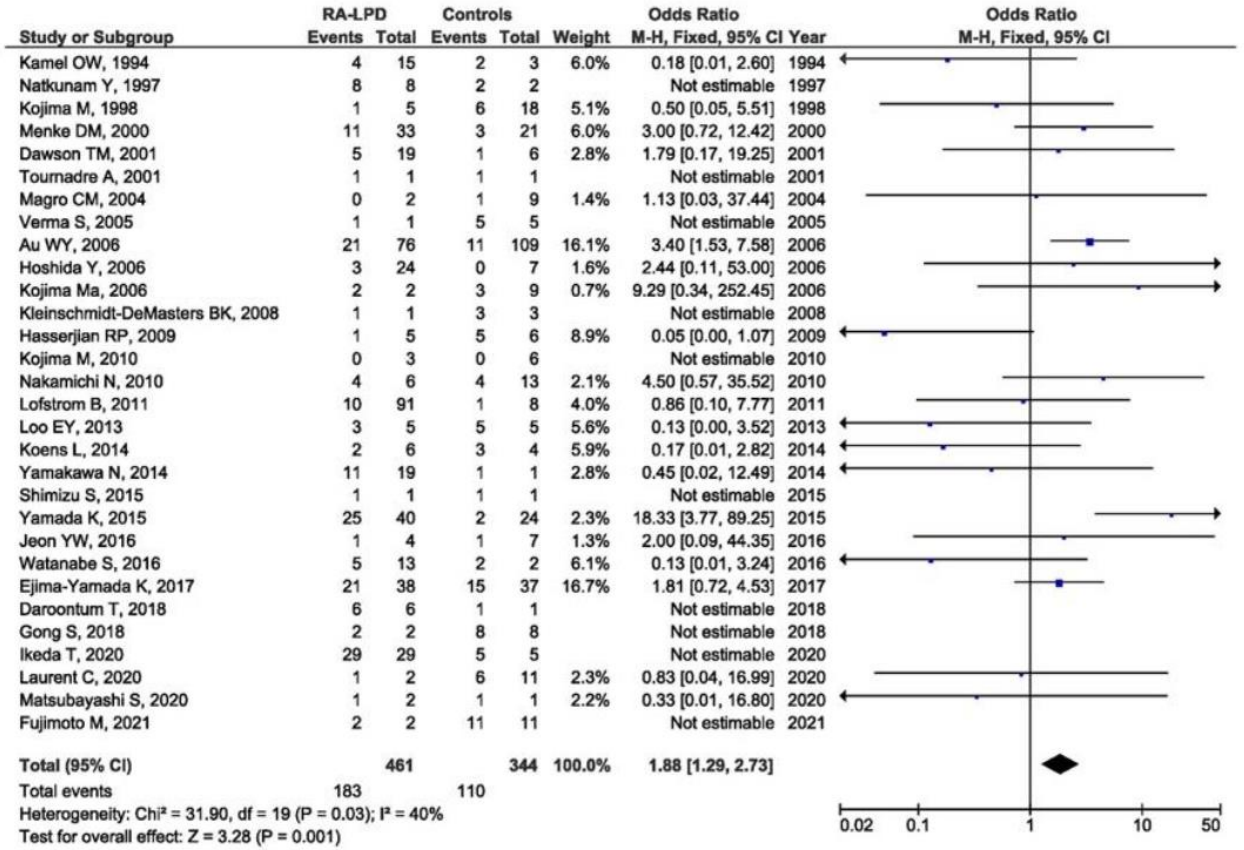
Five HRs are presented: (1) crude; (2) adjusted for age, sex, index year, county of residency (model A); (3) age, sex, index year, county of residency and comorbidities (renal failure, heart failure, ischaemic heart disease, COPD, respiratory infections, hospitalisation) (model B) (4) all the above plus smoking (model C) and (5) as model C with pack-years instead of smoking ever versus never.
ACPA, anticitrullinated peptide antibody; COPD, chronic obstructive pulmonary disease; EIRA, Epidemiological Investigation of RA; RF, rheumatoid factor.

Chatzidionysiou K/ 2022, DOI: 10.1136/rmdopen-2022-002465

RA and risk factors for hematological malignancies development

- Meta-analysis of 79 studies

- Statistically significant association between EBV presence and lymphoproliferative malignancies susceptibility in RA individuals in comparison with all controls (OR: 1.88, 95% CI: 1.29–2.73)



Study or Subgroup	RA-LPD Events	RA-LPD Total	Controls Events	Controls Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Kamel OW, 1994	4	15	2	3	6.0%	0.18 [0.01, 2.60]	1994
Natkunam Y, 1997	8	8	2	2		Not estimable	1997
Kojima M, 1998	1	5	6	18	5.1%	0.50 [0.05, 5.51]	1998
Menke DM, 2000	11	33	3	21	6.0%	3.00 [0.72, 12.42]	2000
Dawson TM, 2001	5	19	1	6	2.8%	1.79 [0.17, 19.25]	2001
Tournadre A, 2001	1	1	1	1		Not estimable	2001
Magro CM, 2004	0	2	1	9	1.4%	1.13 [0.03, 37.44]	2004
Verma S, 2005	1	1	5	5		Not estimable	2005
Au WY, 2006	21	76	11	109	16.1%	3.40 [1.53, 7.58]	2006
Hoshida Y, 2006	3	24	0	7	1.6%	2.44 [0.11, 53.00]	2006
Kojima Ma, 2006	2	2	3	9	0.7%	9.29 [0.34, 252.45]	2006
Kleinschmidt-DeMasters BK, 2008	1	1	3	3		Not estimable	2008
Hasserjian RP, 2009	1	5	5	6	8.9%	0.05 [0.00, 1.07]	2009
Kojima M, 2010	0	3	0	6		Not estimable	2010
Nakamichi N, 2010	4	6	4	13	2.1%	4.50 [0.57, 35.52]	2010
Lofstrom B, 2011	10	91	1	8	4.0%	0.86 [0.10, 7.77]	2011
Loo EY, 2013	3	5	5	5	5.6%	0.13 [0.00, 3.52]	2013
Koens L, 2014	2	6	3	4	5.9%	0.17 [0.01, 2.82]	2014
Yamakawa N, 2014	11	19	1	1	2.8%	0.45 [0.02, 12.49]	2014
Shimizu S, 2015	1	1	1	1		Not estimable	2015
Yamada K, 2015	25	40	2	24	2.3%	18.33 [3.77, 89.25]	2015
Jeon YW, 2016	1	4	1	7	1.3%	2.00 [0.09, 44.35]	2016
Watanabe S, 2016	5	13	2	2	6.1%	0.13 [0.01, 3.24]	2016
Ejima-Yamada K, 2017	21	38	15	37	16.7%	1.81 [0.72, 4.53]	2017
Daroontum T, 2018	6	6	1	1		Not estimable	2018
Gong S, 2018	2	2	8	8		Not estimable	2018
Ikeda T, 2020	29	29	5	5		Not estimable	2020
Laurent C, 2020	1	2	6	11	2.3%	0.83 [0.04, 16.99]	2020
Matsubayashi S, 2020	1	2	1	1	2.2%	0.33 [0.01, 16.80]	2020
Fujimoto M, 2021	2	2	11	11		Not estimable	2021
Total (95% CI)		**461**		**344**	**100.0%**	**1.88 [1.29, 2.73]**	
Total events	183		110				

Heterogeneity: $Chi^2 = 31.90$, $df = 19$ ($P = 0.03$); $I^2 = 40\%$

Test for overall effect: $Z = 3.28$ ($P = 0.001$)

Odds Ratio M-H, Fixed, 95% CI

0.02 0.1 1 10 50

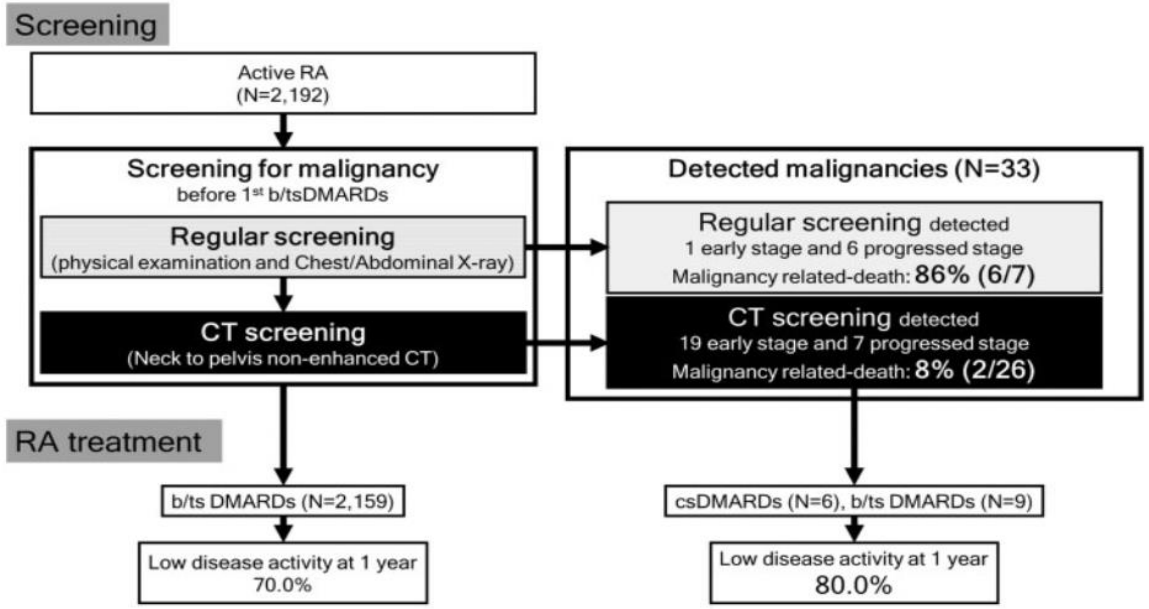
Banko A et al. Viruses 2022

Step 3: Recognize “high risk” individuals and apply “screening” procedures

Malignancy screening in Rheumatoid arthritis

Prospective cohort study:

- Objective: **To clarify the usefulness of screening for malignancies using CT before b/tsDMARDs**
- Methods:
  - RA individuals (n=2192) prior b/tsDMARDs initiation
  - Sensitivity for detecting malignancy plain CT scans vs regular screening (physical examination and X-ray)



33 (1.5%) were diagnosed with malignancy after CT screening

Miyata H, et al. Rheumatology (Oxford). 2023

Malignancy screening in Rheumatoid arthritis

❖ Results:

➢ Patients with early-stage malignancies received treatments after curative resection

➢ 80% achieved low disease activity after 1 year comparable to patients without malignancy (70%)

5-year incidence of malignancy after CT screening was lower than without CT screening (SIR: 0.35)

❖ Conclusion:

➢ Screening using CT before the initiation of b/tsDMARDs allows for the early detection and treatment of malignancy, resulting in safer and more stable b/tsDMARD treatment

Miyata H, et al. Rheumatology (Oxford). 2023

IDENTIFYING RESEARCH GAPS

However limited studies exist evaluating the efficacy of screening procedures for detecting malignancies in individuals with inflammatory arthritides

What should I do as a rheumatologist?

Should we consider screening?

- Rheumatologist has a **central role in the care** of people with autoimmune rheumatic diseases

- The rheumatology community should be aware of the elevated risk of some types of cancer in specific IA

BUT

NO RELEVANT SCREENING is not recommended by the main rheumatology organizations (e.g., EULAR, the ACR, and the APLAR)

Recommendations at national level

Joint Bone Spine 92 (2025) 105944

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Recommendations and metaanalyses

French recommendations for assessing and managing the risk of cancer before the initiation of targeted therapies for chronic rheumatic inflammatory diseases

Table 1
Overarching principles and recommendations.

	Level of Agreement (SD)
Overarching principles	
A. The risk of certain cancers is higher in patients with chronic inflammatory rheumatic disorders compared to the general population. This should be considered in the management of these patients	
B. Cancer risk in patients with CIRDs is primarily mediated by traditional risk factors, which are more prevalent in this population. Chronic inflammatory rheumatism itself and its treatments may contribute to cancer risk	
C. The risk of cancer should be regularly assessed in patients with CIRDs during follow-up and systematically before initiating disease-modifying anti-rheumatic therapies	
Recommendations	
1. The rheumatologist, together with the primary care physician, must ensure that patients with CIRDs undergo organized cancer screening programs recommended for the general population	9.4 (0.7)
2. Smoking cessation must be systematically encouraged to reduce the risk of cancer.	10 (0)
3. Disease activity should be optimally controlled in order to reduce the risk of lymphoma, especially in patients with rheumatoid arthritis	9.4 (0.9)
4. Given the increased risk of cervical cancer in patients with CIRDs, they should be screened more closely than recommended for the general population	9.5 (0.7)
5. In patients under the age of 26 years, it is recommended to check HPV vaccination and to propose catch-up vaccination if not completed	9.6 (0.6)
6. Patients with CIRDs receiving disease-modifying anti-rheumatic therapies should visit a dermatologist at least once during their follow-up to evaluate the risk of skin cancer. The dermatologist will define the follow-up modalities.	9.9 (0.5)
7. In patients with a history and/or genetic predisposition to cancer, the use of JAKi and abatacept should only be considered in the absence of suitable treatment alternatives and contingent on a collegial decision	9.4 (0.7)
8. In patients aged 65 years or older, and/or in those who currently smoke or have smoked for a long time in the past, the use of JAKi should only be considered when suitable treatment alternatives are absent and contingent upon a collegial decision	8.9 (0.9)

CIRDs: chronic inflammatory rheumatic diseases, HPV human papillomavirus; JAKi: JAK inhibitors; SD: standard deviation.

SFR société française de rhumatologie

Recommendations

1. The rheumatologist, together with the primary care physician, must ensure that patients with CIRDs undergo organized cancer screening programs recommended for the general population	9.4 (0.7)
2. Smoking cessation must be systematically encouraged to reduce the risk of cancer.	10 (0)
3. Disease activity should be optimally controlled in order to reduce the risk of lymphoma, especially in patients with rheumatoid arthritis	9.4 (0.9)

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Some points to consider?*

- Discuss with the patient the increased risk of specific malignancies
- Ensure the patient is aware of recommended cancer screening programs for the general population
- Identify high-risk individuals (e.g., male, seropositive, smoker with rheumatoid arthritis should raise concern)
- Ask about red-flag symptoms suggestive of malignancy, including cough, dyspnea, unexplained weight loss, fevers, night sweats
- Perform a focused clinical examination, including assessment for lymphadenopathy and other suspicious findings

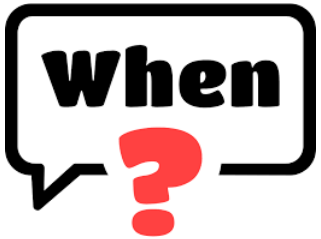
Further assess following an individualized approach with “minimally invasive” risk-free procedures e.g., Serum protein electrophoresis

***Speaker’s opinion**

Is skin cancer different?*

Skin cancer screening is

- non-invasive
- not time-consuming
- Inexpensive



We think that this should be a point for discussion with patients in the context of shared decision making.

*Speaker's opinion

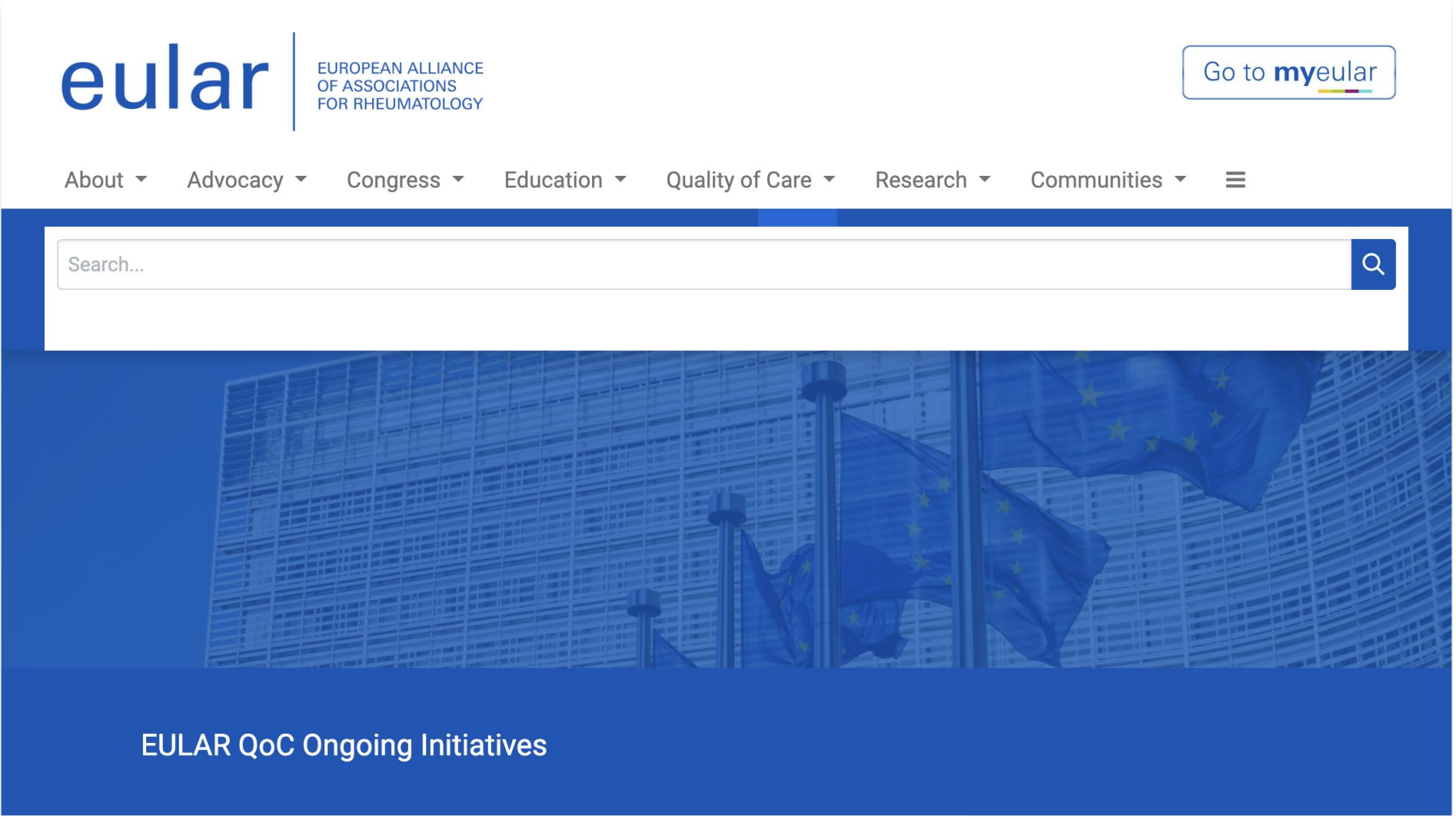
Considerations

Avoid over-screening

Risk-benefit ratio (e.g., ionized radiation weighted modalities)

Treatment-attributed risk (e.g., abatacept and skin cancer)

Rheumatologist has an advisory role!



- QoC032 - EULAR recommendations for the assessment of malignancy risk in autoimmune rheumatic diseases
  Elena Nikiphorou and George Fragoulis

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Σας ευχαριστώ!