


Solid Cancers and Rheumatoid Arthritis

George D. Kalliolias ^{1,2,3}, Efthimia K. Basdra ⁴ and Athanasios G. Papavassiliou ^{4,*} 

¹ Hospital for Special Surgery, Arthritis & Tissue Degeneration, New York, NY 10021, USA; kallioliasg@hss.edu

² Department of Medicine, Weill Cornell Medical College, New York, NY 10065, USA

³ Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591, USA

⁴ Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece; ebasdra@med.uoa.gr

* Correspondence: papavas@med.uoa.gr; Tel.: +30-210-746-2508

1. Introduction

Since the initial observation that patients with rheumatoid arthritis (RA) have an excess risk of developing hematologic malignancies [1], accumulating evidence has established a similar concept for solid tumors [2]. The all-solid tumors risk is ~20% higher in RA patients compared to the general population, with men displaying 1.24 times higher incidence than women [3]. Notably, there are site-specific differences in solid cancer risks, with an increased incidence of solid tumors associated with smoking or oncogenic viral infections (i.e., lung cancer, urinary bladder, kidney, upper urinary tract, ear–nose–throat (ENT) cancers, and cervical cancer) and decreased incidence for breast and colon cancers [4]. The key mechanisms that may explain the differential risk for solid tumors in RA are listed in Table 1.

Table 1. Three mechanisms explaining the differential site-specific risks for cancer in RA: (1) RA and cancer share etiologic factors (e.g., smoking), (2) RA promotes site-specific carcinogenesis (e.g., RA targets the lung and induces chronic lung inflammation and interstitial lung disease), and (3) DMARDs, NSAIDs, and GCs used for the treatment of RA impact the risk for the development of site-specific cancers (e.g., DMARDs decrease immunosurveillance against tumors and oncogenic viruses permitting unopposed tumor development). RA, rheumatoid arthritis; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroid anti-inflammatory drugs; GCs, glucocorticoids; ILD, interstitial lung disease; HPV, human papillomavirus; ENT, ear–nose–throat; UIT, upper urinary tract; NMSC, nonmelanoma skin cancer.

Mechanisms			Cancer Risk
Shared Etiology Between RA and Cancer	Common exposures	Smoking	Increased risk for smoking-related cancers: Lung ENT Kidney UIT Bladder Cervical
	Hyperactivation of lymphoid organs		Increased risk for: Hematologic malignancies
RA Promotes Cancer	Chronic inflammation Tissue damage	ILD Seropositivity	Increased incidence: Lung



Citation: Kalliolias, G.D.; Basdra, E.K.; Papavassiliou, A.G. Solid Cancers and Rheumatoid Arthritis. *Cancers* **2023**, *15*, 5441. <https://doi.org/10.3390/cancers15225441>

Received: 13 November 2023

Accepted: 15 November 2023

Published: 16 November 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Table 1. Cont.

RA Treatment Impacts the Risk for Cancer	Mechanisms		Cancer Risk
	Immunomodulatory DMARDs	Impaired immunosurveillance against: Tumors Oncogenic Viruses (e.g., HPV)	Increased risk for: Melanoma NMSC Cervical cancer ENT cancer
	NSAIDs		Decreased risk for: Colon cancer
	GCs		Impact on the risk for: Breast cancer

Over the last years, the approval of new classes of medications has revolutionized the therapeutic paradigm for RA [5]. The current treatment armamentarium includes conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs), biologic DMARDs (b-DMARDs), and targeted synthetic DMARDs (ts-DMARDs) such as the class of Janus kinase inhibitors (JAKi) [6]. The new standard of care for RA achieves robust immunomodulation with a profound benefit on disease burden, but at the same time raises concerns about its impact on the immunosurveillance against tumors and oncogenic viruses [4]. The continuously changing practices in RA management (i.e., new classes of DMARDs and the diminished need for nonsteroid anti-inflammatory drugs (NSAIDs)), together with life-style modifications (e.g., changes in smoking habits, Westernized diet), and new preventive medicine practices (for example, broad vaccination for human papillomavirus (HPV)) may impact the risks for solid tumor development in RA patients. Cancer development is a low-frequency event which needs a long time to develop. In this context, there is a continuous need for the re-evaluation of solid cancer risk in RA, with new studies including larger numbers of RA patients exposed to the new classes of DMARDs with longer periods of follow-up. Here, we summarize the recent developments in the field of solid tumor surveillance in RA.

2. Increased Risk for Lung Cancer

Three recently published studies, from Sweden [7], South Korea [8], and France [3], including very large numbers of RA patients ($n > 44,000$, $n > 50,000$, and $n > 275,000$, respectively) exposed to all the available classes of DMARDs and with long follow-up periods (median follow-up = 7.3, 4.5, and 8.7 years, respectively), have confirmed the observation made from older studies [2] that patients with RA display 50–100% increased risk for lung cancer compared to the general population. This finding has been explained on the basis of shared etiology between RA and lung cancer [4]. Smoking, chronic lung inflammation, and interstitial lung disease (ILD) have been the proposed etiologic links among the two diseases [4,9].

Smoking increases >20-fold the risk of developing RA in genetically predisposed individuals (carriers of shared epitope or risk variants of *PTPN22*) [10]. According to the *mucosal origin hypothesis*, the initiating events of RA pathogenesis resulting in the break of self-tolerance and the production of anticitrullinated peptide antibodies (ACPAs) may occur in the lung and be triggered by smoking [11]. Cigarette smoking induces local lung inflammation and the activation of the enzyme peptidyl-arginine deiminase (PADI), resulting in the de novo citrullination of lung proteins and emergence of citrullinated neoepitopes [10,11]. Among RA patients, the relative risk for the development of lung cancer is 19.24 for current and 11 for past smokers compared to RA patients who have never smoked [12].

The role of sex, seropositivity, disease duration, and ILD as risk factors for lung cancer development in RA patients has been investigated in several studies. The risk for lung cancer in RA is higher in males compared to females [3], a finding that has been explained primarily because of the higher exposures of males to smoking. The Swedish study has also identified seropositivity for ACPAs and/or rheumatoid factor (RF) as an independent

risk factor for lung cancer development, that even when adjusted for smoking, increases 2–6 times the incidence of lung cancer [7]. This new observation has not been confirmed by the South Korean study [8], but this may suggest that regular CT lung screening should be considered for RA patients who are seropositive and have ever been smokers. Regarding the impact of RA disease duration, according to the Swedish study, during the first 5 and 20 years after the diagnosis of RA, 1% and 3%, respectively, of RA patients were diagnosed with lung cancer [7]. Notably, another study has shown that the risk of lung cancer was lower among patients with an RA disease duration of ≥ 10 years compared to < 1 year [12]. Additionally, ILD is associated with a higher risk of lung cancer, and clinically significant ILD occurs in 5–10% of patients with RA [9,13]. Data from the ORAL Surveillance trial suggest that RA patients with a history of chronic lung disease (ILD or chronic obstructive pulmonary disease) display 2.63-times higher risk for lung cancer compared to RA patients with no history of chronic lung disease [12,14].

The impact of background treatments on the risk for lung cancer development in RA patients has been evaluated recently. The French study [3] compared RA patients exposed to cs-DMARDs ($n > 78,000$), tumor necrosis factor inhibitors (TNFi) ($n > 65,000$), abatacept ($n > 14,000$), rituximab ($n > 13,000$), and anti-IL6 receptor (anti-IL6R) ($n > 14,000$), showing that the highest incidence of lung cancer was observed in RA patients exposed to abatacept (Standardized Incidence Ratio (SIR) = 2.10) and rituximab (SIR = 1.68), followed by RA patients exposed to cs-DMARDs (SIR = 1.42), TNFi (SIR = 1.41), and anti-IL6R (SIR = 1.15). JAKi is the most recently approved class of DMARDs [5], and data on their impact on lung cancer risk are more limited due to lower numbers of exposed RA patients and shorter follow-up [12,14–16]. The ORAL Surveillance Trial has shown a higher incidence of lung cancer in RA patients exposed to tofacitinib (1.08%, 30 cases of lung cancer among 2911 RA patients) than in RA patients exposed to TNFi (0.48%, 7 cases of lung cancer among 1451 RA patients) [12]. On the other hand, it was recently reported that RA patients exposed to tofacitinib displayed a lower incidence of ILD compared to RA patients exposed to adalimumab, abatacept, rituximab, or tocilizumab [13]. In this context, more studies are required to better evaluate the potential long-term impact of JAKi on the risk of lung cancer development.

3. Increased Risks for Other Site-Specific Solid Tumors

Over the last 30 years, more than 18 studies have provided conflicting data on the risk for cervical cancer. In 2015, a meta-analysis of 15 studies has estimated a modestly decreased risk (total pooled SIR = 0.87) [2]. More recent studies with larger numbers of RA patients and longer follow-up periods have shown consistently about 1.5–1.8-times higher risk for cervical intraepithelial neoplasia (CIN) 1–3 and cervical cancer [17,18]. A nationwide study from Sweden has shown that women exposed to TNFi had about two-times higher risk for invasive cervical cancer compared to biologics-naïve women with RA [18]. Cervical dysplasia and invasive cervical cancer arise from infection with HPV [19], and the immunosuppressive DMARDs used to treat RA may impair the clearance of the oncogenic HPV [4]. Shared etiology (i.e., smoking) [20] could be an additional explanation for the association of RA with cervical dysplasia and cancer.

Cumulative evidence over the years suggests that RA patients also display increased risk for skin cancers, including melanoma and nonmelanoma skin cancers (NMSCs) [2,3,21–25]. Therefore, periodic dermatological screening is recommended in RA patients for the early detection of skin cancers. Regarding melanoma, a meta-analysis pooling 21 studies with conflicting results has shown a modestly increased risk (total pooled SIR = 1.23) for RA patients [2]. A recent very large study ($n > 257,000$ RA patients) has also shown an increased risk (SIR = 1.37) for melanoma in RA patients in the French population [3]. Concerns about the impact of immunosuppressive DMARDs on immunosurveillance against the immunogenic melanoma have been explored in a collaborative project of 11 European biologic registries collecting data from $> 130,000$ RA patients [21]. The results of this study have shown that the incidence of melanoma in RA patients who were biologic-

naïve, TNFi-exposed, rituximab-exposed, tocilizumab-exposed, and abatacept-exposed was slightly higher in all RA treatment groups compared to the general population [21]. Also, the comparison between TNFi-exposed versus biologic-naïve RA patients has shown a slightly but not significantly increased incidence rate ratio (IRR = 1.14) of invasive melanoma in TNFi-exposed patients [21], alleviating the concerns raised from prior smaller studies [22,23].

Concerning prostate cancer, the second most commonly occurring cancer in men, a meta-analysis pooling 17 studies over a 20-year period (1993 to 2013) has shown a slightly increased risk (total pooled SIR = 1.15) in RA patients [2]. Along the same lines, a recently published French study has shown insignificant differences in the incidence of prostate cancer between RA patients and the general population (SIR = 1.08) [3].

4. Decreased Risks for Breast and Colon Cancers

Notably, the incidence of colon and breast cancers has been consistently reported to be lower in RA patients compared to the general population [2,3]. For colon cancer, the lower risk has been attributed to the impact of nonsteroid anti-inflammatory drugs (NSAIDs) that have a proven effect on reducing the risk for developing colon cancer [26] and are commonly utilized by RA patients for arthritic pain control. Regarding the lower risk for breast cancer in RA, according to a recent study that adjusted the model of risk estimations for several breast cancer risk determinants, the explanation remains unknown and cannot be attributed to any of the traditional breast cancer risk factors [27]. Despite the decreased risk of breast cancer in RA, it is worth mentioning the potential impact of glucocorticoids (GCs) on the risk for breast cancer. GCs represent a substantial part of the therapeutic armamentarium for RA treatment and are widely administered as a bridging therapy in combination with cs-DMARDs. Nevertheless, given that glucocorticoid receptor (GR) signaling could theoretically augment breast cancer risk and progression by triggering insulin resistance and facilitating immunosuppression [28,29], and that GR polymorphisms might affect GCs action, thus interfering with the pathogenetic mechanism of RA [30], the future position GCs may have in patients with RA should be re-evaluated in order to ameliorate the balance between efficacy and long-term safety.

Author Contributions: Conceptualization, G.D.K., E.K.B. and A.G.P.; writing—original draft preparation, G.D.K.; writing—review and editing, E.K.B. and A.G.P.; supervision, A.G.P. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: G.D.K. is a full-time employee and shareholder at Regeneron Pharmaceuticals, Inc. E.K.B. and A.G.P. declare no conflict of interest.

References

1. Isomäki, H.A.; Hakulinen, T.; Joutsenlahti, U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J. Chronic Dis.* **1978**, *31*, 691–696. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Simon, T.A.; Thompson, A.; Gandhi, K.K.; Hochberg, M.C.; Suissa, S. Incidence of malignancy in adult patients with rheumatoid arthritis: A meta-analysis. *Arthritis Res. Ther.* **2015**, *17*, 212. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Beydon, M.; Pinto, S.; De Rycke, Y.; Fautrel, B.; Mariette, X.; Seror, R.; Tubach, F. Risk of cancer for patients with rheumatoid arthritis versus general population: A national claims database cohort study. *Lancet Reg. Health Eur.* **2023**, *35*, 100768. [\[CrossRef\]](#)
4. De Cock, D.; Hyrich, K. Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. *Best Pract. Res. Clin. Rheumatol.* **2018**, *32*, 869–886. [\[CrossRef\]](#)
5. Bonelli, M.; Kerschbaumer, A.; Kastrati, K.; Ghoreschi, K.; Gadina, M.; Heinz, L.X.; Smolen, J.S.; Aletaha, D.; O’Shea, J.; Laurence, A. Selectivity, efficacy and safety of JAKinibs: New evidence for a still evolving story. *Ann. Rheum. Dis.* **2023**, arid-2023-223850, online first. [\[CrossRef\]](#)
6. Smolen, J.S.; Landewé, R.B.M.; Bergstra, S.A.; Kerschbaumer, A.; Sepriano, A.; Aletaha, D.; Caporali, R.; Edwards, C.J.; Hyrich, K.L.; Pope, J.E.; et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann. Rheum. Dis.* **2023**, *82*, 3–18. [\[CrossRef\]](#)
7. Chatzidionysiou, K.; di Giuseppe, D.; Soderling, J.; Catrina, A.; Askling, J. Risk of lung cancer in rheumatoid arthritis and in relation to autoantibody positivity and smoking. *RMD Open* **2022**, *8*, e002465. [\[CrossRef\]](#)

8. Cho, M.H.; Cho, J.H.; Eun, Y.; Han, K.; Jung, J.; Cho, I.Y.; Yoo, J.E.; Lee, H.; Kim, H.; Park, S.Y.; et al. Rheumatoid Arthritis and Risk of Lung Cancer: A Nationwide Cohort Study. *J. Thorac. Oncol.* **2023**, S1556-0864(23)02293-1, Online ahead of print. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Sparks, J.A.; Jin, Y.; Cho, S.K.; Vine, S.; Desai, R.; Doyle, T.J.; Kim, S.C. Prevalence, incidence and cause-specific mortality of rheumatoid arthritis-associated interstitial lung disease among older rheumatoid arthritis patients. *Rheumatology* **2021**, *60*, 3689–3698. [\[CrossRef\]](#)
10. Kalliolias, G.D.; Skokos, D. Immunological basis of inflammatory arthritides. In *Absolute Rheumatology Review*, 1st ed.; Efthimiou, P., Ed.; Springer: Cham, Switzerland, 2020; pp. 1–36. [\[CrossRef\]](#)
11. Holers, V.M.; Demoruelle, M.K.; Kuhn, K.A.; Buckner, J.H.; Robinson, W.H.; Okamoto, Y.; Norris, J.M.; Deane, K.D. Rheumatoid arthritis and the mucosal origins hypothesis: Protection turns to destruction. *Nat. Rev. Rheumatol.* **2018**, *14*, 542–557. [\[CrossRef\]](#)
12. Curtis, J.R.; Yamaoka, K.; Chen, Y.H.; Bhatt, D.L.; Gunay, L.M.; Sugiyama, N.; Connell, C.A.; Wang, C.; Wu, J.; Menon, S.; et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: Results from the open-label, randomised controlled ORAL Surveillance trial. *Ann. Rheum. Dis.* **2023**, *82*, 331–343. [\[CrossRef\]](#)
13. Baker, M.C.; Liu, Y.; Lu, R.; Lin, J.; Melehan, J.; Robinson, W.H. Incidence of Interstitial Lung Disease in Patients With Rheumatoid Arthritis Treated With Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs. *JAMA Netw. Open* **2023**, *6*, e233640. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Kristensen, L.E.; Danese, S.; Yndestad, A.; Wang, C.; Nagy, E.; Modesto, I.; Rivas, J.; Benda, B. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: An analysis of the open label, randomised controlled study ORAL Surveillance. *Ann. Rheum. Dis.* **2023**, *82*, 901–910. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Ytterberg, S.R.; Bhatt, D.L.; Mikuls, T.R.; Koch, G.G.; Fleischmann, R.; Rivas, J.L.; Germino, R.; Menon, S.; Sun, Y.; Wang, C.; et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N. Engl. J. Med.* **2022**, *386*, 316–326. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Russell, M.D.; Stovin, C.; Alvey, E.; Adeyemi, O.; Chan, C.K.D.; Patel, V.; Adas, M.A.; Atzeni, F.; Ng, K.K.H.; Rutherford, A.I.; et al. JAK inhibitors and the risk of malignancy: A meta-analysis across disease indications. *Ann. Rheum. Dis.* **2023**, *82*, 1059–1067. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Kim, S.C.; Glynn, R.J.; Giovannucci, E.; Hernández-Díaz, S.; Liu, J.; Feldman, S.; Karlson, E.W.; Schneeweiss, S.; Solomon, D.H. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: A population-based cohort study. *Ann. Rheum. Dis.* **2015**, *74*, 1360–1367. [\[CrossRef\]](#)
18. Wadström, H.; Frisell, T.; Sparén, P.; Askling, J.; ARTIS study group. Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden. *Ann. Rheum. Dis.* **2016**, *75*, 1272–1278. [\[CrossRef\]](#)
19. Lei, J.; Ploner, A.; Elfström, K.M.; Wang, J.; Roth, A.; Fang, F.; Sundström, K.; Dillner, J.; Sparén, P. HPV Vaccination and the Risk of Invasive Cervical Cancer. *N. Engl. J. Med.* **2020**, *383*, 1340–1348. [\[CrossRef\]](#)
20. Brinton, L.A.; Schairer, C.; Haenszel, W.; Stolley, P.; Lehman, H.F.; Levine, R.; Savitz, D.A. Cigarette smoking and invasive cervical cancer. *JAMA* **1986**, *255*, 3265–3269. [\[CrossRef\]](#)
21. Mercer, L.K.; Askling, J.; Raaschou, P.; Dixon, W.G.; Dreyer, L.; Hetland, M.L.; Strangfeld, A.; Zink, A.; Mariette, X.; Finckh, A.; et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: Results from a collaborative project of 11 European biologic registers. *Ann. Rheum. Dis.* **2017**, *76*, 386–391. [\[CrossRef\]](#)
22. Raaschou, P.; Simard, J.F.; Holmqvist, M.; Askling, J.; ARTIS Study Group. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: Nationwide population based prospective cohort study from Sweden. *BMJ* **2013**, *346*, f1939. [\[CrossRef\]](#)
23. Dreyer, L.; Møllemlær, L.; Andersen, A.R.; Bennett, P.; Poulsen, U.E.; Juulsgaard Ellingsen, T.; Hansen, T.H.; Jensen, D.V.; Linde, L.; Lindegaard, H.M.; et al. Incidences of overall and site specific cancers in TNF α inhibitor treated patients with rheumatoid arthritis and other arthritides—A follow-up study from the DANBIO Registry. *Ann. Rheum. Dis.* **2013**, *72*, 79–82. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Raaschou, P.; Simard, J.F.; Asker Hagelberg, C.; Askling, J.; ARTIS Study Group. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: Cohort study based on nationwide prospectively recorded data from Sweden. *BMJ* **2016**, *352*, i262. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Simon, T.A.; Dong, L.; Suissa, S.; Michaud, K.; Pedro, S.; Hochberg, M.; Boers, M.; Askling, J.; Frisell, T.; Strangfeld, A.; et al. Abatacept and non-melanoma skin cancer in patients with rheumatoid arthritis: A comprehensive evaluation of randomised controlled trials and observational studies. *Ann. Rheum. Dis.* **2023**, ard-2023-224356, Online ahead of print. [\[CrossRef\]](#)
26. Marnett, L.J.; DuBois, R.N. COX-2: A target for colon cancer prevention. *Annu. Rev. Pharmacol. Toxicol.* **2002**, *42*, 55–80. [\[CrossRef\]](#)
27. Wadström, H.; Pettersson, A.; Smedby, K.E.; Askling, J. Risk of breast cancer before and after rheumatoid arthritis, and the impact of hormonal factors. *Ann. Rheum. Dis.* **2020**, *79*, 581–586. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Moutsatsou, P.; Papavassiliou, A.G. The glucocorticoid receptor signalling in breast cancer. *J. Cell. Mol. Med.* **2008**, *12*, 145–163. [\[CrossRef\]](#)

29. Hirko, K.A.; Eliassen, A.H. Glucocorticoids and breast cancer risk. *BMC Med.* **2021**, *19*, 187. [[CrossRef](#)]
30. Bazsó, A.; Kövesdi, A.; Rásonyi, R.; Nagy, E.; Poór, G.; Patócs, A.; Kiss, E. Glucocorticoid receptor polymorphisms in rheumatoid arthritis: Results from a single centre. *Clin. Exp. Rheumatol.* **2020**, *38*, 858–863.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.