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Review

Cancer and autoimmune diseases

Eitan Giat [a,*], Michael Ehrenfeld [a], Yehuda Shoenfeld [a,b]

[a] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[b] Sackler Faculty in Medicine, Sheba Medical Center, Tel-Aviv University, Israel

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ABSTRACT

Purpose of review: The association between autoimmunity and cancer is well established. Cancer has been implicated in some autoimmune disorders (AID), such as scleroderma and myositis. On the other hand, many autoimmune disorders and immunosuppressive therapy, have been linked to an increased risk for cancer. We reviewed the accumulating data on the association between autoimmunity and cancer during the past three years, with an emphasis on large cohorts, as well as concept changing discoveries in the association of cancer and auto-immunity.

Recent findings: Recent published data from large registries and databases have changed our perspective on the association of AID and cancer, as well as the presumed association between anti-tumor necrosis factor (anti – TNF) therapy and certain malignancies, suggesting a small to no increase in almost all types of cancers. Similarly, the increased risk of malignancies in some AID, such as Sjogren's syndrome (SS) and lupus, may be different from previous estimations. New associations with malignancies were discovered, such as IgG4 related disease, Behcet's and sarcoidosis, which were not clearly associated with cancer in the past.

These newly described associations may have clinical implications and contribute to our understanding of both autoimmunity and cancer.

Similarly, we reviewed studies of autoimmunity secondary to malignancy, and the concomitant appearance of cancer with autoimmune disease, such as the discovery of a specific mutation in scleroderma (SS) patients that developed cancer, which establishes the association between these disorders and sheds light on the pathology behind this association.

Contents

* Corresponding author.
E-mail address: eitan.giat@sheba.gov.il (E. Giat).

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1. Introduction

The association between cancer and autoimmune disorders (AID) is bidirectional. On one hand, an increased risk of malignancies, both hematological and non-hematological, has been observed in different autoimmune disorders. On the other hand, some malignancies may increase the risk of developing an autoimmune disorder. Furthermore, some cancers may present with clinical features resembling an autoimmune disorder. This review discusses the association of malignancies with common autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), inflammatory myopathies (IM), scleroderma (Sc), vasculitis (Vs) and other AID. This topic has been reviewed previously [1], and this article is an update of this topic reviewing literature published in the past two years.

2. Rheumatoid arthritis

Early studies have suggested an increased prevalence of malignancies among RA patients. The pathogenesis of RA involves a dysregulation of different aspects of the innate immune system including cytokines and cells that have been implicated in tumor formation [2], suggesting that the dysregulated immune system may be pro-oncogenic. Over the years, RA was associated with an increased risk of both hematological and solid malignancies [1]. An increased risk of cancer was also implicated in the treatment of DMARDs and biologic therapy.

Large trials assessing the association of RA and its treatment with cancer among different populations have been published in the past years (Table 1). Recently, a retrospective Korean cohort study [3], following 2104 RA patients over a mean follow-up duration of 7.4 years and 17,436 person years, showed that RA patients have an increased risk of non-Hodgkin's lymphoma (standardized incidence ratio (SIR) = 3.387, 95% CI = 1.462–6.673), but a lower risk for gastric cancer (SIR = 0.663, 95% CI = 0.327 to 0.998). Similarly, a larger nationwide Japanese cohort database [4], between 2003 and 2012, composed of 66,953 patient-years yielded an overall incidence of malignancies in patients with RA which was slightly lower than in the general population (SIR 0.89, 95% CI 0.82–0.97). A reduced risk was noted in malignancies of the rectum and the kidney in males, in stomach and rectal cancer in females, and in liver malignancies among both males and females. Nevertheless, the risk of lymphoma was significantly higher (SIR 3.43, 95% CI 2.59–4.28) among RA patients of both sexes, but the incidence of leukemia was markedly reduced in RA females [5].

Similar results were observed in a nationwide dynamic cohort study in Taiwan [6] following 30,504 patients with no history of cancer who were newly diagnosed with RA between 1996 and 2008 and followed up to 2010 (225,432 person-years of follow-up). The overall risk for malignancy was reduced (SIR = 0.93, 95% CI 0.88–0.97); among site-specific solid cancers, only colorectal cancer was significantly reduced (SIR = 0.71, 95% CI 0.61–0.82), while an increased risk was shown for Hodgkin's lymphoma (SIR 3.31, 95% CI 1.24–8.81) and NHL (SIR 3.18, 95% CI 2.64–3.83). Further analysis of this cohort revealed increased risk for both lymphoid and myeloid malignancies in male and for lymphoid malignancies female RA patients.

Surprisingly, another recently published study from a cohort of 3499 Danish RA patients [7] found that neither recent onset nor long-standing RA was associated with the incidence of solid tumors or lymphoproliferative malignancies after adjusting for confounders, but the follow-up period in this cohort was only 4 years.

In a similar accord, a nationwide population based prospective cohort study from Sweden found that RA patients who have not been treated with biological drugs do not exhibit an increased risk of melanoma compared with the general population. Yet another study from Sweden [8], following 125,117 RA patients from 1964 to 2010 (1,212,967 person years, mean follow-up 9.7 years) found a 2-fold increase in NHL. Analysis from the Swedish register also found [9] higher rates of cytology screening, CIN I-II, and CIN III among biologic naive RA patients compared to the general population cohort, albeit no difference in invasive cervical cancer rates. Similar results were found in a smaller Canadian prospective study [10] Conversely, an increased risk of cancer was observed among biologic-naïve RA subjects receiving non-biologic DMARD therapy recruited to the British register BSRBR from 2002 to 2009 [11]. This cohort comprised 3771 RA patients (13,315 person-years of follow-up) revealed an overall increased risk of cancer (SIR = 1.28, 95% CI 1.10–1.48). An increased risk was noted in lung cancer (SIR 2.39, 95% CI 1.75, 3.19), Hodgkin lymphoma (SIR 12.82, 95% CI 4.16, 29.92) and non-Hodgkin lymphoma (SIR 3.12, 95% CI 1.79, 5.07), while the risk of prostate cancer (SIR 0.35, 95% CI 0.11, 0.82) and gynecological cancers (SIR 0.35, 95% CI 0.10, 0.90) was reduced. Current or previous smoking increased the risk 2-fold.

The discrepancy between these results could be explained by an inter-country variance in environment, genetic risk factors, the prevalence of comorbidities, patient compliance and prevention [12]. For example, a meta-analysis performed by Tian et al. [13] found no increased breast cancer risk in RA patients However, the subgroup analysis showed that while the risk was reduced in Caucasians (SIR = 0.82, 95% CI = 0.73–0.93), non-Caucasians exhibited an increased risk (SIR = 1.21, 95% CI = 1.19–1.23). In the same meta-analysis, hospital-based case subjects also showed a reduced risk, suggesting that these subjects also showed a reduced risk severity of the disease and its course may modify the risk of cancer.

Smitten et al. [14]have conducted a meta-analysis in 2008 reviewing incidence of malignancies in RA patient. This was recently updated by Simon et al. [15], supporting their previous data showing increased risk for lymphomas, and to a lower degree, lung cancer, but not for other malignancies. This observational meta-analysis reviewed published studies between 1 January 2008 and 30 November 2014, found a modest increased risk in overall malignancy. An increased risk was found for lymphoma and lung cancer compared with the general population, while colorectal and breast cancers showed a decrease in risk. Cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk in this meta-analysis.

Similarly, Askling et al. compared different registries across the world, finding high consistency in overall cancer rates, excluding non-melanoma skin cancer, across 5 large registries from the US, UK, Japan Sweden and others, following age/sex standardisation. SIR of overall malignancy excluding NMSC varied from 0.56 to 0.87 per 100 person-years.

2.1. Cancer outcomes

Besides the risk for cancer, RA also has an impact on cancer survival in RA patients with cancer. Mortality was increased by 40% and 50% respectively in elderly patients with RA who developed breast or prostate

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Table 1
Large trials assessing the association of RA and its treatment with cancer.

Study	Location	Details	Results
Chang et al., 2014 [3]	Korea	mean follow-up duration of 7.4 years and 17,436 person years	An increased risk of non-Hodgkin's lymphoma (SIR = 3.387, 95% CI = 1.462–6.673), but a lower risk for gastric cancer (SIR = 0.663, 95% CI = 0.327 to 0.998).
Hashimoto et al., 2015 [4]	Japan	66,953 patient-years, between 2003 and 2012,	Lower overall incidence of malignancies (SIR 0.89, 95% CI 0.82–0.97), lower incidence of rectum and the kidney cancer in males, leukemia, stomach and rectal cancer in females, and liver cancer in both males and females. Lymphoma risk was higher (SIR 3.43, 95% CI 2.59–4.28)
Huang et al., 2014 [6]	Taiwan	30,504 newly diagnosed RA patients (between 1996 and 2008), followed up to 2010,225,432 person-years of follow-up	Reduced overall risk (SIR = 0.93, 95% CI 0.88–0.97);
Lin et al., 2015 [5]	Taiwan	Nationwide retrospective cohort study, 17,472 patients, 87,360 controls from the Taiwan National Health Insurance Database covering 1997–2008	Higher incidences of both lymphoid and myeloid malignancies in male RA patients (SIR 3.36, 95% CI = 2.03–5.57, and SIR: 3.69, 95% CI = 2.46–5.53). A significantly increased overall incidence risk in lymphoid malignancies (SIR 3.00, 95% CI = 2.22–4.05) but not significantly increased in myeloid malignancies (SIR 1.54, 95% CI = 0.95–2.50) in female RA.
Andersen et al., 2014 [7]	Denmark	921 patients with recent onset RA and 2578 with long disease duration from the Copenhagen Primary Care Differential Count (CopDiff) Database	Neither recent onset nor long-standing RA was associated with incident lymphoproliferative malignancies or solid cancers.
Raaschou et al., 2013 [28]	Sweden	nationwide population based prospective cohort study following RA patients treated (n = 10,878) or not (n = 42,198) with TNF inhibitors and matched general population comparators in Swedish registers through 2001–2010	RA patients not treated with biological drugs were not at increased risk of melanoma compared with the general population (hazard ratio 1.2, 95% confidence interval 0.9 to 1.5). RA patients treated with TNF inhibitors had an increased risk of melanoma compared with rheumatoid arthritis patients not treated with biological drugs (hazard ratio 1.5, 1.0 to 2.2; 20 additional cases per 100,000 person years) and a non-significant increased risk for a second primary melanoma was ly increased (hazard ratio 3.2, 0.8 to 13.1; n = 3 v 10).
Fallah et al., 2014 [8]	Sweden	Average of 9.4-year follow-up of 878,161 Swedish patients with AID diagnosed in 1964–2010 with 33 different AID	significantly increased risk for non-Hodgkin lymphoma
Fallah et al., 2014 [96]	Sweden	Average of 9.4-year follow-up of 878,161 Swedish patients diagnosed in 1964–2010 with 33 different AID	significantly increased risk 3.2 (2.6–3.9) for Hodgkin lymphoma
Raaschou et al., 2016 [110]	Sweden	Cohort study (ARTIS) based on nationwide prospectively recorded data from Sweden assessing risk of squamous cell and basal cell skin cancer.	Basal cell cancer: Biologics-naïve patients: HR = 1.22 (1.07–1.41) treatment with TNF inhibitors did not increase this risk. Squamous cell cancer: Biologics-naïve patients: HR = 1.88 (1.74–2.03) TNF inhibitors treated patients: 1.30 (1.10 to 1.55; 191 v 847 events) compared with with biologics-naive patients; Among people with a history of squamous cell or basal cell cancer, TNF inhibitors did not further increase risks.
Mercer et al., 2013 [11]	Britain	3771 biologic-naïve RA subjects recruited to the British register BSRBR from 2002 to 2009 (13,315 person-years of follow-up).	Increased overall risk of cancer (SIR = 1.28, 95% CI 1.10–1.48). An increased risk was noted in lung cancer (SIR 2.39, 95% CI 1.75, 3.19), Hodgkin lymphoma (SIR 12.82, 95% CI 4.16, 29.92) and non-Hodgkin lymphoma (SIR 3.12, 95% CI 1.79, 5.07), while the risk of prostate cancer (SIR 0.35, 95% CI 0.11, 0.82) and gynecological cancers (SIR 0.35, 95% CI 0.10, 0.90) was reduced. Current or previous smoking increased the risk 2-fold.
Mercer et al., 2015 [27]	Britain	Rates of solid cancers in 11 767 patients from the BSRBR without prior cancer who received TNFi were compared to those in 3249 patients without prior cancer treated with sDMARDs.	The addition of TNF inhibitors to DMARDs does not alter the risk of cancer in RA patients selected for TNF inhibitors in the UK.
Mercer et al., 2016 [29]	11 biologic registers from 9 European countries	130 315 RA patients, contributing 579 983 person-years	287 developed a first melanoma. Pooled SIRs for biologic-naïve, TNFi and rituximab-exposed patients were 1.1 (95% CI 0.9 to 1.4), 1.2 (0.99 to 1.6) and 1.3 (0.6 to 2.6), respectively. Incidence rates in tocilizumab and abatacept-exposed patients were also not significantly increased. IRR versus biologic-naïve patients were: TNFi 1.1 (95% CI 0.8 to 1.6); rituximab 1.2 (0.5 to 2.9).
Buchbinder et al., 2015 [111]	Australian database (ARAD)	Comparing cancer incidence between TNFi treated RA patients (2145 patients, 5752 person-years) and biologic-naïve group (803 patients, 1682 patient years).	No overall increased risk of malignancy in TNFi-treated RA patients compared with the general population or with biologic-naïve RA patients. The risk of melanoma was increased for both biologic naïve and TNFi-treated patients when compared with the general population (SIR 2.72 (95% CI 1.13 to 6.53) and SIR 2.03 (95% CI 1.09 to 3.78) respectively). The relative risk of melanoma was not increased in the TNFi-exposed group compared with biologic naïve patients (RR 0.54, 95% CI 0.12, 2.40).

SIR - standardized incidence ratio.

cancer in a population based study [16], but this association was not seen for cancers for shorter survival (colorectal or lung). Others have found higher mortality also in patients with lung cancer [17]. Similarly, analysis of the Swedish register data [18] suggests that the increase in mortality among RA patients diagnosed with cancer seems to result from an RA effect and is independent of the cancer.

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2.2. Therapy of RA and cancer

2.2.1. DMARDs

Recent studies show that the RA treatment may also increase cancer risk. Among synthetic disease modifying anti-rheumatic drugs (sDMARDs), Methotrexate (MTX) is an important part of RA treatment. A recent systematic Cochrane review [19] failed to show any increase in cancer risk, but this review was limited to a small number of patients and a short follow-up period. On the other hand, MTX has been shown to increase the risk for non-melanoma skin cancer by 60% [20] in a large Medicare based study.

2.2.2. Anti-TNF therapy in RA and cancer

The introduction of biologics in RA, especially anti-TNF therapy, has raised the possibility of an increased risk of cancer. TNF has been found to have both proliferation and anti-proliferative effects. Most RCT meta-analyses of anti-TNF and other biological agents in RA [13,21–24] do not show significant differences in the incidence of cancer and lymphoma between biologics and control treatments, but a non-significant increase in some cancers warrants further research [25].

Observational data from large registries have provided similar results. A nationwide cohort study between 1997 and 2011 in Taiwan showed a significant risk adjusted reduction for solid tumors among RA patients taking anti TNF therapy (adjusted HR 0.63, 95% CI 0.49 to 0.80, $P < 0.001$), albeit a non-statistically significant increased risk for hematologic malignancies [26]. Similarly, the British Society for Rheumatology Biologics Register (BSRBR) national prospective cohort reported no difference in risk of solid cancers among RA patients treated with any of the anti TNFi compared to sDMARD treated patients [27]. Similarly, US based cohorts, such as the Safety Assessment of Biological Therapeutics study (Haynes 2013) also showed no increased risk for solid tumors.

On the other hand, the Swedish ARTIS nationwide prospective cohort study [28] found anti TNF therapy was associated with an increased risk for new onset of melanoma (hazard ratio 1.5, 1.0 to 2.2; 20 additional cases per 100,000 person years). True, this risk was not confirmed when combining 11 different registries from different European countries [29], but this does not rule out a population or geographical dependent risk. Similarly, a study from the Netherlands [30] following 365 RA patients treated with anti TNF therapy found a slightly higher risk in both solid and hematological cancers, although this study compared the cancer risk rates to risk rates among the general population, and not to risk rates among biological naïve RA patients, therefore making it impossible to draw any conclusions about the contributory effect of anti TNF therapy.

Among RA patients with prior malignancy, treatment with anti TNF therapy does not seem to increase recurrence rates, despite current guidelines, who require at least 5 years of remission. Analysis of the BSRBR data found lower rates of a new malignancy among patients treated with anti-TNF and rituximab compared to synthetic DMARDs [31], although this study included only 425 patients.

Despite evidence from registries, accumulating data from randomized controlled studies suggest that the association of anti TNFs with cancer may have been overestimated [32]. It is also important to point that the identification of any increased risk of malignancy among anti-TNF treated RA patients, does not necessarily apply to patients treated with anti-TNFs for other indications such as AS, PsA, or IBD.

2.2.3. Other biologics

Experience from biologics other than anti –TNF is lacking, though some of the registries included different biologics. In general, data from clinical trials do not show an increased incidence of malignancies. Rituximab, tocilizumab, and tofacitinib, do not increase the incidence of cancer in clinical trials [33–35]. Abatacept, a CTLA4 fusion protein, suppresses T cell activation, which is an important component in the immune response to cancer. The T cells through CTLA4 inhibitor is the therapeutic target of Ipilimumab, an anti-cancer agent. This raises the possibility of abatacept hampering the immune response to potential malignancies in RA. Nevertheless, the incidence rates of total malignancy (excluding NMSC), breast, colorectal, lung cancers and lymphoma in abatacept treated patients in clinical trials, were consistent with those in a comparable RA population [36].

Put together, it seems that in general biologic therapy does not significantly increase the risk of malignancy in RA patients, though there may be regional variations resulting from different ethnic or environmental backgrounds.

3. Psoriasis arthritis (PsA), ankylosing spondylitis (AS), and other seronegative sponyloarthropathies (SpA)

Studies concerning PsA and AS cancer risk are scarce, and provide conflicting results. Similar to RA, an increased prevalence of cervical cancer was reported among PsA patients in a Canadian cohort [10]. Analysis of data from the USA based CORONA registry (2970 patients with PsA,7133 patient-years of follow-up, and 19,260 patients with RA 53,864 patient-years of follow-up) cohort compared and found no difference between PsA and RA risks for malignancy [37]. In contrary, a recent analysis of the data from the Swedish National Patient registry of 8708 AS patients and 19,283 PsA patients [38] assessed the risk for lymphoma among PsA and AS patients compared with RA patients. Compared to the general population the hazard ratio (HR) for lymphoma was 0.9 (95% confidence interval [95% CI] 0.5–1.6) for AS patients, was 1.2 (95% CI 0.9–1.7) for PsA patients, and 1.7 (95% CI 1.0–3.1) for PsA patients treated with methotrexate and/or sulfasalazine, leading the authors to conclude that in contrast to rheumatoid arthritis, the average risks of lymphoma in AS or PsA are not elevated. A recent meta-analysis suggests an increased risk for cancer in AS patients, which is increased among Asian AS patients [39]. Nevertheless, treatment with anti-TNF does not increase the risk among PsA or SpA in RCTs [32] or in registries and other cohorts [40,41].

4. Adult onset Still's disease (AOSD)

AOSD is a rare AID characterized by spiking fevers, rash and arthritis, accompanied with leukocytosis and hyperferritinemia. A recent review of the literature [42] identified approximately 50 published cases of AOSD preceding a diagnosis of a malignancy, but it is unclear whether this observation is coincidental, results from a paraneoplastic AOSD like syndrome, or reflects an inherent risk for malignancy in AOSD.

5. Primary Sjogren syndrome (pSS)

Early studies in pSS have showed an increased incidence of different malignancies among pSS patients, including solid tumors and, most notably, NHL, where the risk may well exceed a ten-fold increase in some reports. The NHL is typically B cell lymphoma, especially mucosa associated lymphoid tissue (MALT) lymphoma. Accordingly, different risk factors have been suggested to identify patients in high risk for developing cancer [1].

Extracting data from pSS studies is difficult, due to different follow-up periods, heterogeneity in diagnostic criteria, and a relatively smaller number of studies from non-European countries. A recent meta-analysis [43] reviewing 14 studies involving >14,523 patients with pSS revealed significantly increased risks of overall cancer (RR 1.53; 95% CI 1.17–1.88), NHL (RR 13.76; 95% CI 8.53 to 18.99) and thyroid cancer (RR 2.58; 95% CI 1.14 to 4.03). Due to the small numbers and heterogeneity, subgroup analysis did not show significant results in other organ-specific cancers. In general, hospital based cohorts revealed higher SIR compared to primary based cohorts, suggesting a role for severe disease. An important drawback in this meta-analysis originates from the data originating from the Taiwanese cohort study based National Health Insurance claims data of 7852 patients with primary SS from 2000 to

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2008. This non – European population based study contributed more than half the patients but provided considerably different results from the other studies. The overall SIR for cancer was 1.04 (95% CI 0.91 to 1.18), though it was higher for patients aged 25–44 years 2.19 (95% CI 1.43 to 3.21). Only female patients with pSS had a higher risk of NHL (SIR 7.1, 95% CI 4.3 to 10.3), multiple myeloma (SIR 6.1, 95% CI 2.0 to 14.2) and thyroid gland cancer (SIR 2.6, 95% CI 1.4 to 4.3) and a lower risk of colon cancer (SIR 0.22, 95% CI 0.05 to 0.65). This cohort had multiple advantages, being large and nationwide, and being the only large study addressing male pSS patients, which were not found to be at any higher risk of developing cancer in particular sites. Nevertheless, the Taiwanese study had a short mean follow-up time, which could have resulted in an underestimation of the cancer risk. The authors excluded all patients who were diagnosed with cancer before pSS to avoid secondary Sjogren's syndrome, but this might have also excluded true pSS patients who were misdiagnosed prior to their cancer. True enough, the Taiwanese cohort revealed an increase of dental and ophthalmologic visits prior to the diagnosis, reflecting a considerable delay in diagnosis. Finally, the reporting structure of this study may have resulted in an over-diagnosis of pSS in primary care settings for insurance claims. In contrast, European studies were relatively non-heterogenic, consisted of longer follow-ups, and constantly showed a significant risk of different solid tumors. For instance, a recent retrospective study of long-term outcomes in 152 patients with pSS [44] showed that malignancy affected 28.3% of pSS patients, compared with 2.9% in the Taiwanese cohort. Similarly, this study showed that 10.5% of pSS patients developed NHL, compared to <0.5% in the Taiwanese cohort. Vasculitis and the presence of glandular complications (parotid swelling, lymphadenopathy) were the strongest risk factors for developing NHL. Of note, the small percentage of male patients in pSS in all cohorts prevents drawing any conclusions for this population, warranting further research. For example, Taiwanese male pSS patients had an observed rate 3 times higher than expected rate of NHL, but due to a small number, this rate did not reach statistical significance.

5.1. Predictors of lymphoma in pSS

Different markers and symptoms have been described as prognostic factors in predicting lymphoma risk. A recent study has assessed the prognostic value of routinely performed minor salivary gland biopsy assessments in pSS patients. A lymphocytic focus score equal or higher than 3 was found to have a positive predictive value of 16% and a negative predictive value of 98% to develop NHL, suggesting routine histopathological minor salivary gland assessment may have a role in assessing cancer risk. Another study [45] based on the ASSESS cohort has shown BAFF and beta2-microglobulin to be higher in pSS patients with lymphoma (1173.3(873.1–3665.5) vs 898.9 (715.9–1187.2) pg/ml, $P = 0.01$ and 2.6 (2.2–2.9) vs 2.1 (1.8–2.6) mg/l, $P = 0.04$, respectively). Another study [46] has shown the development of purpura, peripheral neuropathy, and glomerulonephritis concurring with lymphoma, but not later on, suggesting these may be paraneoplastic manifestations of the NHL. A recent study [47] analyzing 77 pSS patients that developed NHL found that the EULAR Sjögren's syndrome disease activity index (ESSDAI) is an important independent poor prognostic factor. Subsequently, a recent review article by the same group [48] analyzed risk factors for the development of lymphoma. Clinical symptoms such as parotid gland enlargement, purpura, lymphadenopathy, glomerulonephritis, peripheral neuropathy or splenomegaly were associated with an increased risk as well as other histologic and laboratory factors (neutropenia, CD-4 T-cell lymphopenia, lymphocytic focal score, germinal centers, serum BAFF levels and more). Recently, a meta-analysis [49] identified lymphadenopathy, parotid enlargement, palpable purpura, low C4 serum levels and cryoglobulins to be the most consistent non-Hodgkin's lymphoma/lymphoproliferative disease predictors. Still, these findings await further studies to determine whether they have any screening value.

Taken together, current evidence strongly suggests that pSS, especially a severe disease, procures an increased risk of cancer, especially NHL. The risk is pronounced in European patients and in females, and further research is warranted for Asian and male patients.

6. SLE and cancer

SLE has been associated with different types of cancer, including hematological malignancies and other organ specific tumors [1]. Extensive studies have been undertaken to identify types of lupus and other co-morbidities that are common among SLE patients that develop cancer.

6.1. Overall risk

A recent systematic review of publications [50] assessing the risk of malignancies after SLE through February 2015, was recently published. This study reviewed 18 studies from different countries from Asia Europe and America. SLE patients had an increased risk of developing cancer, particularly among Asians and females. Age and SLE duration were found to be inversely associated with the risk of overall malignancies, reflecting the increasing risk with age among the non SLE population. An increased IR of malignancies was observed in NHL, vagina/vulva, hematology, head/neck, leukemia, thyroid, liver/gallbladder, kidney, anal, cervix, esophagus, lung and pancreas. A decreased IR of malignancies was observed in ovary and colon/rectum. This review supports the results of an earlier met-analysis that showed an increased risk of cancer, particularly lung, bladder and liver, albeit a decreased risk for prostate cancer [51].

A recent retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD) estimating the co-morbidity associated with Systemic Lupus Erythematosus (SLE) in the UK during 1999–2012 [52], compared 7732 prevalent cases of SLE with 28,079 matched controls. This study found SLE patients to have an incidence rate ratios (IRR) for cancer of 1.28 (95% CI: 1.17, 1.40), being slightly higher in males.

6.2. Breast cancer

Contrary to earlier data suggesting SLE may be protective against breast cancer, a Medicare claims data based cohort [53] found a 2.23 (95% CI 1.94–2.55) age-adjusted risk per 100 women for breast cancer in women with SLE compared with 2.14 (95% CI 1.96–2.34) in controls, suggesting that there is no decreased risk for breast cancer among SLE women.

A small study from Brazil [54] followed 395 SLE patients for 10 years in an outpatient clinic, and found that breast and uterine cervix tumors were more common in SLE compared to the general population. In contrary, a large international cohort study [55] and review [56] shows decreased rates of breast and prostate cancer, but a recent multi-center international study conducted by the same group [57] could not identify any associated SLE related factor that might explain this relationship.

6.3. Thyroid cancer

A recent meta-analysis reviewed the association of SLE and thyroid cancer. The pooled SIR was 2.22, (95% CI 2.11–2.34), but due to lack of data, this review did not adjust for confounding factors, such as age, environmental triggers, etc., nor was it able to determine the relationship of thyroid carcinoma to autoimmune thyroditis [58].

6.4. Sub-populations

The risk in different lupus sub-populations has been also studied. It seems that cancer risk is increased in pediatric SLE as well [59]. A nationwide population-based study from Taiwan [60] reviewed 904 SLE pediatric patients followed for 6 years in Taiwan's registry and found

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that children with SLE were more susceptible to malignancy, compared to the non-SLE pediatric population.

Only limited data exists for small lupus subsets. Case reports of squamous cell carcinoma have been reported in discoid lupus [61]. A recent small study [62] (Singh ACR abstr 2628) including 66 cutaneous SLE (SCLE) suggests that the risk of cancer may not be increased in SCLE. These findings await confirmation from larger cohorts.

Finally, despite the clear increased risk for cancer, a recent review [63] found no original study addressing the necessity of specific cancer screening strategies for lupus patients. The authors recommend adhering to the usual screening guidelines as in the general population. This may be due to the fact, that despite the increased risk for cancer, cancer remains to be a rare event in lupus patients. Alternatively, despite the clear increase in both hematological and solid malignancies, the extent of this increased risk has yet to be determined in larger studies before determining cost-effective preventive measures.

7. Cancer and systemic sclerosis (Sc)

Early studies have suggested an increased risk for cancer among Sc patients, particularly breast and lung cancer [1]. A recent cohort analysis of 1044 patients [64] from the John Hopkins Scleroderma Center database identified significant risk factors for the development of cancer, including age in years at onset of Sc (OR 1.04) and white race (OR 2.71). Previous work by this group has shown that cancer risk is associated with the presence of anti-RNA poymerase III subunit, but not other antibodies such as anti-Scl70 [65], contradicting previous data from an Italian cohort that found a relationship between Scl-70 and lung cancer [66]. While this finding can be explained by the higher prevalence of lung disease associated with anti Scl-70, the Italian group also found a 2-fold increase in breast cancer risk which was not associated to a specific antibody [67]. Further research by John Hopkins group revealed that tumors from patients who were diagnosed with cancer more or less concurrently with the diagnosis of Sc, were found to harbor mutations in the polymerase III polypeptide A (POLR3A) gene, suggesting a role and a novel mechanism for cancer in the pathogenesis of Sc.

Anti RNA Polymerase III may not be the only antibodies associated with cancer. A recent report [68] found a prevalence of 20% of cancer in a cohort of 70 scleroderma patients with anti PM/Scl-100 antibodies. The cancer onset in these patients was within 36 months of the diagnosis of Sc. Furthermore, this group described the resolution of Sd symptoms following the disappearance of paraneoplastic anti PM/Scl-100 antibodies after a curative resection of a pancreatic tumor, suggesting a similar mechanism as in POLR3A antibodies.

8. Cancer associated with polymyositis (PM) and dermatomyositis (DM)

The association of PM/DM with cancer was recognized in the beginning of the 20th century [69] though meta-analyses addressing the magnitude of this risk are few. The strong association of cancer with the anti p155/140 antibody targeting transcriptional intermediary factor 1-γ (TIF1-γ) [70] suggests a probable role for cancer in the pathogenesis of myositis among these patients, similar to the mechanism found in scleroderma. True enough, a TIF1γ-overexpressing, highly progressive endometrial carcinoma was reported in a patient with dermatomyositis positive for malignancy-associated anti-p155/140 autoantibody [71]. A recent systematic review [72] including 20 original studies from different countries assessed the risk of DM or PM for different malignancies, providing interesting results. The SIR for malignancy in PM was 1.62 (95% CI 1.19–2.04), 5.50 (4.31–6.70) for DM, and 4.07 (3.02–5.12) for PM/DM combined. Increased risks were more significant in patients within the first year of myositis diagnosis and in male patients. A significant association was also found between PM or DM and most site-specific malignancies with the exception of stomach and prostate cancers. This meta-analysis did not include a recently published study from southern China [73] that followed 246 dermatomyositis patients from 2003 to 2012. Sixty patients (24.4%) had cancer, mostly (65%) within one year of diagnosis, and all cancer cases occurred within three years of diagnosis. Nasopharyngeal carcinoma and ovarian carcinoma were most common, accounting for 35% (21/60) and 15% (9/60) of malignancies, respectively, followed by lung and colon cancer. Another recent meta-analysis [74] supports these results, demonstrating the cancer risk in DM to be 17.29 in the first year, 2.7 between 1 and 5 years, and 1.37 after 5 years.

The types of cancers seem to vary geographically. For instance, nasopharyngeal cancer seems to be common among Chinese and Korean populations, but other cancers predominate among other populations [72]. Surprisingly, a small cohort [75] from Jordan, including 94 PM/DM patients, found a relatively low prevalence (four patients) of malignancy among patients with PM/DM. Interestingly however, in this cohort, two of these patients (50%) had nasopharyngeal cancer. These studies suggest environmental and geographical factors may play a role in the development of PM/DM in different types of cancer.

9. Cancer and ANCA associated vasculitis (AAV)

Few data is available assessing the association between cancer and granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EPGA) and microscopic polyangiitis (MPA). A recent meta-analysis [76] reviewing 2578 AAV patients found increased risk for Non melanoma skin cancer (SIR 5.18), leukemia (SIR 4.89) and bladder cancer (3.84), lymphoma (SIR 3.79), liver (SIR 3.5) and lung (SIR 1.67). The vast majority of these patients had GPA and received cyclophosphamide, and the increased risk probably reflects the oncogenic side effects of the drug rather than an association to the disease. This is further emphasized by a recent Dutch cohort [77] that did not find an increase in patients that did not receive cyclophosphamide more than a year.

10. Cancer and other autoimmune diseases (AID)

The association of cancer with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) is not clear. In the first 6 months after diagnosis of PMR patients were significantly more likely to receive a cancer diagnosis (adjusted risk 1.69 (1.18 to 2.42)) according to an analysis of the UK General Practice Research Database [78]. Similarly, patients hospitalized for PMR and GCA were found to have a marginally increased risk of cancer [79]. On the other hand, population-based case-control studies suggest no risk [80], or even a reduced risk [81] for malignancies in GCA, and a recent similar study found no risk for cancer in PMR [82].

Autoimmune pancreatitis does not seem to confer any risk for cancer [83]. Nodules in autoimmune thyroiditis have been connected to cancer in surgical series, but this may reflect a selection bias [84].

An increased risk for malignancies among patients with IGG4 related disease (IG4RD) has been suggested by some [85], but this has been recently disputed by a cohort study of 113 patients [86]. Yet this study excluded malignancies that were diagnosed at the time of the IgG4RD onset. Similarly, cancer was infrequent among 55 patients from a Spanish register [87]. On the contrary, a recent cohort based study [88] found a two-fold increased risk for cancer among IG4RD patients, and this increase was higher within the first year of diagnosis (3.53, 95% CI 1.23–5.83) suggesting a direct link between cancer and this disorder. One must take into account that some IGG4RD may be erroneously considered as metastases, which may lead to under-reporting of this disorder.

Behcet's disease (BD), a common vasculitis in endemic areas, may increase cancer risk. The Taiwanese Health Insurance Research Database (including 1314 BD patients) found that female BD patients have a higher risk of overall cancer (SIR = 1.8). A high risk was noted for: NHL (SIR 8.3), hematological malignancy (SIR 4.2) and breast cancer (SIR 2.2). This increase was highest within the first year, as 75% of the hematological malignancies were found within the first year [89].

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The risk of cancer in sarcoidosis has been assessed in a cohort of Olmsted County, Minnesota [90]. Overall, the risk of malignancy was similar among sarcoidosis patients compared to non-sarcoidosis controls. However, the risk of incident hematologic malignancy was significantly higher among patients with sarcoidosis with extra-thoracic involvement compared to patients without extra-thoracic disease.

11. AID in malignancies

It seems that AID patients are prone to develop certain types of cancer. For example, in a single center in New York, a fifth of all chronic myelomoncytic leukemia patients had at least one AID, while patients with myelodysplastic syndrome (MDS) had AID rates similar to the general population [91]. The authors suggested that MDS may have evolved through an immune mediated process. Similarly, in another study group of 1408 MDS patients, 28% had an autoimmune disease [92]. On the other hand, others [93] described 8 cases of myelodysplastic syndrome presenting with autoimmune symptoms, including seronegative RA which responded to MTX, pyoderma gangrenosum, cutaneous vasculitis, SLE, IBD and hemophagocytic lymphohistiocytosis. In another cohort [94], 4.4% of MDS patients presented with AID around MDS diagnosis, suggesting AID as a paraneoplastic manifestation of MDS.

According to one center's experience, half of marginal zone lymphoma patients had an AID, with significantly increased rates for immune thrombocytopenia (ITP), auto-immune hemolytic anemia (AIHA), Hashimoto thyroiditis and RA [95]. Similarly, a study from the Swedish Cancer Registry [96] found that the overall incidence of non-Hodgkin lymphoma was increased after AID (SIR 1.6), especially in autoimmune hemolytic anemia (SIR = 27.2), immune thrombocytopenic purpura (SIR = 7.5), pSS (SIR = 4.9), SLE (SIR = 4.4), PM/DM (SIR = 4.1), primary biliary cirrhosis (SIR = 3.9), as well as polyarteritis nodosa, discoid LE, sarcoidosis, myasthenia gravis, Crohn's, Sc, RA, Behcet, Rheumatic fever, ulcerative colitis, polymyalgia rheumatica, Hashimoto and psoriasis. The SIR was higher in younger age groups, and was increased for all histology subtypes, suggesting autoimmunity in general increases the risk for developing cancer.

The risk for solid tumors may also be related to local auto-immunity. A Swedish national based dataset study [97] found an increased risk for primary liver and gallbladder cancer among AID, including, primary biliary cirrhosis, inflammatory bowel disease, and Celiac disease, suggesting a role for a local auto-immune process.

Can cancer trigger autoimmunity? The development of scleroderma in cancer patients harboring the relatively rare POLR3A cancer mutation suggests that cancer may directly induce AID [98]. Malignancies may induce AID such as myositis, which has a clear association with cancer, as well as other miscellaneous AID such as autoimmune hemolytic anemia [99], hepatitis [100], and neurological syndromes [101]. Similarly, specific autoantibodies (i.e., anti-topoisomerase, anti PM-Scl, anti TIF, etc.) in Sc or PM/DM patients are related to an increased risk for cancer. The role of cancer as an inducer of AID is also implied by paraneoplastic autoimmune syndromes such as paraneoplastic pemphigus, Eaton-Lambert syndrome, paraneoplastic polyarthritis, periostitis related to hypertrophic osteoarthropathy, and palmar fasciitis (reviewed by Manger and Schett [102]). Similarly, childhood cancer survivors are at increased risk for AID [103], though this may be related to cancer therapy. Autoantibodies targeting tumors have been suggested as biomarkers for the early detection of esophageal [104], gastric [105], colorectal [106] ovarian [107], and breast [108] cancers. Finally, alarmins, such as HMGN1, have been proposed as anti-tumor mediators that might contribute to autoimmunity [109].

12. Summary

In summary, AID have a clear association with cancer, though the strength of this association varies between different AID, different types of malignancies, and different populations. Therapy of AID may also contribute to this association. This variance may pose a challenge when inferring conclusions from meta-analyses and reviews and should encourage policy makers to create local cohorts and registries. Recent evidence has contributed to our understanding of the mechanisms involved in this association, suggesting that while on one hand AID may procure an increased risk for cancer, on the other hand cancer may also cause autoimmunity in different mechanisms. Hopefully, the elucidation of these mechanisms in the future might allow us to exploit these mechanisms to detect and treat both cancer and AID.

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