Cancer and systemic lupus erythematosus

Ladouceur, Alexandra; Tessier-cloutier, Basile; Clarke, Ann E.; Ramsey-goldman, Rosalind; Gordon, Caroline; Hansen, James E.; Bernatsky, Sasha

DOI:
10.1016/j.rdc.2020.05.005

Document Version
Peer reviewed version

Citation for published version (Harvard):
Ladouceur, A, Tessier-cloutier, B, Clarke, AE, Ramsey-goldman, R, Gordon, C, Hansen, JE & Bernatsky, S 2020, 'Cancer and systemic lupus erythematosus', *Rheumatic Diseases Clinics of North America*, vol. 46, no. 3, pp. 533-550. https://doi.org/10.1016/j.rdc.2020.05.005

Cancer and Systemic Lupus Erythematosus

Alexandra Ladouceur MD PhD[a]; Basile Tessier-Cloutier MD[b]; Ann E. Clarke MD MSc[c], Rosalind Ramsey-Goldman MD DrPh[d]; Caroline Gordon MD[e]; James E. Hansen MD, MS[f]; Sasha Bernatsky, MD PhD[a,g]*

[a] Department of Medicine, McGill University, 1001 Decarie Boulevard, suite D05-2212, Montreal, Quebec, H4A 3J1 Canada

[b]Department of Pathology and Laboratory Medicine, University of British Columbia, Rm. G227 – 2211 Wesbrook Mall, Vancouver, British Columbia, V6T 2B5 Canada

[c] Division of Rheumatology, University of Calgary, 3330 Hospital Drive Northwest, Calgary, Alberta T2N 4N1, Canada;

[d] Division of Rheumatology, Northwestern University Feinberg School of Medicine, McGaw Pavilion, 240 East Huron Street, Suite M-300, Chicago, IL 60611, USA;

[e] Division of Rheumatology, College of Medical and Dental Sciences, University of Birmingham, Edgbaston B15 2TT, UK;

[f] Department of Therapeutic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA

[g] Division of Clinical Epidemiology, Research Institute of McGill University Health Centre, 5252 de Maisonneuve West, 3rd floor, Montreal, Quebec H4A 3S5, Canada;

KEYWORDS
• Systemic lupus erythematosus • Cancer • Malignancy • Epidemiology

KEY POINTS

- Systemic lupus erythematosus (SLE) is associated with a small overall increased cancer risk compared to the general population. This includes a 4-fold increased risk of non-Hodgkin lymphoma (NHL), but a decreased risk of other cancers (such as breast cancer).
- The pathophysiology underlying the increased risk of hematologic cancer is not fully understood, but many potential mechanisms have been proposed, including dysfunction of the tumor necrosis factor (TNF) and other pathways.
- A decreased risk of breast, ovarian and endometrial cancer might be driven by hormonal factors or lupus-related antibodies, but these links have not been proven.
- Cyclophosphamide may be a risk factor for hematological cancers in SLE, but this does not entirely explain the altered cancer risk profile in SLE. Exposure to hydroxychloroquine may be inversely related to breast and possibly other cancers.
- Recent evidence suggests that higher disease activity itself may be associated with lymphoma risk in SLE, but not with non-hematologic malignancies.
- Cancer preventive methods such as smoking cessation and regular cancer screening remain important in the SLE population.

Disclosure: None.

* Corresponding author. Dr. Sasha Bernatsky. Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, 5252 de Maisonneuve West, office 3F.51, Montreal, Quebec H4A 3S5, Canada.
E-mail address: sasha.bernatsky@mcgill.ca

E-mail addresses of the authors:
Alexandra Ladouceur: Alexandra.ladouceur@mail.mcgill.ca; Basile Tessier-Cloutier : basile.tessiercloutier@mail.mcgill.ca; Ann E. Clarke : aeclarke@ucalgary.ca; Rosalind Ramsey-Goldman: rgramsey@northwestern.edu; Caroline Gordon: p.c.gordon@bham.ac.uk; James Hansen: james.e.hansen@yale.edu

1. INTRODUCTION

Over the last two decades, there has been an increasing interest in links between autoimmune disorders such as SLE and cancer risk. The most recent evidence comparing SLE to the general population shows a slight increase in cancer risk overall (standardized incidence ratio [SIR], 1.14; 95% confidence interval [CI], 1.05–1.23).[1] Many recent large cohort studies and meta-analyses have also demonstrated an increased risk of malignancy.[2, 3, 4, 5, 6] The underlying pathophysiologic mechanisms are still not fully understood, but possible factors include lupus-related medications, inherent immune system abnormalities,[7] overlap with Sjögren's syndrome,[8] viral infections, and/or traditional cancer risk factors.[9] Although the risk in SLE for hematologic cancers, especially non-Hodgkin lymphoma (NHL), is increased about four-fold,[1, 2, 10, 11] breast, endometrial, and possibly ovarian cancers seem to be associated with a decreased risk in the SLE population.[1, 2, 12, 13, 14, 15]. This review will first focus on hematologic, lung, and other cancers with an increased risk in SLE, and then review the data regarding cancers where SLE patients may in fact have a decreased risk.

2. HEMATOLOGIC CANCERS

2.1 Epidemiology

A link between hematologic cancer and SLE was initially suggested more than three decades ago [16] and has been supported by many studies, which suggest an increased risk of about three-fold.[1, 2, 10, 11, 17] (Table 1) Based on incidence and mortality data generated from the large, multicenter, international SLE cohort contributed by the Systemic Lupus International Collaborating Clinics (SLICC) and other investigators, it was observed that NHL incidence (SIR, 4.39; 95% CI, 3.48–5.49) and mortality due to NHL (Standardized mortality ratio [SMR] 2.8; 95% CI, 1.2–5.6) were particularly increased in patients with SLE, compared with the general population.[1, 18] A recent systematic literature review confirmed that both lymphoma incidence and mortality is increased in SLE.[19]

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL[6] and SLE patients may present at more advanced stages at diagnosis and have a worse prognosis.[20] As in the general population, lymphoma risk in SLE increases with age.[21] SLE patients are also at increased risk of Hodgkin lymphoma (HL)[5, 22, 23] and leukemia [1, 2, 10]. Although many individual cohort studies were not able to show an increased risk of multiple myeloma (MM) in SLE [1, 2, 6], the frequency of monoclonal gammopathy was found to be higher than expected in one study [24] and a recent meta-analysis reported a moderate increased risk of MM in SLE (pooled SIR: 1.48; 95% CI: 1.02-2.14).[5] In a review of SLE MM cases, 80% of the patients were of black race/ethnicity.[22] It was not clear if this may be due to race/ethnicity itself versus disease activity, medication exposures, or other factors.

2.2 Pathophysiology

2.2.1 Increased disease activity

Disease activity has been invoked as a potential factor to explain the increased lymphoma risk in SLE.(Table 2) One analysis has suggested that higher disease activity in SLE may be associated with greater risk of hematologic cancers, but a possible decreased risk for other

cancer types.[25] Although increased disease activity has been associated with higher lymphoma risk in certain other autoimmune disorders (for example, rheumatoid arthritis, RA[26]), the association in SLE is less clear, [21, 27] but there is a growing body of 'circumstantial' evidence, which we review below.

2.2.2 High expression of APRIL (A Proliferation-Inducing Ligand)

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype in SLE.[13] Since DLBCL lesions arise from activated lymphocyte (the cell line responsible for most of the inflammation in autoimmune disorders such as SLE), it may be that the chronic inflammatory state seen in patients with SLE contributes to the cancer risk. Furthermore, DLBCL lesions that develop in patients with SLE were shown to highly express APRIL (A PRoliferation-Inducing Ligand), a cytokine from the tumor necrosis factor (TNF) ligand superfamily that is essential for B-cell survival and development.[7] The investigators proposed that APRIL might mediate the development of lymphoma in SLE and other rheumatic diseases, possibly by allowing NHL B cells to escape apoptosis.(Table 2)[28] DLBCL is classified by gene expression into two major groups according to the 'cell of origin': germinal center B-cell (GCB) or non-germinal center (non-GCB).[29] In the general population, the GCB subtype is the most common.[30] However, the majority (60%) of DLBCL in SLE are non-GCB.[31] Non-GCB DLBCL are defined by activation of the NF-κB and JAK-STAT pathways, which are both involved in SLE through dysfunctions of A20, TNF superfamily (TNFSF4), and other molecular pathways.[32]

2.2.3 Polymorphism of TNF Alpha-induced protein 3 (TNFAIP3) and other genetic factors

Given findings that the link between SLE and NHL may be bi-directional, potentially shared genetic risk factors are of great interest.[33] One particularly interesting potential mechanism linking lymphoma risk to autoimmune rheumatic disease is via polymorphisms of TNF Alpha-Induced protein 3 (TNFAIP3), related to the A20 protein important in NF-κB activation. Indeed, polymorphisms of that protein have been found in mucosa-associated lymphoid tissue (MALT) lymphoma in primary Sjögren's as well as in HL in RA.[34] However, in our analyses of genome wide association studies (GWAS), data could not confirm a strong relationship with the lupus-related TNFAIP3 single nucleotide polymorphism (SNP) rs7749323 specifically for DLBCL; this could be explained by a lack of power due to the sample size.[35] In those GWAS analyses, the rs2205960 SNP, related to TNFSF4, was associated with an odds ratio (OR) per risk allele of 1.07 (95% CI 1.00-1.16). SLE interferon regulatory factor risk allele rs12537284 (chromosome 7q32, IRF5 gene) was associated with an OR of 1.08 (95% CI 0.99-1.18). The STAT4 lupus risk SNP rs7582694 was not clearly associated with DLBCL although this could also be a sample size issue. A recent evaluation of polygenic risk scores using multiple GWAS datasets suggested complex genetic risk factors may be shared between autoimmune diseases (including SLE), and NHL, but ultimately the autoimmune disease-related polygenic risk scores were not highly predictive of NHL risk, although in SLE a link between one gene (TERT) and chronic lymphocytic leukemia was noted.[36]

Polymorphism of the Fas gene and close relationships between Fas and Sle1 genes have been reported in SLE, [37, 38, 39, 40, 41, 42] and defective Fas-mediated apoptosis of lymphocytes contributes to the pathophysiology of autoimmune lymphoproliferative syndrome (ALPS), a rare, autosomal dominant disorder with increased risk of both autoimmunity (including many SLE manifestations: rash, nephritis, arthritis, and autoantibodies) and lymphoma. Although ALPS is

an example of how a genetic defect can increase an individual's risk for both autoimmune disease and lymphoma, this specific genetic disorder does not explain most of the lymphoma cases that arise in SLE. As mentioned earlier, recent analyses of autoimmune disease GWAS data (including SLE) found more genetic commonalities with NHL than with solid cancers.[35]
Our conclusion is that TNF superfamily and perhaps interferon pathways warrant more study to determine their potential role in mediating the risk of DLBCL (particularly non-GCB type) in SLE.

2.2.4 The role of cytokines

Cytokines also potentially play a role in the increased risk of NHL in SLE. SLE patients have elevated levels of interleukin (IL)-6 [43] and IL-10, and these cytokines are also associated with NHL risk in the general population, [44] particularly non-GCB DLBCL, [45] the most frequent DLBCL subtype in SLE .(Table 2).[31, 46]

2.2.5 Epstein-Barr Virus (EBV)

The Epstein-Barr virus (EBV) is suggested to have a role in the pathophysiology of SLE,[47, 48, 49] and since it is also associated with some cancers in the general population, EBV has been proposed as a potential risk factor driving cancers in SLE. EBV seropositivity is only slightly increased in patients with SLE compared with the general population, but some data indicate altered ability to clear this viral infection in SLE.[50] Increased viral load, EBV mRNA expression, EBV-directed antibodies, and decreased EBV-directed cell immunity have all been shown in patients with SLE compared with healthy controls.[49, 50] This finding is relevant to studies of the association of SLE and cancer because EBV has been associated with several cancers known to be increased in SLE including HL, DLBCL, and some head and neck cancers.[51] The mechanisms by which EBV promotes malignancy may involve B-cell immortalization, manipulation of host chromatin-remodeling machinery, and promoting cell migration and resistance to apoptosis through p53, BCL-2, A20 and Fas modulation.[51, 52] Although links between EBV and SLE-related malignancies are interesting, there is no clear evidence of a strong role of EBV as a driver in cancer risk in SLE.(Table 2)[19]

2.2.6 Secondary Sjogren's syndrome

It has been suggested that lupus induced secondary Sjögren's syndrome could account for some of the heightened risk of hematologic malignancies. Our case-cohort analyses based on the large multicenter international SLE cohort showed a trend supporting an increased risk for lymphoma development in patients with Sjögren's syndrome (hazard ratio (HR), 1.79; 95% CI, 0.88–3.62).[21] Here, Sjögren's syndrome was based on clinical judgment, as opposed to requiring patients to fulfill specific criteria, and thus may have been subject to nondifferential misclassification of the exposure, which could have biased this result toward the null value. Thus, it remains possible that secondary Sjögren's syndrome may explain some (but not all) of the increased lymphoma risk in SLE. (Table 2)

2.2.7 Immunosuppressive therapy

Another potential cause of increased hematological malignancy is the effect of immunosuppressive therapy. Our multicenter case-cohort study reported an increased risk of hematological cancer with immunosuppressant exposure (HR:2.29, 95% CI: 1.02-5.15).[53]

When the effect was decomposed to specifically assess each drug separately, the risk after cyclophosphamide exposure was 3.55 (95% CI: 0.94-13.37); after azathioprine 1.02 (95% CI: 0.34-3.03); and after methotrexate 2.57 (95% CI: 0.80-8.27). In a case-cohort study published later, the majority of the patients who developed lymphoma (56%) were never exposed to cyclophosphamide, azathioprine, methotrexate or mycophenolate.[21] (Table 2) Moreover, the cases and the controls did not differ in their exposure to immunosuppressive treatment except for a slightly more frequent exposure to cyclophosphamide in patients diagnosed with lymphoma compared to controls (20% vs 16.8%). One of the difficulties in interpreting these results is that SLE patients receiving potent immunosuppressive therapies, especially cyclophosphamide, are sicker and probably have higher disease activity. There is a strong association between disease activity and the increased risk of lymphoma in RA,[26] and although the contribution of disease activity to lymphoma risk in SLE remains unclear,[21, 53] it is a confounding variable that needs to be controlled for.

3. LUNG CANCERS

3.1 Epidemiology

Studies have systematically reported an increased risk of lung cancer with autoimmune rheumatologic conditions, including SLE[1, 3, 54], RA,[55] and scleroderma.[56] It is, in fact, the second most frequent cancer in SLE.[57] SLE patients are not only at increased risk of developing lung cancer (Table 1) [3] but also of dying from it.[18] Although a potential trend toward overrepresentation of rarer types (including bronchoalveolar and carcinoid) was identified in one study, the overall histologic distribution was comparable with that of the general population.[58]

3.2. Pathophysiology

3.2.1 Smoking

Smoking may represent a shared environmental risk factor between both lung cancer and SLE. Data support an association between lupus and smoking[59], since the vast majority of lung cancer cases in SLE occur in smokers.[58] In analyses of data from 49 incident lung cancer cases from a multi-center SLE cohort, 84.2% were smokers compared with 40.8% of SLE patients without lung cancer, and the association persisted in multivariate analyses.(Table 2) [57]

3.2.2 Fibrosis and inflammation

The proven link between lung cancer, inflammation and fibrosis in the general population [60] [61] invokes the possibility that alveolitis and/or pulmonary fibrosis in SLE may drive lung cancer risk. In case-cohort analyses of the multi-centre international SLE dataset, there was a trend towards an increased lung malignancy risk in the patients who developed pulmonary fibrosis (unadjusted HR 3.29, 95% CI: 0.86-12.6 and adjusted HR 2.41, 95% CI: 0.63-9.22).(Table 2) [57]

3.2.3 Genetic factors

Genetic associations are an interesting possible explanation for the association between SLE and lung cancer, including shared susceptibility loci on chromosome 4 (p15.1–15.3) and 6 (p21).[58] More precisely, rs13194781 and rs1270942 on the gene region 6p21-22 are of great

interest, as they play a role in pathophysiological pathways of both SLE and lung cancer. (Table 2) [62] Although it remains unclear how much of the increased risk of lung cancer in SLE these genetic factors may play, one study did suggest polygenic links between SLE and lung adenocarcinoma.[36]

3.2.4 Immunosuppressive therapy

There is no clear association between the risk of lung cancer and medication use in SLE. In our multi-cohort study assessing lung cancer risk in SLE, none of the patients who developed a lung cancer were exposed to cyclophosphamide.[57] In addition, only 20% of patients affected by lung cancer from the large international SLE cohort had previously been exposed to immunosuppressive therapy [58]; this may suggest that drugs are not the primary cause of lung cancer in patients with SLE.(Table 2)

4. CERVICAL AND VULVAR CANCERS

4.1 Epidemiology

It has constantly been shown that SLE patients are at increased risk of developing the squamous intraepithelial lesions which precede cervical cancer development.[63, 64, 65, 66] A recent meta-analysis reported a higher risk of high grade squamous intraepithelial lesions (HSIL) in SLE patients (OR 8.66; 95% CI, 3.75-20.00).(Table 1)[64] The magnitude of risk may vary from one country to another, as studies from countries where cervical cancer screening is effectively implemented report a considerably lower risk than the countries where the screening program is less accessible[67] as screening identifies early stage lesions which can be treated prior to progression to more advanced stages. The low incidence of cervical cancer in countries with effective screening programs (about 6.6 per 100,000 North American women) makes it a challenge to assess its relation to SLE with sufficient power. There may also be ascertainment issues, because cancer registries often do not record noninvasive malignancies. This may explain why a systematic review found a higher risk of squamous intraepithelial lesions in SLE but was not able to conclude that SLE patients have a higher risk of cervical cancer than the general population.[63] SLE patients have increased risk of other malignancies that are also strongly associated with HPV,[1, 11, 17, 54] including vulvar (SIR, 3.78; 95% CI, 1.52–7.78) and anal carcinoma (SIR, 26.9; 95% CI, 8.7–83.4).[1, 68]

4.2 Pathophysiology

4.2.1 Human papilloma virus (HPV)

It has been hypothesized that SLE patients are more vulnerable to develop cervical dysplasia since patients with SLE are more vulnerable to infection with HPV[11, 68], particularly the high-risk aggressive variants that are linked to cervical dysplasia and cancer.[69, 70] Furthermore, immunosuppressants may cause reduced clearance of HPV in SLE [71] and predispose to cervical dysplasia.[72, 73, 74], [71].(Table 2) [72, 73, 74] A vaccine against HPV is available and despite the fact that the immune response engendered might be lower in SLE patients versus the general populations, studies suggest it is safe and efficient in patients with autoimmune diseases, including SLE.[75, 76] Moreover, studies of the vaccine against HPV suggested that immunogenicity at five years is maintained in the majority of the SLE patients.[77] Accordingly,

the US Center for Disease Control recommends the vaccine for any immunocompromised patients up to age 26.[78] The 2019 update of EULAR recommends that all SLE patients should be vaccinated against HPV according to the recommendations for the general population.[79] In the latest recommendations for the assessment and monitoring of SLE, the Canadian Rheumatology Association does not comment on HPV vaccination.[80]As with cervical dysplasia, poor HPV clearance, due to baseline defects and/or immunosuppression could drive the risk of vulvar and anal cancer in SLE.[74, 81]

Routine screening for cervical dysplasia is important for patients with SLE, and these exams could also bring to clinical attention the more rare vulvar and vaginal malignancies. However, one study observed that female patients with SLE with the most severe disease burden (based on SLICC/American College of Rheumatology damage index scores) were the least likely to have undergone cervical screening.[82]. Recent Canadian SLE guidelines recommend Pap tests annually in patients from the time they begin sexual activity until the age of 69.[80] EULAR guidelines recommend annual pap tests in heavily immunosuppressed SLE patients (e.g., exposure to cyclophosphamide), but to follow local guidelines for low-risk patients.[83]

5. OTHER CANCERS WITH INCREASED RISK

SLE patients are at increased risk of other types of malignancy including head and neck, thyroid and liver.(Table 1) A recent study [84] reported a SIR for head and neck cancers of 2.16 (95% CI, 1.13–4.13) in SLE, consistent with previous data.[17] However, both of these studies were in Asian populations (which have a higher general population risk for head and neck malignancy), therefore the relevance of these data to North American and European SLE populations is uncertain. Nevertheless, a recent systematic review also found an increased risk of oropharynx and larynx cancer in SLE, indicating that these data may be generalizable to other populations.[5] Again, since head and neck malignancies may be associated with HPV [85] and potentially, in some immunosuppressed individuals, EBV[86, 87, 88], altered viral clearance in SLE may be a risk factor for this malignancy type. Smoking cigarettes remains a major risk factor for the development of oral cancers in general, and further studies are required to determine the potential contribution of smoking specifically in SLE.

In a recent review, it was found that thyroid cancer is consistently increased in SLE patients.[5] Interestingly, one study found that thyroid antibodies (anti-thyroglobulin and anti-thyroid peroxidase) were more frequent in SLE patients with concomitant thyroid cancer (80%) than in cancer-free SLE patients (31%).(Table 2) [89] A similar association between thyroid auto-antibodies and thyroid cancer has also been described in scleroderma.[90] The prevalence of hypothyroidism, which is often itself a manifestation of autoimmune disease, is increased in SLE, but hypothyroidism per se is not associated with an increase in the risk of developing thyroid malignancy in either lupus, scleroderma or the general population.[91]

The conclusions of a recent meta-analysis also suggest a higher risk of both kidney (SIR 2.10, 95% CI: 1.11-3.96) and bladder cancers (SIR 1.86, 95% CI: 1.16-2.99).[5] Cyclophosphamide is known to increase the risk of bladder cancer in the general population[92], although its role in SLE-related bladder cancer remains unclear.[68] Cyclophosphamide, particularly oral and high cumulative dose, has also been associated with bladder cancer in granulomatosis with polyangiitis, RA and NHL.[93] A single study reported that the risk of bladder cancer in SLE is highest with daily oral cyclophosphamide, especially when the cumulative dose was greater than

six grams.[94] However, in SLE, intravenous cyclophosphamide is generally used, and there has long been a trend towards use of lower cumulative doses. These factors may explain why cyclophosphamide has not been found to be strongly associated with renal or bladder cancer in SLE. However, it is recommended that patients with SLE who have received cyclophosphamide should be monitored life-long with annual urine cytology with prompt investigation of any abnormal cytology.[95]

An increased risk of liver cancer in SLE is also consistently reported in the literature; a recent meta-analysis found a SIR of 2.37 (95% CI: 1.37-3.38).[5] Although it has been proposed that decreased clearance of both hepatitis B (HBV) and C (HCV) viruses could contribute to this, their role in SLE remains unclear.

Many cohort studies have reported an increased risk of non-melanoma skin cancer.[10, 17, 68] In a recent systematic review and meta-analysis, Song et al. also found an increased risk of non-melanoma skin cancer but a decreased risk of melanoma, with a pooled SIR of 0.72 (95% CI: 0.56-0.93).[5] This is consistent with a previous meta-analysis that also found a lower risk of melanoma.[4] In immunosuppressed organ transplanted patients, the risk of both melanoma and non-melanoma skin cancers are increased.[96] The increased risk in non-melanoma skin cancer has been related to immunosuppressive therapies in inflammatory bowel disease[97, 98], and one study has suggested an association with cyclophosphamide in SLE.[99]

6. DECREASED CANCER RISK IN SLE

6.1 Epidemiology

SLE patients may have a decreased incidence rate of certain cancers compared to the general population.[15] One meta-analysis of studies primarily involving clinically confirmed SLE patients found a decreased risk of breast cancer,[13] though another meta-analysis (which included several administrative-data based studies that did not clinically confirm SLE) found a pooled SIR for breast cancer of 0.89, with a CI that just included the null value (95% CI: 0.77-1.04).[5] However, it should be noted that, in the general population, black and Asian women have lower breast cancer risk than whites; since blacks and Asians may be more susceptible to SLE, some of the lower breast cancer risk in SLE could be driven by race/ethnicity (via either genetic or other factors).

Several studies including a meta-analysis have suggested that ovarian and endometrial cancers may be decreased in SLE (Table 1)[1, 13] although one meta-analysis (which included large administrative data-base studies that did not clinically confirm SLE) found a pooled SIR of 0.70 (95% CI: 0.46-1.07) for ovarian cancers where the 95% CI barely included the null value.[5]

6.2 Pathophysiology

6.2.1 Hormonal factors

Multiparity is a protective factor against ovarian cancer [100], and long-term use of a combined oral contraceptive (COC) is associated with a decreased risk of ovarian as well as endometrial cancer in the general population.[100] However, SLE patients tend to have fewer children than

the general population, and COC use is relatively low in SLE [101]. Because breast, endometrial and possibly ovarian cancers are often driven by hormonal factors, it has been suggested that altered estrogen metabolism in SLE could at least in part explain the negative association between SLE and these cancers. SLE patients are known to have their menarche at an older age and their menopause at a younger age compared to the general population.[13, 102] The result may equal a total endogenous estrogen exposure in SLE patients, possibly explaining why they appear less inclined to develop some cancers, particularly hormone-receptor positive breast cancer.

As in the general population, the most frequent breast cancer type in SLE is ductal carcinoma, yet breast cancers in SLE are more often estrogen receptor (ER) and progesterone receptor (PR) negative.[95] Although it is possible that the cancer type is influenced by the young age of SLE patients, one study reported a tendency towards an increased prevalence of triple-negative breast cancers (that is, breast cancers that do not express estrogen, progesterone, and HER2 receptors) in lupus patients.[103] These observations suggest a complex interplay of influential mechanisms, possibly linking the immune and endocrine systems to cancer risk in SLE.

6.2.2 Medications

There is also speculation regarding a possible protective role of certain medications used in treating patients with SLE, such as antimalarials (i.e. hydroxychloroquine), in long-term cancer risk.[104] The proposed mechanism involves its role on promoting the autophagy (a form of self-induced cell death) of malignant cells.[105, 106] Emerging evidence suggests that antimalarials may indeed decrease risk of breast cancer in SLE.(Table 2)[99]. In addition, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked with a decreased risk of some cancers in the general population.[107, 108] However, there is at present no robust evidence of a clear effect of aspirin and NSAIDs on cancer risk in SLE.

6.2.3 Genetic factors

As noted earlier, it is possible that the cancer risk profile in SLE may be, at least in part, genetically mediated. However, analyses of genome-wide association study data did not demonstrate any differences in the frequency of ten SLE-related single-nucleotide polymorphisms in breast cancer cases (in the general population) compared with cancer-free controls. If decreased breast cancer risk in SLE is influenced by genetic profiles, this may be caused by complex interactions and/or epigenetic factors.[109]

6.2.4 Autoantibodies

Another potential explanation for the decreased risk of breast cancer in women with SLE is that lupus autoantibodies may be suppressing the emergence of certain types of malignant cells. A cell-penetrating, lupus-related, anti-DNA antibody was shown to inhibit DNA repair and to be toxic to cancer cells with intrinsic defects in DNA repair.[110] Triple-negative breast cancers are known to harbor defects in DNA repair and thus are likely to be particularly susceptible to the effects of such lupus autoantibodies. It is thus possible that suppression of triple-negative and BRCA-deficient breast cancers by anti-DNA antibodies may partly account for the lower-than-expected rates of breast cancer in women with SLE. This line of reasoning is supported by a trend for

decreased ductal carcinoma in SLE, which are predominantly triple-negative breast cancers.[14, 111] A cell-penetrating monoclonal antibody from a lupus mouse model that targets single-stranded DNA has received particular attention in this regard.[112] In abnormal, cancer-promoting cells carrying double-strand DNA breaks, this cell-penetrating antibody promotes cell death.[113] However, only a subset of anti-DNA antibodies are cell-penetrating, and so far, there has been no clear role for anti-DNA antibodies mediating cancer risk in SLE.(Table 2)[114]

6.2.5 Regulatory T-cells

Regulatory T cells (T_{regs}) may also play a role in suppressing the development of breast cancer in SLE. T_{regs} are responsible for attenuating immune responses and in some cases may protect malignant cells from the immune system's role in deleting abnormal cancer cells, such as breast cancers. T_{regs} that are highly expressed in some breast tumors in patients who do not have lupus are associated with a poor prognosis.[115] However, because T_{reg} functions are altered in SLE, it is possible that this favors a more effective antitumor response (in SLE) from unopposed helper T cells.(Table 2) This specific hypothesis is yet unproven.

SUMMARY

In this review, we have summarized data published in the last decade regarding SLE and malignancy. The data regarding the relationship between medications used to treat SLE and cancer risk suggest that cyclophosphamide may be a risk factor for hematological and non-melanoma skin cancers in SLE, but even this drug exposure only explains a small proportion of the altered cancer risk profile in SLE. Antimalarial drugs may be associated with lower risk of breast and skin cancers in SLE. Many molecular mechanisms such as increased expression of APRIL, higher levels of IL-6 and IL-10 and polymorphism of TNFAIP3 are possibly involved in the increased risk of hematological cancers in SLE. The possible mechanism of SLE-related cell-penetrating anti-DNA antibodies in suppression of breast cancer in SLE provides a useful direction for future research. At present, promotion of preventive measures such as smoking cessation and encouraging HPV vaccination and regular cancer screening programs (particularly for cervical dysplasia) are common-sense interventions for SLE patients.

1. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun. 2013 May;42:130-5. doi: 10.1016/j.jaut.2012.12.009. PubMed PMID: 23410586; PubMed Central PMCID: PMCPMC3646904.
2. Parikh-Patel A, White RH, Allen M, et al. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control. 2008 Oct;19(8):887-94. doi: 10.1007/s10552-008-9151-8. PubMed PMID: 18386139; PubMed Central PMCID: PMCPMC4357418.
3. Ni J, Qiu LJ, Hu LF, et al. Lung, liver, prostate, bladder malignancies risk in systemic lupus erythematosus: evidence from a meta-analysis. Lupus. 2014 Mar;23(3):284-92. doi: 10.1177/0961203313520060. PubMed PMID: 24429300.
4. Cao L, Tong H, Xu G, et al. Systemic lupus erythematous and malignancy risk: a meta-analysis. PLoS One. 2015;10(4):e0122964. doi: 10.1371/journal.pone.0122964. PubMed PMID: 25885411; PubMed Central PMCID: PMCPMC4401738.
5. Song L, Wang Y, Zhang J, et al. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther. 2018 Dec 6;20(1):270. doi: 10.1186/s13075-018-1760-3. PubMed PMID: 30522515; PubMed Central PMCID: PMCPMC6282326.
6. Tallbacka KR, Pettersson T, Pukkala E. Increased incidence of cancer in systemic lupus erythematosus: a Finnish cohort study with more than 25 years of follow-up. Scand J Rheumatol. 2018 Jan 10:1-4. doi: 10.1080/03009742.2017.1384054. PubMed PMID: 29318934.
7. Lofstrom B, Backlin C, Pettersson T, et al. Expression of APRIL in diffuse large B cell lymphomas from patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol. 2011 Sep;38(9):1891-7. doi: 10.3899/jrheum.101190. PubMed PMID: 21724695.
8. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med. 1978 Dec;89(6):888-92. doi: 10.7326/0003-4819-89-6-888. PubMed PMID: 102228.
9. Bernatsky S, Boivin JF, Joseph L, et al. Prevalence of factors influencing cancer risk in women with lupus: social habits, reproductive issues, and obesity. J Rheumatol. 2002 Dec;29(12):2551-4. PubMed PMID: 12465150.
10. Bjornadal L, Lofstrom B, Yin L, et al. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol. 2002;31(2):66-71. PubMed PMID: 12109649.
11. Mellemkjaer L, Andersen V, Linet MS, et al. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum. 1997 Apr;40(4):761-8. doi: 10.1002/1529-0131(199704)40:4<761::AID-ART23>3.0.CO;2-P. PubMed PMID: 9125261.
12. Dey D, Kenu E, Isenberg DA. Cancer complicating systemic lupus erythematosus--a dichotomy emerging from a nested case-control study. Lupus. 2013 Aug;22(9):919-27. doi: 10.1177/0961203313497118. PubMed PMID: 23857987; PubMed Central PMCID: PMCPMC4107831.
13. Bernatsky S, Ramsey-Goldman R, Foulkes WD, et al. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. Br J Cancer. 2011 Apr 26;104(9):1478-81. doi: 10.1038/bjc.2011.115. PubMed PMID: 21487409; PubMed Central PMCID: PMCPMC3101932.
14. Tessier Cloutier B, Clarke AE, Ramsey-Goldman R, et al. Breast cancer in systemic lupus erythematosus. Oncology. 2013;85(2):117-21. doi: 10.1159/000353138. PubMed PMID: 23887245; PubMed Central PMCID: PMCPMC3934367.
15. Gadalla SM, Amr S, Langenberg P, et al. Breast cancer risk in elderly women with systemic autoimmune rheumatic diseases: a population-based case-control study. Br J Cancer. 2009 Mar 10;100(5):817-21. doi: 10.1038/sj.bjc.6604906. PubMed PMID: 19190628; PubMed Central PMCID: PMCPMC2651404.
16. Green JA, Dawson AA, Walker W. Systemic lupus erythematosus and lymphoma. Lancet. 1978 Oct 7;2(8093):753-6. doi: 10.1016/s0140-6736(78)92645-4. PubMed PMID: 80683.
17. Chen YJ, Chang YT, Wang CB, et al. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. Am J Med. 2010 Dec;123(12):1150 e1-6. doi: 10.1016/j.amjmed.2010.08.006. PubMed PMID: 21183006.
18. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006 Aug;54(8):2550-7. doi: 10.1002/art.21955. PubMed PMID: 16868977.
19. Klein A, Polliack A, Gafter-Gvili A. Systemic lupus erythematosus and lymphoma: Incidence, pathogenesis and biology. Leuk Res. 2018 Dec;75:45-49. doi: 10.1016/j.leukres.2018.11.004. PubMed PMID: 30458319.
20. Knight JS, Blayney DW, Somers EC. Patients with systemic lupus erythematosus and haematological malignancy at a tertiary care centre: timing, histopathology and therapy. Lupus Sci Med. 2014;1(1):e000051. doi: 10.1136/lupus-2014-000051. PubMed PMID: 25452880; PubMed Central PMCID: PMCPMC4246917.
21. Bernatsky S, Ramsey-Goldman R, Joseph L, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Ann Rheum Dis. 2014 Jan;73(1):138-42. doi: 10.1136/annrheumdis-2012-202099. PubMed PMID: 23303389; PubMed Central PMCID: PMCPMC3855611.
22. Lu M, Bernatsky S, Ramsey-Goldman R, et al. Non-lymphoma hematological malignancies in systemic lupus erythematosus. Oncology. 2013;85(4):235-40. doi: 10.1159/000350165. PubMed PMID: 24107608; PubMed

Central PMCID: PMCPMC3880772.
23. Bernatsky S, Ramsey-Goldman R, Rajan R, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. Ann Rheum Dis. 2005 Oct;64(10):1507-9. doi: 10.1136/ard.2004.034504. PubMed PMID: 16162903; PubMed Central PMCID: PMCPMC1755239.
24. Ali YM, Urowitz MB, Ibanez D, et al. Monoclonal gammopathy in systemic lupus erythematosus. Lupus. 2007;16(6):426-9. doi: 10.1177/0961203307079045. PubMed PMID: 17664233.
25. Ladouceur A, Clarke AE., Ramsey-Goldman R., Urowitz MB., Hanly JG., Gordon C, Petri M., Ginzler EM., Wallace DJ., Bae S-C., Romera-Diaz J., Dooley MA., Peschnken C., Isenberg DA., Rahman A., Manzi S., Aranow C., Sanchez-Guerrero L., Gladman D., Fortin PR., Alcaron GS., Merrill JT., Khamashta MA., Bruce IN and Bernatsky S. . Hematologic and Non-hematologic Cancer Risk in a Large Inception SLE Cohort. Canadian Rheumatology Association (CRA); 26th-29th Februart; Victoria, British Columbia, Canada 2020.
26. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701. doi: 10.1002/art.21675. PubMed PMID: 16508929.
27. Koyama T, Tsukamoto H, Miyagi Y, et al. Raised serum APRIL levels in patients with systemic lupus erythematosus. Ann Rheum Dis. 2005 Jul;64(7):1065-7. doi: 10.1136/ard.2004.022491. PubMed PMID: 15576416; PubMed Central PMCID: PMCPMC1755547.
28. He B, Chadburn A, Jou E, et al. Lymphoma B cells evade apoptosis through the TNF family members BAFF/BLyS and APRIL. J Immunol. 2004 Mar 1;172(5):3268-79. doi: 10.4049/jimmunol.172.5.3268. PubMed PMID: 14978135.
29. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med. 2002 Jun 20;346(25):1937-47. doi: 10.1056/NEJMoa012914. PubMed PMID: 12075054.
30. Ennishi D, Mottok A, Ben-Neriah S, et al. Genetic profiling of MYC and BCL2 in diffuse large B-cell lymphoma determines cell-of-origin-specific clinical impact. Blood. 2017 May 18;129(20):2760-2770. doi: 10.1182/blood-2016-11-747022. PubMed PMID: 28351934.
31. Tessier-Cloutier B, Twa DD, Baecklund E, et al. Cell of origin in diffuse large B-cell lymphoma in systemic lupus erythematosus: molecular and clinical factors associated with survival. Lupus Sci Med. 2019;6(1):e000324. doi: 10.1136/lupus-2019-000324. PubMed PMID: 31205728; PubMed Central PMCID: PMCPMC6541753.
32. Compagno M, Lim WK, Grunn A, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature. 2009 Jun 4;459(7247):717-21. doi: 10.1038/nature07968. PubMed PMID: 19412164; PubMed Central PMCID: PMCPMC2973325.
33. Wang LH, Wang WM, Lin SH, et al. Bidirectional relationship between systemic lupus erythematosus and non-Hodgkin's lymphoma: a nationwide population-based study. Rheumatology (Oxford). 2019 Feb 4. doi: 10.1093/rheumatology/kez011. PubMed PMID: 30726952.
34. Nocturne G, Boudaoud S, Miceli-Richard C, et al. Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjogren's syndrome. Blood. 2013 Dec 12;122(25):4068-76. doi: 10.1182/blood-2013-05-503383. PubMed PMID: 24159176; PubMed Central PMCID: PMCPMC3862283.
35. Bernatsky S, Velasquez Garcia HA, Spinelli JJ, et al. Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma. Lupus Sci Med. 2017;4(1):e000187. doi: 10.1136/lupus-2016-000187. PubMed PMID: 29214033; PubMed Central PMCID: PMCPMC5715504.
36. Din L, Sheikh M, Kosaraju N, et al. Genetic overlap between autoimmune diseases and non-Hodgkin lymphoma subtypes. Genet Epidemiol. 2019 Oct;43(7):844-863. doi: 10.1002/gepi.22242. PubMed PMID: 31407831; PubMed Central PMCID: PMCPMC6763347.
37. Lu MM, Ye QL, Feng CC, et al. Association of FAS gene polymorphisms with systemic lupus erythematosus: A case-control study and meta-analysis. Exp Ther Med. 2012 Sep;4(3):497-502. doi: 10.3892/etm.2012.625. PubMed PMID: 23181125; PubMed Central PMCID: PMCPMC3503889.
38. Shi X, Xie C, Kreska D, et al. Genetic dissection of SLE: SLE1 and FAS impact alternate pathways leading to lymphoproliferative autoimmunity. J Exp Med. 2002 Aug 5;196(3):281-92. doi: 10.1084/jem.20010955. PubMed PMID: 12163557; PubMed Central PMCID: PMCPMC2193943.
39. Pettersson T, Pukkala E, Teppo L, et al. Increased risk of cancer in patients with systemic lupus erythematosus. Ann Rheum Dis. 1992 Apr;51(4):437-9. PubMed PMID: 1586239; PubMed Central PMCID: PMCPMC1004687.
40. Moss KE, Ioannou Y, Sultan SM, et al. Outcome of a cohort of 300 patients with systemic lupus erythematosus attending a dedicated clinic for over two decades. Ann Rheum Dis. 2002 May;61(5):409-13. doi: 10.1136/ard.61.5.409. PubMed PMID: 11959764; PubMed Central PMCID: PMCPMC1754082.
41. Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. Lupus. 2001;10(6):394-400. doi: 10.1191/096120301678646128. PubMed PMID: 11434573.
42. Lofstrom B, Backlin C, Sundstrom C, et al. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. Ann Rheum Dis. 2007 Dec;66(12):1627-32. doi: 10.1136/ard.2006.067108. PubMed PMID: 17517757; PubMed Central PMCID:

PMCPMC2095297.
43. Arenas-Padilla M, Mata-Haro V. Regulation of TLR signaling pathways by microRNAs: implications in inflammatory diseases. Cent Eur J Immunol. 2018;43(4):482-489. doi: 10.5114/ceji.2018.81351. PubMed PMID: 30799997; PubMed Central PMCID: PMCPMC6384427.
44. Makgoeng SB, Bolanos RS, Jeon CY, et al. Markers of Immune Activation and Inflammation, and Non-Hodgkin Lymphoma: A Meta-Analysis of Prospective Studies. JNCI Cancer Spectr. 2018 Dec;2(4):pky082. doi: 10.1093/jncics/pky082. PubMed PMID: 30873511; PubMed Central PMCID: PMCPMC6400235.
45. Qiu H, Gong S, Xu L, et al. MYD88 L265P mutation promoted malignant B cell resistance against T cell-mediated cytotoxicity via upregulating the IL-10/STAT3 cascade. Int Immunopharmacol. 2018 Nov;64:394-400. doi: 10.1016/j.intimp.2018.09.024. PubMed PMID: 30253331.
46. Tamma R, Ingravallo G, Albano F, et al. STAT-3 RNAscope Determination in Human Diffuse Large B-Cell Lymphoma. Transl Oncol. 2019 Mar;12(3):545-549. doi: 10.1016/j.tranon.2018.12.008. PubMed PMID: 30639963; PubMed Central PMCID: PMCPMC6370997.
47. James JA, Neas BR, Moser KL, et al. Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure. Arthritis Rheum. 2001 May;44(5):1122-6. doi: 10.1002/1529-0131(200105)44:5<1122::AID-ANR193>3.0.CO;2-D. PubMed PMID: 11352244.
48. James JA, Kaufman KM, Farris AD, et al. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest. 1997 Dec 15;100(12):3019-26. doi: 10.1172/JCI119856. PubMed PMID: 9399948; PubMed Central PMCID: PMCPMC508514.
49. Moon UY, Park SJ, Oh ST, et al. Patients with systemic lupus erythematosus have abnormally elevated Epstein-Barr virus load in blood. Arthritis Res Ther. 2004;6(4):R295-302. doi: 10.1186/ar1181. PubMed PMID: 15225364; PubMed Central PMCID: PMCPMC464871.
50. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. Clin Dev Immunol. 2013;2013:535738. doi: 10.1155/2013/535738. PubMed PMID: 24062777; PubMed Central PMCID: PMCPMC3766599.
51. Pattle SB, Farrell PJ. The role of Epstein-Barr virus in cancer. Expert Opin Biol Ther. 2006 Nov;6(11):1193-205. doi: 10.1517/14712598.6.11.1193. PubMed PMID: 17049016.
52. Saha A, Robertson ES. Epstein-Barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. Clin Cancer Res. 2011 May 15;17(10):3056-63. doi: 10.1158/1078-0432.CCR-10-2578. PubMed PMID: 21372216; PubMed Central PMCID: PMCPMC4287361.
53. Bernatsky S, Joseph L, Boivin JF, et al. The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case-cohort study. Ann Rheum Dis. 2008 Jan;67(1):74-9. doi: 10.1136/ard.2006.069039. PubMed PMID: 17545189.
54. Hemminki K, Liu X, Ji J, et al. Effect of autoimmune diseases on risk and survival in histology-specific lung cancer. Eur Respir J. 2012 Dec;40(6):1489-95. doi: 10.1183/09031936.00222911. PubMed PMID: 22323571.
55. De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. Best Pract Res Clin Rheumatol. 2018 Dec;32(6):869-886. doi: 10.1016/j.berh.2019.03.011. PubMed PMID: 31427060.
56. Maria ATJ, Partouche L, Goulabchand R, et al. Intriguing Relationships Between Cancer and Systemic Sclerosis: Role of the Immune System and Other Contributors. Front Immunol. 2018;9:3112. doi: 10.3389/fimmu.2018.03112. PubMed PMID: 30687318; PubMed Central PMCID: PMCPMC6335319.
57. Bernatsky S, Ramsey-Goldman R, Petri M, et al. Smoking Is the Most Significant Modifiable Lung Cancer Risk Factor in Systemic Lupus Erythematosus. J Rheumatol. 2018 Mar;45(3):393-396. doi: 10.3899/jrheum.170652. PubMed PMID: 29335347; PubMed Central PMCID: PMCPMC5834350.
58. Bin J, Bernatsky S, Gordon C, et al. Lung cancer in systemic lupus erythematosus. Lung Cancer. 2007 Jun;56(3):303-6. doi: 10.1016/j.lungcan.2007.01.007. PubMed PMID: 17291624.
59. Ekblom-Kullberg S, Kautiainen H, Alha P, et al. Smoking and the risk of systemic lupus erythematosus. Clin Rheumatol. 2013 Aug;32(8):1219-22. doi: 10.1007/s10067-013-2224-4. PubMed PMID: 23515599; eng.
60. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. Anticancer Res. 2012 Apr;32(4):1119-36. PubMed PMID: 22493341; PubMed Central PMCID: PMCPMC3349285.
61. Hubbard R, Venn A, Lewis S, et al. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. 2000 Jan;161(1):5-8. doi: 10.1164/ajrccm.161.1.9906062. PubMed PMID: 10619790.
62. Rosenberger A, Sohns M, Friedrichs S, et al. Gene-set meta-analysis of lung cancer identifies pathway related to systemic lupus erythematosus. PLoS One. 2017;12(3):e0173339. doi: 10.1371/journal.pone.0173339. PubMed PMID: 28273134; PubMed Central PMCID: PMCPMC5342225.
63. Santana IU, Gomes Ado N, Lyrio LD, et al. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. Clin Rheumatol. 2011 May;30(5):665-72. doi: 10.1007/s10067-010-1606-0. PubMed PMID: 21072553.
64. Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous intraepithelial lesions in

systemic lupus erythematosus: A meta-analysis of the literature. Autoimmun Rev. 2014 Jul;13(7):730-5. doi: 10.1016/j.autrev.2014.03.001. PubMed PMID: 24657969.
65. Kim SC, Glynn RJ, Giovannucci E, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Ann Rheum Dis. 2015 Jul;74(7):1360-7. doi: 10.1136/annrheumdis-2013-204993. PubMed PMID: 24618265; PubMed Central PMCID: PMCPMC4161656.
66. Wadstrom H, Arkema EV, Sjowall C, et al. Cervical neoplasia in systemic lupus erythematosus: a nationwide study. Rheumatology (Oxford). 2017 Apr 1;56(4):613-619. doi: 10.1093/rheumatology/kew459. PubMed PMID: 28039412; PubMed Central PMCID: PMCPMC5850736.
67. Dugue PA, Lynge E, Rebolj M. Increased risk of high-grade squamous intraepithelial lesions in systemic lupus erythematosus: additional data from Denmark. Autoimmun Rev. 2014 Dec;13(12):1241-2. doi: 10.1016/j.autrev.2014.08.004. PubMed PMID: 25151614.
68. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis Rheum. 2011 Oct;63(10):3032-7. doi: 10.1002/art.30483. PubMed PMID: 21953088.
69. Nath R, Mant C, Luxton J, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum. 2007 May 15;57(4):619-25. doi: 10.1002/art.22667. PubMed PMID: 17471531.
70. Lee YH, Choe JY, Park SH, et al. Prevalence of human papilloma virus infections and cervical cytological abnormalities among Korean women with systemic lupus erythematosus. J Korean Med Sci. 2010 Oct;25(10):1431-7. doi: 10.3346/jkms.2010.25.10.1431. PubMed PMID: 20890422; PubMed Central PMCID: PMCPMC2946651.
71. Tam LS, Chan PK, Ho SC, et al. Risk factors for squamous intraepithelial lesions in systemic lupus erythematosus: a prospective cohort study. Arthritis Care Res (Hoboken). 2011 Feb;63(2):269-76. doi: 10.1002/acr.20367. PubMed PMID: 20890985.
72. Bernatsky S, Ramsey-Goldman R, Gordon C, et al. Factors associated with abnormal Pap results in systemic lupus erythematosus. Rheumatology (Oxford). 2004 Nov;43(11):1386-9. doi: 10.1093/rheumatology/keh331. PubMed PMID: 15280571.
73. Klumb EM, Araujo ML, Jr., Jesus GR, et al. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? J Clin Rheumatol. 2010 Jun;16(4):153-7. doi: 10.1097/RHU.0b013e3181df5261. PubMed PMID: 20407390.
74. Tam LS, Chan AY, Chan PK, et al. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. Arthritis Rheum. 2004 Nov;50(11):3619-25. doi: 10.1002/art.20616. PubMed PMID: 15529372.
75. Grein IH, Groot N, Lacerda MI, et al. HPV infection and vaccination in Systemic Lupus Erythematosus patients: what we really should know. Pediatr Rheumatol Online J. 2016 Mar 8;14(1):12. doi: 10.1186/s12969-016-0072-x. PubMed PMID: 26956735; PubMed Central PMCID: PMCPMC4782298.
76. Mok CC, Ho LY, Fong LS, et al. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Ann Rheum Dis. 2013 May;72(5):659-64. doi: 10.1136/annrheumdis-2012-201393. PubMed PMID: 22589375; eng.
77. Mok CC, Ho LY, To CH. Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus. Vaccine. 2018 May 31;36(23):3301-3307. doi: 10.1016/j.vaccine.2018.04.056. PubMed PMID: 29699792.
78. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2014 Aug 29;63(Rr-05):1-30. PubMed PMID: 25167164; eng.
79. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020 Jan;79(1):39-52. doi: 10.1136/annrheumdis-2019-215882. PubMed PMID: 31413005.
80. Keeling SO, Alabdurubalnabi Z, Avina-Zubieta A, et al. Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus. J Rheumatol. 2018 Oct;45(10):1426-1439. doi: 10.3899/jrheum.171459. PubMed PMID: 30173152.
81. Tam LS, Chan PK, Ho SC, et al. Natural history of cervical papilloma virus infection in systemic lupus erythematosus - a prospective cohort study. J Rheumatol. 2010 Feb;37(2):330-40. doi: 10.3899/jrheum.090644. PubMed PMID: 20032093.
82. Bernatsky SR, Cooper GS, Mill C, et al. Cancer screening in patients with systemic lupus erythematosus. J Rheumatol. 2006 Jan;33(1):45-9. PubMed PMID: 16331804.
83. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017 Mar;76(3):476-485. doi: 10.1136/annrheumdis-2016-209770. PubMed PMID: 27457513; PubMed Central PMCID: PMCPMC5446003.
84. Chang SL, Hsu HT, Weng SF, et al. Impact of head and neck malignancies on risk factors and survival in

systemic lupus erythematosus. Acta Otolaryngol. 2013 Oct;133(10):1088-95. doi: 10.3109/00016489.2013.800228. PubMed PMID: 24032572.
85. Koslabova E, Hamsikova E, Salakova M, et al. Markers of HPV infection and survival in patients with head and neck tumors. Int J Cancer. 2013 Oct 15;133(8):1832-9. doi: 10.1002/ijc.28194. PubMed PMID: 23564321.
86. Sisk EA, Bradford CR, Carey TE, et al. Epstein-Barr virus detected in a head and neck squamous cell carcinoma cell line derived from an immunocompromised patient. Arch Otolaryngol Head Neck Surg. 2003 Oct;129(10):1115-24. doi: 10.1001/archotol.129.10.1115. PubMed PMID: 14568799.
87. Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. J Rheumatol. 1999 Aug;26(8):1705-14. PubMed PMID: 10451066.
88. Knight A, Askling J, Granath F, et al. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis. 2004 Oct;63(10):1307-11. doi: 10.1136/ard.2003.019125. PubMed PMID: 15130900; PubMed Central PMCID: PMCPMC1754772.
89. Antonelli A, Mosca M, Fallahi P, et al. Thyroid cancer in systemic lupus erythematosus: a case-control study. J Clin Endocrinol Metab. 2010 Jan;95(1):314-8. doi: 10.1210/jc.2009-0677. PubMed PMID: 19906791.
90. Antonelli A, Ferri C, Ferrari SM, et al. Increased risk of papillary thyroid cancer in systemic sclerosis associated with autoimmune thyroiditis. Rheumatology (Oxford). 2016 Mar;55(3):480-4. doi: 10.1093/rheumatology/kev358. PubMed PMID: 26424836.
91. Lim H, Devesa SS, Sosa JA, et al. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA. 2017 Apr 4;317(13):1338-1348. doi: 10.1001/jama.2017.2719. PubMed PMID: 28362912.
92. International Agency of Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Vol.26: some antineoplastic and immunosuppressive agents. Lyon (France): International Agency for Research on Cancer; 1981.
93. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum. 2010 Jan;62(1):9-21. doi: 10.1002/art.25061. PubMed PMID: 20039416.
94. Kang KY, Kim HO, Yoon HS, et al. Incidence of cancer among female patients with systemic lupus erythematosus in Korea. Clin Rheumatol. 2010 Apr;29(4):381-8. doi: 10.1007/s10067-009-1332-7. PubMed PMID: 20041274.
95. Tessier-Cloutier B, Clarke AE, Pineau CA, et al. What investigations are needed to optimally monitor for malignancies in SLE? Lupus. 2015 Jul;24(8):781-7. doi: 10.1177/0961203315575587. PubMed PMID: 25742688.
96. Collins L, Quinn A, Stasko T. Skin Cancer and Immunosuppression. Dermatol Clin. 2019 Jan;37(1):83-94. doi: 10.1016/j.det.2018.07.009. PubMed PMID: 30466691.
97. Hagen JW, Pugliano-Mauro MA. Nonmelanoma Skin Cancer Risk in Patients With Inflammatory Bowel Disease Undergoing Thiopurine Therapy: A Systematic Review of the Literature. Dermatol Surg. 2018 Apr;44(4):469-480. doi: 10.1097/DSS.0000000000001455. PubMed PMID: 29315147.
98. Moran GW, Lim AW, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Nov;38(9):1002-24. doi: 10.1111/apt.12491. PubMed PMID: 24099467.
99. Bernatsky S, Ramsey-Goldman R, Urowitz M, et al. . Cancer risk in a large inception SLE cohort: effects of age, smoking and medications. ACR/ARP Annual meeting; November 8-13; Atlanta 2019.
100. Bermas BL, Sammaritano LR. Fertility and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Fertil Res Pract. 2015;1:13. doi: 10.1186/s40738-015-0004-3. PubMed PMID: 28620518; PubMed Central PMCID: PMCPMC5424288.
101. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005 Dec 15;353(24):2550-8. doi: 10.1056/NEJMoa051135. PubMed PMID: 16354891.
102. Cooper GS, Dooley MA, Treadwell EL, et al. Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. Arthritis Rheum. 2002 Jul;46(7):1830-9. doi: 10.1002/art.10365. PubMed PMID: 12124867.
103. Chan K, Clarke AE, Ramsey-Goldman R, et al. Breast cancer in systemic lupus erythematosus (SLE): receptor status and treatment. Lupus. 2018 Jan;27(1):120-123. doi: 10.1177/0961203317713146. PubMed PMID: 28595511.
104. Ruiz-Irastorza G, Ugarte A, Egurbide MV, et al. Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. Ann Rheum Dis. 2007 Jun;66(6):815-7. doi: 10.1136/ard.2006.067777. PubMed PMID: 17204564; PubMed Central PMCID: PMCPMC1954667.
105. Amaravadi RK. Autophagy-induced tumor dormancy in ovarian cancer. J Clin Invest. 2008 Dec;118(12):3837-40. doi: 10.1172/JCI37667. PubMed PMID: 19033653; PubMed Central PMCID: PMCPMC2582935.
106. Rahim R, Strobl JS. Hydroxychloroquine, chloroquine, and all-trans retinoic acid regulate growth, survival, and histone acetylation in breast cancer cells. Anticancer Drugs. 2009 Sep;20(8):736-45. doi: 10.1097/CAD.0b013e32832f4e50. PubMed PMID: 19584707.

107. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, et al. Aspirin and lung cancer in women. Br J Cancer. 2002 Jul 1;87(1):49-53. doi: 10.1038/sj.bjc.6600370. PubMed PMID: 12085255; PubMed Central PMCID: PMCPMC2364276.
108. Moran EM. Epidemiological and clinical aspects of nonsteroidal anti-inflammatory drugs and cancer risks. J Environ Pathol Toxicol Oncol. 2002;21(2):193-201. PubMed PMID: 12086406.
109. Bernatsky S, Easton DF, Dunning A, et al. Decreased breast cancer risk in systemic lupus erythematosus: the search for a genetic basis continues. Lupus. 2012 Jul;21(8):896-9. doi: 10.1177/0961203312443992. PubMed PMID: 22495874.
110. Hansen JE, Chan G, Liu Y, et al. Targeting cancer with a lupus autoantibody. Sci Transl Med. 2012 Oct 24;4(157):157ra142. doi: 10.1126/scitranslmed.3004385. PubMed PMID: 23100628; PubMed Central PMCID: PMCPMC3713477.
111. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium. Lancet. 1997 May 24;349(9064):1505-10. PubMed PMID: 9167459.
112. Rattray Z, Dubljevic V, Rattray NJW, et al. Re-engineering and evaluation of anti-DNA autoantibody 3E10 for therapeutic applications. Biochem Biophys Res Commun. 2018 Feb 12;496(3):858-864. doi: 10.1016/j.bbrc.2018.01.139. PubMed PMID: 29374508.
113. Noble PW, Bernatsky S, Clarke AE, et al. DNA-damaging autoantibodies and cancer: the lupus butterfly theory. Nat Rev Rheumatol. 2016 Jul;12(7):429-34. doi: 10.1038/nrrheum.2016.23. PubMed PMID: 27009542.
114. Bernatsky S, Ramsey-Goldman R, Petri M, et al. Breast cancer in systemic lupus. Lupus. 2017 Mar;26(3):311-315. doi: 10.1177/0961203316664595. PubMed PMID: 27687028; PubMed Central PMCID: PMCPMC5250552.
115. Bates GJ, Fox SB, Han C, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol. 2006 Dec 1;24(34):5373-80. doi: 10.1200/JCO.2006.05.9584. PubMed PMID: 17135638.