Cancer and Systemic Lupus Erythematosus

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KEYWORDS

- Systemic lupus erythematosus • Cancer • Malignancy • Epidemiology

KEY POINTS

- Systemic lupus erythematosus (SLE) is associated with a small overall increased cancer risk compared with the general population. This risk includes a 4-fold increased risk of non-Hodgkin lymphoma, 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 and other pathways. Recent evidence suggests that higher disease activity itself may be associated with lymphoma risk in SLE, but not with nonhematologic malignancies.
- 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 proved.
- 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.
- Cancer preventive methods, such as smoking cessation and regular cancer screening, remain important in the SLE population.

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INTRODUCTION

Over the last 2 decades, there has been an increasing interest in links between auto-immune disorders such as systemic lupus erythematosus (SLE) and cancer risk. The most recent evidence comparing SLE with 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 shown an increased risk of malignancy.[2–6] The underlying pathophysiologic mechanisms are still not fully understood, but possible factors include lupus-related medications, inherent immune system abnormalities,[7] overlap with Sjögren 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 4-fold,[1,2,10,11] breast, endometrial, and possibly ovarian cancers seem to be associated with a decreased risk in the SLE population.[1,2,12–15] This article first focuses on hematologic, lung, and other cancers with an increased risk in SLE, and then reviews the data regarding cancers for which patients with SLE may have a decreased risk.

HEMATOLOGIC CANCERS
Epidemiology

A link between hematologic cancer and SLE was initially suggested more than 3 decades ago[16] and has been supported by many studies, which suggest an increased risk of about 3-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 caused by 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 are increased in SLE.[19]

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL[6] and patients with SLE 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] Patients with SLE 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 higher than expected in 1 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 whether this may be caused by race/ethnicity itself versus disease activity, medication exposures, or other factors.

Pathophysiology

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 (eg, rheumatoid arthritis [RA][26]), the association in SLE is less clear,[21,27] but there is a growing body of circumstantial evidence, which is reviewed later.

Table 1
Cancer risk profiles in systemic lupus erythematosus

Cancer Type	Risk Compared with the General Population	References
Hematologic (lymphoma, leukemia, multiple myeloma)	At least 3-fold increased risk	[1,2,10,11,17]
NHL	About 4-fold higher risk	[1,18,21]
Lung	Several studies report an increased risk	[3]
Cervical	Increased risk of squamous intraepithelial lesions (preceding cancer)	[64]
Vulva/vagina	At least 1 study found an increased risk	[1]
Head and neck	At least 1 study found an increased risk	[84]
Thyroid	Several studies report an increased risk	[5]
Bladder and kidney	A meta-analysis reported an increased risk	[5]
Liver	Several studies report an increased risk	[3]
Nonmelanoma skin	Several studies report an increased risk	[4]
Breast Ovarian Endometrial	Several studies report a decreased risk	[1,13]

Data from Refs.[1–5,10,11,13,17,18,21,64,84]

High expression of a proliferation-inducing ligand

DLBCL is the most common lymphoma subtype in SLE.[13] Because 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 (see **Table 2**).[28] DLBCL is classified by gene expression into 2 major groups according to the cell of origin: germinal center B cell (GCB) or non-GCB.[29] In the general population, the GCB subtype is the most common.[30] However, most (60%) DLBCLs in SLE are non-GCB.[31] Non-GCB DLBCLs are defined by activation of the nuclear factor (NF)-κB and Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways, which are both involved in SLE through dysfunctions of A20, TNF superfamily 4 (TNFSF4), and other molecular pathways.[32]

Polymorphism of tumor necrosis factor alpha–induced protein 3 and other genetic factors

Given findings that the link between SLE and NHL may be bidirectional, potentially shared genetic risk factors are of great interest.[33] One particularly interesting potential

Table 2
Factors that have been suggested as mediating cancer risk in systemic lupus erythematosus

Cancer Type	Mechanisms Potentially Involved	References
Hematologic (including all lymphomas, leukemias, and MM)	Potential effect of disease activity (for lymphoma), but still unclear	[21]
	High expression of APRIL could possibly allow NHL B cells to escape apoptosis	[28]
	For DLBCL, single nucleotide polymorphisms including TNFSF4 and SLE IRF5. Importance of polygenic risk scores remains unclear although 1 gene (TERT) was identified as associated with both SLE and chronic lymphocytic leukemia	[35,36]
	SLE has increased levels of IL-6 and IL-10 and these cytokines are associated with increased NHL in the general population	[44]
	EBV: no clear evidence	[19]
	Secondary Sjögren syndrome may explain some of the increased risk	[21]
	Possibly increased risk with cyclophosphamide	[53]
Lung	Smoking is associated with increased risk	[57]
	No clear association with the exposure to immunosuppressive therapy	[57,58]
	Lung fibrosis may be associated with increased risk	[57]
	Genetic factors, possibly polygenic	[36,58,62]
Cervical and vulva/vagina	HPV infection and immunosuppressants	[11,72]
Head and neck	Smoking is a major risk factor in the general population, but more studies are needed to establish its role in SLE	—
	Possible decreased clearance of oncogenic viruses such as HPV and EBV	[85,86]
Thyroid	Thyroid antibodies are more frequent in SLE with thyroid cancer vs cancer-free patients, but their significance is unclear	[89]
Bladder and kidney	The role of cyclophosphamide as a causative agent in SLE remains unclear	[68]
Liver	Possible decreased clearance of HBV and HCV	—
Skin	Antimalarials may decrease risk, cyclophosphamide may increase risk	[99]
Breast	Later menarche and earlier menopause in SLE vs the general population	[13]
	In the general population, black and Asian people have greater risk of SLE and these race/ethnic groups have lower breast cancer risk than white people. This finding may invoke genetic factors, but to date none have been specifically identified	[109]
	Antimalarials might decrease the risk of breast cancer	[99]
	Possible subset of anti-DNA antibodies may decrease risk	[110]
	Highly expressed regulatory T cells may favor efficient antitumor response	[115]

Table 2 (continued)		
Cancer Type	Mechanisms Potentially Involved	References
Ovarian	Later menarche and earlier menopause in SLE vs the general population	[13]
Endometrial	Later menarche and earlier menopause in SLE vs the general population	[13]

Abbreviations: APRIL, a proliferation-inducing ligand; EBV, Epstein-Barr virus; HPV, human papilloma virus; IL, interleukin; IRF5, interferon regulatory factor 5; TNF, tumor necrosis factor; TNFSF4, tumor necrosis factor superfamily 4.

Data from Refs.[11,13,19,21,28,35,36,44,53,57,58,62,68,72,85,86,89,99,109,110,115]

mechanism linking lymphoma risk to autoimmune rheumatic disease is via polymorphisms of TNF-alpha–induced protein 3 (TNFAIP3), related to the A20 protein, which is important in NF-κB activation. Polymorphisms of that protein have been found in mucosa-associated lymphoid tissue lymphoma in primary Sjögren 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 caused by 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 (IRF) risk allele rs12537284 (chromosome 7q32, IRF5 gene) was associated with an OR of 1.08 (95% CI, 0.99–1.18). The signal transducer and activator of transcription 4 (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 that 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 1 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,[37–42] 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.

The role of cytokines

Cytokines also potentially play a role in the increased risk of NHL in SLE. Patients with SLE have increased 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 (see **Table 2**).[31,46]

Epstein-Barr virus

The Epstein-Barr virus (EBV) is suggested to have a role in the pathophysiology of SLE,[47–49] and because 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 messenger RNA 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 (see **Table 2**).[19]

Secondary Sjögren syndrome

It has been suggested that lupus-induced secondary Sjögren 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 syndrome (hazard ratio [HR], 1.79; 95% CI, 0.88–3.62).[21] Here, Sjögren 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 syndrome may explain some (but not all) of the increased lymphoma risk in SLE (see **Table 2**).

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, most of the patients who developed lymphoma (56%) were never exposed to cyclophosphamide, azathioprine, methotrexate, or mycophenolate[21] (see **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 with controls (20% vs 16.8%). One of the difficulties in interpreting these results is that patients with SLE 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.

LUNG CANCERS
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 the second most frequent cancer in SLE.[57] Patients with SLE are at increased risk not only of developing lung cancer (see **Table 1**)[3] but also of dying of it.[18] Although a potential trend toward overrepresentation of rarer types (including bronchoalveolar and carcinoid) was identified in 1 study, the overall histologic distribution was comparable with that of the general population.[58]

Pathophysiology

Smoking

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

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 multicenter international SLE dataset, there was a trend toward 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) (see **Table 2**).[57]

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, because they play a role in pathophysiologic pathways of both SLE and lung cancer (see **Table 2**).[62] Although it remains unclear how much of the increased risk of lung cancer in SLE these genetic factors may play, 1 study did suggest polygenic links between SLE and lung adenocarcinoma.[36]

Immunosuppressive therapy

There is no clear association between the risk of lung cancer and medication use in SLE. In our multicohort 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 (see **Table 2**).

CERVICAL AND VULVAR CANCERS
Epidemiology

It has constantly been shown that patients with SLE are at increased risk of developing the squamous intraepithelial lesions that precede cervical cancer development.[63–66] A recent meta-analysis reported a higher risk of high-grade squamous intraepithelial lesions in patients with SLE (OR, 8.66; 95% CI, 3.75–20.00) (see **Table 1**).[64] The magnitude of risk may vary from one country to another, because 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] because screening identifies early-stage lesions that can be treated before 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, which may explain why a systematic review found a higher risk of squamous intraepithelial lesions in SLE but was not able to conclude that patients with SLE have a higher risk of cervical cancer than the general population.[63] Patients with SLE have increased risk of other malignancies that are also strongly associated with human papilloma virus (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]

Pathophysiology

Human papilloma virus

It has been hypothesized that patients with SLE are more vulnerable to developing cervical dysplasia because 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[71–74] (see **Table 2**). A vaccine against HPV is available and, despite the fact that the immune response engendered might be lower in patients with SLE 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 5 years is maintained in most patients with SLE.[77] Accordingly, the US Centers for Disease Control and Prevention recommends the vaccine for any immunocompromised patients up to age 26 years.[78] The 2019 update of European League Against Rheumatism (EULAR) recommends that all patients with SLE 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, caused by 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 examinations could also bring to clinical attention the more rare vulvar and vaginal malignancies. However, 1 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 years.[80] EULAR guidelines recommend annual Pap tests in heavily immunosuppressed patients with SLE (eg, exposure to cyclophosphamide) but to follow local guidelines for low-risk patients.[83]

OTHER CANCERS WITH INCREASED RISK

Patients with SLE are at increased risk of other types of malignancy, including head and neck, thyroid, and liver (see **Table 1**). A recent study[84] reported an 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, because head and neck malignancies may be associated with HPV[85] and potentially, in some immunosuppressed individuals, EBV,[86–88] 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, thyroid cancer was consistently increased in patients with SLE.[5] One study found that thyroid antibodies (antithyroglobulin and anti–thyroid peroxidase) were more frequent in patients with SLE with concomitant thyroid cancer (80%) than in cancer-free patients with SLE (31%) (see **Table 2**).[89] A similar association between thyroid autoantibodies 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 6 g.[94] However, in SLE, intravenous cyclophosphamide is generally used, and there has long been a trend toward 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 lifelong 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 an SIR of 2.37 (95% CI, 1.37–3.38).[5] Although it has been proposed that decreased clearance of both hepatitis B virus (HBV) and hepatitis C virus (HCV) could contribute to this, their role in SLE remains unclear.

Many cohort studies have reported an increased risk of nonmelanoma skin cancer.[10,17,68] In a recent systematic review and meta-analysis, Song and colleagues[5] also found an increased risk of nonmelanoma skin cancer but a decreased risk of melanoma, with a pooled SIR of 0.72 (95% CI, 0.56–0.93). This finding is consistent with a previous meta-analysis that also found a lower risk of melanoma.[4] In immunosuppressed organ transplant patients, the risks of both melanoma and nonmelanoma skin cancers are increased.[96] The increased risk in nonmelanoma skin cancer has been related to immunosuppressive therapies in inflammatory bowel disease,[97,98] and 1 study suggested an association with cyclophosphamide in SLE.[99]

DECREASED CANCER RISK IN SYSTEMIC LUPUS ERYTHEMATOSUS
Epidemiology

Patients with SLE may have a decreased incidence rate of certain cancers compared with the general population.[15] One meta-analysis of studies primarily involving

patients with clinically confirmed SLE found a decreased risk of breast cancer,[13] although another meta-analysis (which included several administrative-database 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, in the general population, black and Asian women have lower breast cancer risk than white women; because black and Asian women may be more susceptible to SLE, some of the lower breast cancer risk in SLE could be driven by race/ethnicity (via genetic or other factors).

Several studies including a meta-analysis have suggested that ovarian and endometrial cancers may be decreased in SLE (see **Table 1**)[1,13] although 1 meta-analysis (which included large administrative-database 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]

Pathophysiology

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, patients with SLE tend to have fewer children than the general population, and COC use is 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. Patients with SLE are known to have their menarche at an older age and their menopause at a younger age compared with the general population.[13,102] The result may equal a total endogenous estrogen exposure in patients with SLE, possibly explaining why they seem 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, but breast cancers in SLE are more often estrogen receptor and progesterone receptor negative.[95] Although it is possible that the cancer type is influenced by the young age of patients with SLE, 1 study reported a tendency toward an increased prevalence of triple-negative breast cancers (ie, breast cancers that do not express estrogen, progesterone, and HER2 receptors) in patients with lupus.[103] These observations suggest a complex interplay of influential mechanisms, possibly linking the immune and endocrine systems to cancer risk in SLE.

Medications

There is also speculation regarding a possible protective role of certain medications used in treating patients with SLE, such as antimalarials (ie, hydroxychloroquine), in long-term cancer risk.[104] The proposed mechanism involves its role in promoting the autophagy (a form of self-induced cell death) of malignant cells.[105,106] Emerging evidence suggests that antimalarials may decrease risk of breast cancer in SLE (see **Table 2**).[99] In addition, aspirin and nonsteroidal antiinflammatory 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.

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 GWAS data did not show any differences in the frequency of 10 SLE-related SNPs in patients with breast cancer (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]

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 carcinomas 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 (see **Table 2**).[114]

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 (see **Table 2**). This specific hypothesis is still unproved.

SUMMARY

This article summarizes 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 nonmelanoma 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 patients with SLE.

CLINICS CARE POINTS

- At present, promotion of preventive measures such as smoking cessation and regular cancer screening programs (particularly for cervical dysplasia) are common-sense interventions for patients with SLE.

- Smoking is associated with increased lung cancer risk; Lung fibrosis may be associated with increased risk. No specific screening tests are recommended at this time.
- It has constantly been shown that patients with SLE are at increased risk of developing the squamous intraepithelial lesions that precede cervical cancer development. Patients with SLE have increased risk of other malignancies that are also strongly associated with human papilloma virus, including vulvar and anal carcinoma.
- Screening for cervical dysplasia is important for patients with SLE, and these examinations could also bring to clinical attention the more rare vulvar and vaginal malignancies. Recent Canadian SLE guidelines recommend Pap tests annually in patients from the time they begin sexual activity until the age of 69 years. EULAR guidelines recommend annual Pap tests in heavily immunosuppressed patients with SLE (eg, exposure to cyclophosphamide) but to follow local guidelines for low-risk patients
- Regarding bladder cancer, it is recommended that patients with SLE who have received cyclophosphamide should be monitored lifelong with annual urine cytology with prompt investigation of any abnormal cytology
- Skin cancer- antimalarials may decrease risk, cyclophosphamide may increase risk. No specific screening is recommended at this time.

DISCLOSURE

None.

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