Published in final edited form as:

Curr Opin Rheumatol. 2015 September ; 27(5): 454–460. doi:10.1097/BOR.0000000000000202.

Malignancies in Systemic Lupus Erythematosus – a 2015 Update

Gillian C Goobie, MD¹, Sasha Bernatsky, MD, PhD², Rosalind Ramsey-Goldman, MD, DrPH³, and Ann E. Clarke, MD, MSc⁴

¹Department of Medicine, Cumming School of Medicine, Health Sciences Centre, Foothills Campus, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada, T2N-4N1. gcgooobie@ucalgary.ca. Phone: 403-710-9242

²Departments of Medicine and of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada

³Department of Medicine, Division of Rheumatology, Feinberg School of Medicine, Northwestern University, Chicago, IL

⁴Department of Medicine, Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Abstract

Purpose of Review—Patients with systemic lupus erythematosus (SLE) have altered incidences of certain malignancies as compared to the general population. This review summarizes the recent literature on risk of malignancy in SLE and proposed mechanisms for these altered susceptibilities.

Recent Findings—Recent studies have confirmed previous data showing an increased risk of non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal, and thyroid malignancies, while demonstrating a decreased risk of breast and prostate cancer. Lymphomagenesis in SLE has been linked to increased activity of multiple inflammatory cytokines as well as possible viral etiologies. The decreased rates of hormone-sensitive cancers such as breast and prostate is speculated to be related to the presence of lupus autoantibodies and down-regulation of certain proteins in SLE. This knowledge has been utilized to investigate new therapeutic modalities for these malignancies.

Summary—Recent data confirm previously reported altered malignancy rates in SLE. Most striking in recent years are publications further elucidating mechanisms underlying cancer development in SLE, and subsequent investigations of potential therapeutics modulating these pathways.

Keywords

Malignancy; systemic lupus erythematosus; lymphoma; breast cancer

Introduction/Overall Risk of Malignancy

Multiple studies have assessed the overall rates of malignancy in SLE patients versus general population controls. Bernatsky *et al.*, in a large multinational study involving 16,409 patients primarily from the Systemic Lupus International Collaborating Clinics (SLICC), the Canadian Network for Improved Outcomes in Systemic Lupus, and other international collaborators, demonstrated a slightly increased overall risk of malignancy in patients with SLE as compared to controls (standardized incidence ratio (SIR) 1.14, 95% CI, 1.05, 1.23) [1]. This trend has been demonstrated in multiple other cohorts, including a Taiwanese cohort of 11,763 patients [2], a UK cohort of 595 patients [3], and a Danish cohort of 576 patients [4]. Most recently, a meta-analysis by Ni *et al.* corroborated this data by demonstrating a pooled increased incidence of malignancy in SLE (pooled SIR 1.16, 95% CI, 1.14, 1.21)[5].

Thomas *et al.* in a retrospective cohort study found that the standardized mortality ratio (SMR) from malignancy was quite low in SLE patients (SMR 0.40, 95% CI, 0.34, 0.48) [6]. Similarly, Yurkovich *et al.* in their meta-analysis reported that the SMR for malignancy was not increased in SLE patients (SMR 1.16, 95% CI, 0.57, 2.35) [7]. Thomas *et al.* suggest that this lower SMR may be explained by an increased SMR for cardiovascular and infectious diseases at a younger age in SLE patients. This may prevent a significant proportion of the SLE population from reaching an age where malignancy has a greater impact on mortality [6].

Hematologic Malignancies

Bernatsky *et al.* has demonstrated an increased risk for all hematologic malignancies in SLE (SIR 3.02, 95% CI, 2.48, 3.63), particularly for non-Hodgkin's lymphoma (NHL) (SIR 4.39, 95% CI, 3.46, 5.49)[1,8]. The most common form of non-lymphoma malignancy in this international cohort was of the myeloid type (specifically myelodysplastic syndromes and acute myeloid leukemias)[8]. A recent study by Fallah *et al.* linking 12,207 SLE patients identified from the Swedish Hospital Discharge Registry with the Swedish Cancer Registry found an increased risk of NHL (SIR 4.4, 95% CI, 3.6, 5.3)[9].

A meta-analysis by Apor *et al.* demonstrated a heightened risk of all forms of hematologic malignancy in SLE (pooled SIR 2.9, 95% CI, 2.0, 4.4), most notably for NHL (pooled SIR 5.7, 95% CI, 3.6, 9.1)[10]. They demonstrated that these increased incidences were seen across a wide variation of ages, sexes, and geographical populations. Apor *et al.* also demonstrated an increased risk of Hodgkin's lymphoma (pooled SIR 3.1, 95% CI, 2.1, 4.4), leukemia (pooled SIR 2.3, 95% CI, 1.9, 2.7), and myeloma (pooled SIR 1.5, 95% CI, 1.0, 2.0)[10].

It has been postulated that increased disease activity in SLE may mediate this increased risk of hematologic malignancies. However, a case-cohort study nested within Bernatsky *et al.*'s international cohort compared SLE patients with and without lymphoma and did not demonstrate increased SLE activity in cases of lymphoma (hazard ratio (HR) 0.68, 95% CI, 0.36, 1.29)[11]. The case-cohort study did demonstrate a trend towards an increased risk of lymphoma in SLE patients exposed to cyclophosphamide (HR 2.80, 95% CI, 0.87, 8.9) and

glucocorticoids (HR 2.57, 95% CI, 0.94, 7.04) [11]. The effects of cyclophosphamide may be direct, through immunosuppression and cytotoxicity, or indirect, by promoting emergence of oncogenic viruses like Epstein-Barr Virus (EBV) and Human Papilloma Virus (HPV).

Multiple studies have suggested that EBV may play a role in the pathogenesis of SLE and may mediate an increased risk of malignancy. Epstein-Barr viral load, mRNA expression and EBV-directed antibodies have all been shown to be elevated in SLE [12]. Rasmussen *et al.* recently demonstrated that IgM, IgG, and IgA levels against EBV early antigen/diffuse (EA/D) were significantly higher in SLE patients, which they suggest may be related to aberrant control of EBV reactivation in these patients [13]. Hanlon *et al.*, in a recent meta-analysis including 25 case-control studies, demonstrated a higher prevalence of anti-viral capsid antigen (anti-VCA) IgG (OR 2.08, 95% CI, 1.15, 3.76) in SLE patients [14]. Anti-VCA IgG is a marker of prior EBV infection that develops a few months after exposure to EBV and lasts for life [14]. Epstein-Barr Virus has also been shown to play an important role in the pathogenesis of various hematologic malignancies, including Burkitt's lymphoma, HL, and diffuse large B cell lymphoma (DLBCL) in immunosuppressed patients. Based on this understanding, recent successful adjuvant therapies for HL and NHL have been developed, which use cytotoxic T-cells targeted against latent membrane proteins of EBV to induce remission [15]. Capone *et al.* recently demonstrated an Epstein-Barr nuclear antigen (EBNA1) peptide sequence that is intrinsic to the EBV viral genome, but which is not present in the human host [16]. They suggest that creating a vaccine based on this peptide could potentially decrease the risk of autoimmune diseases such as SLE as well as EBV-associated malignancies [16].

A review by Yao *et al* suggests there may be a relationship between increased interleukin-6 (IL-6) activity in SLE and the increased risk of hematologic malignancies [17]. Interleukin-6 is a cytokine released from monocytes and macrophages during inflammatory states that leads to increased growth and differentiation with decreased apoptosis in neutrophils, monocytes, and T- and B-cells [18]. Interleukin-6 receptors have been demonstrated on mantle cell lymphoma cells, some of which also secrete IL-6 [19]. In vitro inhibition of IL-6 in mantle cell lymphomas has led to inhibition of growth and spontaneous apoptosis of malignant cells as well as increased responsiveness to chemotherapy [19]. A recent study by Maier-Moore *et al.* has shown that IL-6 activity is associated with many of the disease manifestations seen in SLE [20]. Interleukin-6 deficient mice had less nephritis, lung disease, and autoantibody production, and notably decreased numbers of germinal B-cells and IgG-producing plasma cells in the spleen [20]. Inhibition of IL-6 via tocilizumab, a monoclonal antibody against the IL-6 receptor, in SLE patients resulted in decreased lymphocyte activation and normalization of B and T-cell homeostasis [21]. Thus, it could be speculated that increased IL-6 activity may underlie some of the increased risk of hematologic malignancies in SLE.

B-cell activating factor (BAFF, also known as B-lymphocyte stimulator - BLyS) and a proliferation-inducing ligand (APRIL) are two cytokines within the TNF family that are essential to B-cell survival and proliferation. Overexpression of BAFF has been demonstrated in SLE patients [22] and BAFF mRNA levels have been shown to correlate

with global disease activity in SLE patients as well as proteinuria and elevated anti-dsDNA and ESR [23]. The APRIL and BAFF axis may also play a role in the increased risk of hematologic malignancies in SLE. These cytokines act on the BAFF-Receptor 3 (BR3), transmembrane activator and cyclophilin ligand interactor (TACI), and B-Cell Maturation Antigen (BCMA). Belimumab, a monoclonal antibody that inhibits circulating BAFF, was approved relatively recently for the treatment of SLE after Phase III trials demonstrated improvements primarily in the cutaneous and musculoskeletal manifestations of SLE [24,25]. Research is also currently underway evaluating the utility of novel therapeutics targeting the BAFF/APRIL pathways and their receptors in treating hematologic malignancies. A fusion protein Bax345/BAFF has been shown by Lyu *et al.* to induce apoptosis when delivered to malignant B-cells [26].

Overexpression of APRIL has been observed in SLE patients that have developed DLBCLs [27]. Hoffmann *et al.* have recently demonstrated that soluble TACI (sTACI), a soluble receptor for APRIL and BAFF, is elevated in patients with SLE [28]. Lascano *et al.* demonstrated increased malignant B-cell survival in chronic lymphocytic leukemia when APRIL binds to sTACI [29]. As such, the fusion protein against TACI and BCMA receptors, atacicept, is currently being studied for the treatment of both SLE and various hematologic malignancies [30,31]. Atacicept has also been shown to prevent B-cell expansion in mouse models of chronic lymphocytic leukemia [32], and is currently being evaluated in phase I trials for the treatment of chronic lymphocytic leukemia, NHL, and multiple myeloma [30].

Lung Malignancies

Bernatsky *et al.* reported a slightly elevated risk of lung malignancy in SLE (SIR 1.30, 95% CI, 1.04, 1.60)[1]. These findings were confirmed by the meta-analysis of Ni *et al.* (pooled SIR for lung cancer 1.68, 95% CI, 1.33, 2.13)[5]. Hemminki *et al.* in a study involving 7624 SLE patients identified from the Swedish Hospital Discharge Registry demonstrated an even higher incidence of all forms of lung cancer (SIR 2.47, 95% CI, 1.97, 3.05)[33], and they delineated the rates of specific histologic types of lung malignancies in SLE patients. The risk was most significantly increased for small cell lung cancer (SIR 3.38, 95% CI, 1.89, 5.59), followed by squamous cell carcinoma (SIR 2.97, 95% CI, 1.86, 4.50), large cell carcinoma (SIR 2.55, 95% CI, 1.53, 3.99), and adenocarcinoma (SIR 2.12, 95% CI, 1.34, 3.18) [33]. The SMR was also increased for small cell lung cancer in SLE patients (SMR 2.69, 95% CI, 2.11, 3.38), suggesting increased mortality in SLE patients with this form of lung cancer [33].

Ni *et al.* suggest that there may be a link between the increased rate of lung cancer and the increased rates of smoking in SLE patients as well as increased disease activity associated with smoking in SLE [5]. Smoking has also been associated with the development of SLE [34].

There may also be increased rates of lung cancer in patients with pulmonary manifestations of SLE. Hemminki *et al.* assessed multiple forms of autoimmune disease and noted that only diseases with lung manifestations were associated with an increased risk of lung malignancy [33]. They postulated that this increased incidence is related to local inflammation and

associated oxidative lesions [33]. However, there have been no studies that clearly associate the development of lung malignancy in SLE patients with prior pulmonary involvement of the disease.

As described above, IL-6 activity has been implicated in the pathogenesis and activity of SLE [17]. IL-6 has been particularly associated with lung manifestations in SLE [20]. A recent study by Kim *et al.* demonstrated that the anti-IL-6R-targeted antibody, tocilizumab, was effective in inducing apoptosis in non-small cell lung cancer cell lines [35]. Preliminary studies indicate tocilizumab may also be efficacious in treating SLE [36]. Based on this data, it could be speculated that increased IL-6 activity could represent a common mechanism between SLE activity and lung cancer development.

Hepatobiliary Malignancies

Bernatsky *et al.* demonstrated an increased risk of hepatobiliary malignancies in the SLICC international cohort (SIR 1.30, 95% CI, 1.40, 1.60)[1], which was supported by Ni *et al.*'s meta-analysis (pooled SIR 2.44, 95% CI, 1.46, 4.05)[5]. A recent study involving 6350 patients with SLE identified through the Swedish Hospital Discharge Registry also demonstrated an increased incidence of hepatobiliary cancers (SIR 2.70, 95% CI, 1.83, 3.83) and increased mortality associated with these cancers (HR 1.54, 95% CI, 1.07, 2.22) [37]. More specifically, the incidence of primary liver cancer was increased (SIR 4.17, 95% CI, 2.42, 6.69), but the rates of gallbladder and extrahepatic bile duct cancer were not [37]. However, the mortality from gallbladder and extrahepatic bile duct cancer was increased in this study (HR 2.08, 95% CI, 1.03, 4.21 and HR 9.24, 95% CI, 2.31, 36.94, respectively) [37].

It has been suggested that SLE patients may have increased rates of viral hepatitis or decreased viral clearance that may account for the increased rate of liver cancer [4]. Ahmed *et al.* substantiated this hypothesis by demonstrating an increased prevalence of Hepatitis C Virus in SLE patients [38].

Breast Cancer

It has been demonstrated that the rates of hormone-associated malignancies may be decreased in SLE patients [1,3,4]. Specifically, Bernatsky *et al.* found the rate of breast cancer in the SLE population to be substantially decreased (SIR 0.76, 95% CI, 0.69, 0.85) [1,39].

Recent data has suggested that SLE autoantibodies may contribute to the decreased risk of certain hormone-sensitive malignancies. A cell-penetrating, lupus-related, anti-DNA antibody was shown to inhibit DNA repair, and was thus toxic to cancer cells with intrinsic defects in DNA repair [40]. Triple-negative (i.e. breast cancers that don't express estrogen, progesterone, or human epidermal growth factor 2 (HER2) receptors) and BRCA2-mutated breast cancers harbour defects in DNA repair. It is possible that suppression of the emergence of triple-negative and BRCA2-mutated breast cancers by lupus anti-DNA antibodies may be partially responsible 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, which is predominantly triple negative, in Bernatsky *et al.*'s cohort [41]. In addition, Noble *et al.* demonstrated that a nucleolytic lupus autoantibody, anti-5C6, triggered senescence in BRCA2-mutated colon cancer cells [42]. Anti-5C6 may also help prevent DNA repair mechanisms in breast, ovarian, and prostate cancers associated with BRCA2 mutations [42].

Decreased expression of anti-apoptotic mediators, such as heat shock protein 27 (HSP-27), in patients with SLE may contribute to the decreased incidence of breast cancer in SLE. Recently, Rai *et al.* have demonstrated SLE patients with ENA positivity express lower levels of HSP-27 in their serum [43]. Grzegorzolka *et al.* have shown that 92% of cases of invasive ductal carcinoma express HSP-27 [44]. Further, they showed that increased HSP-27 levels correlated with higher breast cancer grade and HER-2 positivity [44]. Several studies have also demonstrated that suppression of HSP-27 in breast cancer causes dormancy [45] and increases susceptibility to treatment [46]. Thus, it could be speculated that if patients with SLE have decreased levels of HSP-27, they may have less propensity to develop aggressive invasive ductal carcinomas.

Vaginal, Vulvar and Cervical Cancers

Bernatsky *et al.* reported an increased risk of vulvar malignancies (SIR 3.78, 95% CI, 2.41, 4.31)[1]. Chen *et al.* and Dreyer *et al.* also showed significantly increased incidences of vaginal/vulvar cancers (SIR 4.76, 95% CI, 4.24, 5.33 and SIR 9.10, 95% CI, 2.30, 36.50) in their Taiwanese and Danish cohorts, respectively [2,4].

There have been conflicting reports regarding the incidence of cervical cancer in patients with SLE. This may be related to the relatively low rate of cervical cancers in general, as a result of improved cervical cancer screening. Nonetheless, Dreyer *et al.* demonstrated that the rate of cervical dysplasia/ carcinoma was significantly increased (SIR 1.8, 95% CI, 1.2, 2.7)[4]. This was supported by a recent meta-analysis by Zard *et al.*, which demonstrated a substantially increased risk of high-grade squamous intra-epithelial lesions in SLE (pooled OR 8.66, 95% CI, 3.75, 20.00)[47].

Dreyer *et al.* suggested that the increased risk of vaginal/vulvar and cervical malignancies may be related to impaired HPV clearance in SLE [4]. Zard *et al.* also supported increased HPV activity as a potential etiology for the increased risk of cervical dysplasia in SLE [47]. It has been demonstrated in a Brazilian cross-sectional analysis that the rates of HPV infection are increased in patients with SLE compared to controls (OR 7.2, 95% CI, 2.9, 17.8)[48]. This study did not show a correlation between higher doses of immunosuppressive treatment and HPV prevalence [48].

Prostate Cancer

There have been varied results regarding the rates of prostate cancer in SLE patients. Ni *et al.*'s meta-analysis, which includes data from Bernatsky *et al.*'s international cohort, has demonstrated a decreased incidence of prostate cancer (pooled) [5]. Huang *et al.*'s recent systematic review of urologic malignancies in SLE also supported this conclusion [49]. In contrast, a study by Liu *et al.* of 7613 SLE patients identified through the Swedish Hospital

Discharge Registry demonstrated that the risk of prostate cancer was similar to that of the general population (SIR 1.03, 95% CI, 0.73, 1.41)[50].

Heat shock protein-27 has been implicated in prostate cancer progression and metastases [51] and HSP-27 levels have also been shown to be an independent predictor of poor prognosis in prostate cancer [52]. Inhibition of HSP-27 in castrate-resistant prostate cancer has been found to increase apoptosis, inhibit growth of the tumors, and increase survival in mouse models [53]. As noted above, HSP-27 has been demonstrated to be decreased in ENA-positive SLE patients [43]. As such, it could be speculated that decreased levels of HSP-27 in SLE patients may contribute to a decreased incidence of prostate cancer.

Bladder Cancer

Liu *et al* demonstrated through analysis of the Swedish Hospital Discharge Registry that the rate of bladder cancer was significantly increased in the 7,624 SLE patients studied (SIR 2.28, 95% CI, 1.62, 3.12). The relative risk of death from bladder cancer was also increased in SLE as compared to controls (HR 2.13, 95% CI, 1.46, 3.11) [50]. Dreyer *et al.* corroborated increased bladder cancer rates (SIR 3.6, 95% CI, 1.4, 9.7) and found that all SLE patients with bladder cancer in their cohort had received cyclophosphamide [4]. However, Ni *et al.*'s meta-analysis demonstrated that the rate of bladder cancer was not significantly increased in their pooled analysis in SLE patients compared to controls (pooled SIR 1.78, 95% CI 0.85, 3.72)[5].

Thyroid Malignancies

A recent meta-analysis by Zhang *et al.* demonstrated an increased incidence of thyroid cancer based on seven international cohort studies (pooled SIR 2.22, 95% CI, 2.11, 2.34) [54]. Antonelli *et al.* found that 80% of SLE patients with papillary thyroid cancer had concomitant autoimmune thyroid disease, whereas only 30% of SLE patients without thyroid malignancy had thyroid autoimmunity [55].

Implications for Clinical Practice

Tessier-Cloutier *et al.* recently published a systematic review on cancer screening specifically for patients with SLE and concluded that there are no studies directly comparing screening in SLE and the general population [56]. However, they did report that all studies concurred that general population screening measures, especially for cervical cancer, are necessary in SLE patients [56]. They also suggest that there may be added utility for urine cytology screening in patients exposed to cyclophosphamide as well as lung cancer screening through a directed history and physical exam in SLE patients who were heavy smokers [56].

Zard *et al.* support ensuring regular cervical cancer screening in patients with SLE [47]. Despite demonstrating an increased prevalence of high-grade squamous intraepithelial lesions in SLE patients, they do not recommend increased frequency of pap smears or HPV vaccination in newly diagnosed patients with SLE [47]. They reason that most patients will have been infected with HPV at the time of SLE diagnosis, and vaccination or increased

frequency of screening will likely not change the already low cervical cancer risk. However, both males and females who are diagnosed with SLE in the pre- and young adolescent period are unlikely to have already been infected with HPV and should receive vaccinations against this virus in accordance with general population guidelines [57–58].

Future clinical practice may be heavily impacted by new therapeutics that target common pathways involved in SLE and malignancy. The development of novel vaccines against EBV may confer a future decreased risk of both SLE and malignancies linked to this oncogenic virus [16]. Anti-IL-6 monoclonal antibodies, such as tocilizumab, may decrease the downstream inflammatory cascade and dysregulation present in both SLE and malignancy [17–21,35,36]. Drugs that target BAFF/APRIL and their downstream targets, such as belimumab and atacicept, have already shown efficacy in the management of SLE, and are currently being assessed in hematologic malignancies [22–31]. In addition, anti-DNA targets such as anti-dsDNA and anti-5C6 are currently being assessed as possible mechanisms underlying the decreased risk of breast and prostate cancer in SLE [40,42]. Therefore, it is anticipated that therapies targeting pathways such as these may revolutionize the approach to both autoimmune and malignant diseases in the future.

Conclusion

It has been well established that there are altered rates of certain malignancies in SLE. Recent studies have not only confirmed increased rates of NHL, and lung, hepatobiliary, vulvar/vaginal, and thyroid malignancies, as well as cervical dysplasia, but they have also postulated mechanisms to explain this increased incidence. Non-Hodgkin's lymphoma may be intrinsically related to altered BAFF and APRIL signalling, and IL-6 may also play a role in increased rates of NHL and lung malignancies in SLE. Increased incidence of certain malignancies may also be related to increased SLE disease activity within a specific organ, altered viral clearance, and/or specific medication use.

Recent studies have also documented decreased rates of breast and prostate cancer in SLE and speculated on potential underlying mechanisms. Of note, cell-penetrating anti-DNA autoantibodies may play an important role in decreasing the risk of breast cancer in SLE patients. Cytokine pathways such as those mediated by HSP-27 may also play an important role in decreasing the risk of breast and prostate cancer in SLE.

Despite an apparent decreased risk of breast and prostate cancer, patients with SLE should adhere to general population cancer screening recommendations and they should be particularly vigilant for cervical dysplasia.

Acknowledgements

None

Financial Support:

1. Dr. Clarke is The Arthritis Society Chair in Rheumatic Diseases at the University of Calgary.

Sponsorships: None

References

1. Bernatsky S, Ramsay-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun.* 2013; 42:130–135. [PubMed: 23410586]
2. Chen YJ, Chang YT, Wang CB, et al. Malignancy in Systemic Lupus Erythematosus: a nation-wide cohort study in Taiwan. *Am J of Medicine.* 2010; 123(12):1150–1156.
3. Dey D, Kenu E, Isenberg DA. Cancer complicating systemic lupus erythematosus – a dichotomy emerging from a nested case-control study. *Lupus.* 2013; 22:919–927. [PubMed: 23857987]
4. Dreyer L, Faurschou M, Mogensen M, Jacobsen S. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term follow-up study in a Danish cohort. *Arthritis Rheum.* 2011; 63(10):3032–3037. [PubMed: 21953088]
5. Ni J, Qui LJ, Hu LF, et al. Lung, liver, prostate, bladder malignancies risk in systemic lupus erythematosus: a meta-analysis. *Lupus.* 2014; 23:284–92. [PubMed: 24429300] *A meta-analysis including seven cohort studies published between 1997–2013 (total number of patients 63,585). Demonstrated an increased risk of cancer overall as well as lung and liver cancer, but a decreased risk of prostate cancer.
6. Thomas G, Mancini J, Jourde-Ciche N, et al. Mortality Associated With Systemic Lupus Erythematosus in France Assessed by Multiple-Cause-of-Death Analysis. *Arthritis Rheum.* 2014; 66(9):2503–2511.
7. Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and Cause-Specific Mortality in Patients With Systemic Lupus Erythematosus: A Meta-Analysis of Observational Studies. *Arthritis Care & Res.* 2014; 66(4):608–616.
8. Lu M, Bernatsky S, Ramsey-Goldman R, et al. Non-lymphoma hematologic malignancies in systemic lupus erythematosus. *Oncology.* 2013; 85(4):235–240. [PubMed: 24107608]
9. Fallah M, Liu X, Ji J, et al. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. *Annals of Oncol.* 2014; 25:2025–2030. **Using the Swedish Cancer Registry, this study assessed close to 1 million Swedish patients diagnosed with autoimmune diseases and found that non-Hodgkin's lymphoma was elevated in a large number of autoimmune diseases, including a greatly increased in risk SLE.
10. Apor E, O'Brien J, Stephen M, Castillo JJ. Systemic lupus erythematosus is associated with increased incidence of hematologic malignancies: A meta-analysis of prospective cohort studies. *Leukemia Research.* 2014; 38:1067–1071. [PubMed: 25052307] *A large meta-analysis evaluating cohorts published between 1992–2013 (including approximately 68,000 SLE patients) demonstrating increased incidences of all hematologic malignancies.
11. Bernatsky S, Ramsey-Goldman R, Joseph L, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. *Ann Rheum Dis.* 2014; 73(1):138–142. [PubMed: 23303389] **A case-cohort study nested within an international cohort that compared disease activity and medication exposure between SLE cases with and without lymphoma. Disease activity did not differ and higher cumulative steroid doses and cyclophosphamide exposure conferred an increased risk of lymphoma.
12. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. *Clin Dev Immunol.* 2013; 2013:535738. [PubMed: 24062777]
13. Rasmussen NS, Draborg AH, Nielsen CT, et al. Antibodies to early EBV, CMV, and HHV6 antigens in systemic lupus patients. *Scand J Rheumatol.* 2014; 44:143–149. [PubMed: 25562120]
14. Hanlon P, Avenell A, Aucott L, Vickers MA. Systematic review and meta-analysis of the sero-epidemiological association between Epstein-Barr virus and systemic lupus erythematosus. *Arthritis Res & Ther.* 2014; 16:R3. [PubMed: 24387619]
15. Bollard CM, Gottschalk S, Torrano S, et al. Sustained Complete Responses in Patients With Lymphoma Receiving Autologous Cytotoxic T Lymphocytes Targeting Epstein-Barr Virus Latent Membrane Proteins. *J Clin Onc.* 2014; 32(8):798–808.
16. Capone G, Fasano C, Lucchese G, et al. EBV-Associated Cancer and Autoimmunity: Searching for Therapies. *Vaccines.* 2015; 3:74–89. [PubMed: 26344947] **First study to find an Epstein-Barr nuclear antigen (EBNA) peptide sequence that is not found in the human genome and it may serve

as a sequence for future vaccine development. They suggest this type of vaccine may help to decrease EBV-associated malignancy and autoimmunity, including SLE.

17. Yao X, Huang J, Zhong H, et al. Targeting interleukin-6 in inflammatory autoimmune diseases and cancers. *Pharmacol & Therap.* 2014; 141:125–139. [PubMed: 24076269]
18. Heinrich PC, Behrmann I, Haan S, et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J.* 2003; 374:1–20. [PubMed: 12773095]
19. Zhang L, Yang J, Qian J, et al. Role of the microenvironment in mantle cell lymphoma: IL-6 is an important survival factor for the tumor cells. *Blood.* 2012; 120(18):3783–3792. [PubMed: 22968454]
20. Miaer-Moore JS, Horton CG, Mathews SA, et al. Interleukin-6 Deficiency Corrects Nephritis, Lymphocyte Abnormalities, and Secondary Sjögren's Syndrome Features in Lupus-Prone *Sle1.Yaa* Mice. *Arthritis Rheum.* 2014; 66(9):2521–2531. **This study implicated IL-6 in the pathogenesis of SLE, B-cell proliferation and autoantibody production. Inhibition of IL-6 resulted in decreased autoantibodies, decreased proliferation and differentiation of T- & B-cells, and decreased lymphocytic infiltration of the kidneys, lungs and salivary glands.
21. Shirota Y, Yarboro C, Fischer R, et al. Impact of anti-interleukin-6 receptor blockade on circulating T and B cell subsets in patients with systemic lupus erythematosus. *Ann Rheum Dis.* 2013; 72:118–128. [PubMed: 22858586]
22. Vincent FB, Morand EF, Schneider P, Mackay F. The BAFF/APRIL system in SLE pathogenesis. *Nat Rev Rheumatol.* 2014; 10:365–373. [PubMed: 24614588]
23. Zollars E, Fang H, Bienkowska J, et al. Only BAFF mRNA, not BAFF protein level in blood, is associated with SLE activity over one year. *Ann Rheum Dis.* 2015; 74:A74.
24. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2011; 377(9767):721–731. [PubMed: 21296403]
25. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis & Rheum.* 2011; 63(12):3918–3930. [PubMed: 22127708]
26. Lyu MA, Pham LV, Sung B, et al. The therapeutic effects of rGel/BLyS fusion toxin in in vitro and in vivo models of mantle cell lymphoma. *Biochem Pharmacol.* 2012; 84:451–458. **First study to show that inhibition of BAFF pathways may present a target for the treatment of aggressive forms of non-Hodgkin's lymphoma, such as mantle cell lymphoma. Targeted mantle cell lymphoma in mice with an rGel/BLyS (i.e. rGel/BAFF) fusion protein and found increased survival.
27. Löfström 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; 38(9):1891–1897. [PubMed: 21724695]
28. Hoffman FS, Kuhn PH, Laurent SA, et al. The Immunoregulator Soluble TACI Is Released by ADAM10 and Reflects B Cell Activation in Autoimmunity. *J Immunol.* 2015; 194:542–552. [PubMed: 25505277] *Found that sTACI levels were increased in sera of SLE patients and were associated with increased disease activity.
29. Lascano V, Guadagnoli M, Schot JG, et al. Chronic lymphocytic leukemia disease progression is accelerated by APRIL-TACI interaction in the TCL1 transgenic mouse model. *Blood.* 2013; 122:3960–3963. [PubMed: 24100449]
30. Kufer P, Raum T, Hoffmann P, et al. BINDING MOLECULES FOR BCMA AND CD3. United States Amegen Research (Munich). 2014 20140348837<<http://www.freepatentsonline.com/y2014/0348837.html>>.
31. Isenberg D, Gordon C, Licu D, et al. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE: 52-week data (APRIL-SLE randomised trial). *Ann Rheum Dis.* 2014;1–10. [PubMed: 24092418]
32. Guadagnoli M, Kimberley FC, Phan U, et al. Development and characterization of APRIL antagonistic monoclonal antibodies for treatment of B-cell lymphomas. *Blood.* 2011; 117(25)
33. Hemminki K, Liu X, Ji J, et al. Effect of autoimmune diseases on risk and survival in histology-specific lung cancer. *Eur Resp J.* 2012; 40:1489–1495.

34. Ekblom-Kullberg S, Kautiainen H, Alha P, et al. Smoking and the risk of systemic lupus erythematosus. *Clin Rheumatol*. 2013; 32(8):1219–1222. [PubMed: 23515599]
35. Kim NH, Kim SK, Kim DS, et al. Anti-proliferative action of IL-6R-targeted antibody tocilizumab for non-small cell lung cancer cells. *Oncol Letters*. 2015; 9:2283–2288.
36. Rossi JF, Lu Zy, Jourdan M, Klein B. Interleukin-6 as a Therapeutic Target. *Clin Cancer Res*. 2015; 21(6):1248–1257. [PubMed: 25589616]
37. Castro FA, Liu X, Forsti A, et al. Increased Risk of Hepatobiliary Cancers After Hospitalization for Autoimmune Disease. *Clinical Gastroenterology and Hepatology*. 2014; 12:1038–1045. [PubMed: 24246767] **Large cohort study based on Swedish cancer registries that demonstrated a link between primary liver cancer and 14 different autoimmune diseases, including SLE. Also looked at the rates of gallbladder and extrahepatic bile duct cancers in autoimmune diseases, but did not find increased incidences in SLE.
38. Ahmed MM, Berney SM, Wolf RE, et al. Prevalence of active hepatitis C virus infection in patients with systemic lupus erythematosus. *Am J Med Sci*. 2006; 331:252–225. [PubMed: 16702794]
39. Bernatsky S, Ramsey-Goldman R, Foulkes W, et al. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: A meta-analysis. *British J Cancer*. 2011; 104:1478–1481.
40. Hansen JE, Chan G, Liu Y, et al. Targeting cancer with a lupus autoantibody. *Sci Transl Med*. 2012; 4(157):142–157.
41. Tessier-Cloutier B, Clarke AE, Ramsey-Goldman R, et al. Breast cancer in systemic lupus erythematosus. *Oncology*. 2013; 85(2):117–121. [PubMed: 23887245]
42. Noble PW, Young MR, Bernatsky S, et al. A nucleolytic lupus autoantibody is toxic to BRCA2-deficient cancer cells. *Sci Rep*. 2014; 5(5958):1–4. **Second major study (first is reference 40) to demonstrate that an anti-dsDNA antibody (anti-5C6) results in decreased survival and increased susceptibility to treatment of BRCA2-deficient cancer cells.
43. Rai R, Chauhan SK, Singh VV, et al. Heat shock protein 27 and its regulatory molecules express differentially in SLE patients with distinct autoantibody profiles. *Immunol Letters*. 2015; 164:25–32. **First study to demonstrate significantly decreased levels of HSP-27 in SLE patients, and found this specifically in patients who were ENA positive. HSP-27 is characterized by its anti-apoptotic properties, and thus decreased expression of this protein may result in increased apoptosis of malignant cell lines.
44. Grzegorzolka J, Kurnol K, Piotrow P, et al. Hsp27 expression in invasive ductal breast carcinoma. *Folia Histo Cytobio*. 2012; 50(4):527–533.
45. Straume O, Shimamura T, Lampa MJG, et al. Suppression of heat shock protein 27 induces long-term dormancy in human breast cancer. *Proc Natl Acad Sci USA*. 2012; 109(22):8699–8704. [PubMed: 22589302]
46. Díaz-Chávez J, Fonseca-Sánchez MA, Arechaga-Ocampo E, et al. Proteomic Profiling Reveals That Resveratrol Inhibits HSP27 Expression and Sensitizes Breast Cancer Cells to Doxorubicin Therapy. *PLoS ONE*. 2013; 8(5):e64378. [PubMed: 23724044]
47. Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous cell intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. *Autoimmunity Reviews*. 2014; 13:730–735. [PubMed: 24657969] *Meta-analysis of seven studies published between 2001–2012 looking at the rates of high grade cervical squamous epithelial lesions in 416 SLE patients that demonstrated increased risk of these lesions. They suggest this may be related to altered HPV clearance in SLE.
48. Lyrio LDC, Grassi MFR, Santana IU, et al. Prevalence of cervical human papillomavirus infection in women with systemic lupus erythematosus. *Rheumatol Int*. 2013; 33:335–340. [PubMed: 22451033]
49. Huang HB, Jiang SC, Han J, et al. A systematic review of the epidemiological literature on the risk of urological cancers in systemic lupus erythematosus. *J Cancer Res Clin Oncol*. 2014; 140:1067–1073. [PubMed: 24525705] *Systematic review of 12 papers, including a total of 68,336 SLE patients that assesses the risk of prostate, bladder and kidney cancer. It reported decreased rates of prostate cancer and a trend towards increased bladder cancer.

50. Liu X, Ji J, Forsti A, et al. Autoimmune diseases and subsequent urological cancer. *J of Urol*. 2013; 189:2262–2268. [PubMed: 23228387]
51. Ischia J, Saad F, Gleave M. The promise of heat shock protein inhibitors in the treatment of castration resistant prostate cancer. *Curr Opin Urol*. 2013; 23(3):194–200. [PubMed: 23385973]
52. Foster CS, Dodson AR, Ambrosine L, et al. Hsp-27 expression at diagnosis predicts poor clinical outcome in prostate cancer independent of ETS-gene rearrangement. *British J Cancer*. 2009; 101(7):1137–1144.
53. Lamoureux F, Thomas C, Yin MJ, et al. Suppression of Heat Shock Protein 27 Using OGX-427 Induces Endoplasmic Reticulum Stress and Potentiates Heat Shock Protein 90 Inhibitors to Delay Castrate-resistant Prostate Cancer. *Eur Urol*. 2014; 66:145–155. [PubMed: 24411988]
54. Zhang M, Li XM, Wang GS, et al. Thyroid cancer in systemic lupus erythematosus: a meta analysis. *Int J Clin Exp Pathol*. 2014; 7(9):6270–6273. [PubMed: 25337279] *Meta-analysis of seven cohorts published between 2003–2013 that demonstrated an increased risk of thyroid cancer in 66,093 SLE patients. This study suggested there may be a link between autoimmune thyroid disease and thyroid cancer in SLE patients.
55. Antonelli A, Mosca M, Fallahi P, et al. Thyroid cancer in systemic lupus erythematosus: a case-control study. *J Clin Endocrinol Metab*. 2010; 95(1):314–318. [PubMed: 19906791]
56. Tessier-Cloutier B, Clarke AE, Pineau CA, et al. What investigations are needed to optimally monitor for malignancies in SLE? *Lupus*. 2015; 0:1–7. **Systematic review to identify original research on cancer screening recommendations specifically for patients with SLE. No such recommendations were found and they recommended adherence to general population recommendations.
57. Dawar M, Harris T, McNeil S. National Advisory Committee on Immunization (NACI) Update on Human Papillomavirus (HPV) Vaccines. *Canada Communicable Disease Report*. 2012; 38:ACS-1.
58. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case–control study. *Ann Rheum Dis*. 2013; 72:659–664. [PubMed: 22589375]

Key Points

- SLE is associated with an overall increased risk of malignancy, particularly non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal, and thyroid, and a decreased risk of breast and prostate cancer.
- The increased risk of non-Hodgkin's lymphoma is likely related to multiple mechanisms, including increased viral reactivation, and up-regulation of cytokines such as BAFF/APRIL and IL-6.
- The decreased risk of breast and prostate cancer may be related to anti-dsDNA antibodies that increase the susceptibility of malignant cells to apoptosis and chemotherapeutic agents.
- There are no guidelines on cancer screening specifically for SLE patients, and these patients should adhere to general population screening recommendations, particularly for cervical cancer.