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A Review on SLE and Malignancy

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by autoantibody production, complement activation, and immune complex deposition. It predominantly affects young and middle-aged women. While improvements in the diagnosis and treatment of SLE have altered prognosis, morbidity and mortality rates remain higher than the general population. In addition to renal injury, cardiovascular disease, and infection, malignancy is known to be a significant cause of death in this population. There is increasing evidence to suggest that patients with SLE have a slightly higher overall risk of malignancy. The risk of malignancy in SLE is of considerable interest because the immune and genetic pathways underlying the pathogenesis of SLE as well as the immunosuppressant drugs (ISDs) used in its management may mediate this altered risk. Our current understanding of these and other risk factors and the implications for treating SLE and screening for malignancy is still evolving.

This review summarizes the association between SLE and malignancy. The first section will discuss the risk of overall and site-specific malignancies in both adult and pediatric-onset SLE. Next, we evaluate the risk factors and possible mechanisms underlying the link between malignancy and SLE, including the use of ISDs, presence of certain SLE-related autoantibodies,

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chronic immune dysregulation, environmental factors, and shared genetic susceptibility. Finally, we review guidelines regarding cancer screening and vaccination for human papilloma virus (HPV).

Keywords

SLE; malignancy; autoimmune disease; adult; pediatric

A. Malignancy risk in adult SLE

Overall Risk of Malignancy

Over the last four decades, there have been numerous studies examining the risk of malignancy in adult patients with SLE compared to a matched general population. These studies are based either on observational clinical cohorts [1] or cohorts identified through administrative data such as hospital discharge [2] and national health insurance databases [3]; they are summarized in Table 1 and additional details are provided in Supplementary Table 1. In most of these studies, cancer was ascertained either by chart review or by linking the SLE cohorts to regional tumor registries. The most robust studies are those where the cancer diagnosis was ascertained similarly in patients and controls and the control population was appropriately matched to the SLE population. About half of the studies [1-12] reported a small increase in the overall incidence of malignancy in SLE with standardized incidence ratios (SIR) ranging between 1.14 in the larger studies to 3.6 in a study involving only 175 patients. A large multisite cohort study by Bernatsky et al. [1] in 2013 from the Systemic International Collaborating Clinics (SLICC), involving 30 centres and 16,409 patients, reported a SIR of 1.14 (95% confidence interval (CI): 1.05–1.23). Two other large cohort studies involving 30,478 patients in California, USA [2] and 11,763 patients in Taiwan [3] have also reported an increased risk of malignancy of similar or greater magnitude (American study: SIR 1.14, 95% CI 1.07–1.20 and Taiwanese study: SIR 1.76, 95% CI 1.74–1.79). Many of the remaining cohort studies [13-23] reported a trend towards increased risk but with CIs including the null hypothesis. These studies may have been underpowered due to smaller sample sizes.

Recently, there have been several large meta-analyses incorporating these adult SLE cohort studies [24-27] (summarized in Table 2). In 2014, Ni et al. [24] evaluated seven cohort studies, including 63,585 patients with SLE, specifically assessing the risk of developing solid tumors (lung, liver, bladder, and prostate). They demonstrated an overall increased cancer risk (pooled SIR 1.16, 95% CI: 1.12–1.21). In 2015, Cao et al. [25] included 16 studies with 59,662 patients with SLE and found a pooled relative risk (RR) of 1.28 (95% CI: 1.17–1.41) for cancer overall. Mao et al. [26] included several studies from Asia for a total of 18 studies with 86,069 patients and reported a pooled incidence rate (IR) of 1.44 (95% CI: 1.23–1.69) with a higher pooled IR in the Asian studies from Taiwan and Korea (pooled IR 1.62, 95% CI: 1.38–1.89) compared to those from North America (pooled IR 1.18, 95% CI: 1.01–1.39). It should be noted that there is considerable overlap between the individual studies included in each meta-analysis and hence it is to be expected that the pooled risks across meta-analyses are reasonably similar.

Hematologic Malignancies

The association between SLE and hematologic malignancies is well supported by numerous cohort studies [1-8, 12, 14, 18, 19, 23, 28, 29]. They suggest that patients with SLE are at a moderately increased risk of hematologic malignancies, particularly non-Hodgkin's lymphoma (NHL). In the 2013 multisite SLICC cohort study by Bernatsky et al. [1], the SIR for all hematologic cancers including lymphoma, leukemia, and multiple myeloma was 3.02 (95% CI: 2.48–3.63); the highest SIR was observed for NHL (4.39, 95% CI: 3.46–5.49). Myeloid malignancies such as myelodysplastic syndrome and acute myeloid leukemia were the most common non-lymphoma hematologic malignancies observed [30].

The meta-analysis by Cao et al. [25] demonstrated an increased incidence of NHL, the most common being diffuse large B cell lymphoma (DLBCL) with pooled RRs of 5.40 (95% CI: 3.75–7.77) for NHL, 3.26 (95% CI: 2.17–4.88) for Hodgkin's lymphoma (HL), and 2.01 (95% CI: 1.61–2.52) for leukemia. In a meta-analysis by Apor et al., including eight cohort studies with 67,929 patients with SLE, there was a 2.9-fold increase (95% CI: 2.0–4.4) in the incidence of all hematologic malignancies, including NHL, HL, leukemia, and multiple myeloma [31]. As this meta-analysis included some of the same studies as in the Cao et al. meta-analysis [25], the risk of NHL, HL, and leukemia was similar with SIRs of 5.7 (95% CI: 3.6–9.1), 3.1 (95% CI: 2.1–4.4), and 2.3 (95% CI: 1.9–2.7), respectively. In a cohort study of 13,296 cases of hematologic malignancies and 10,539 potential patients with SLE identified through claims data or the presence of anti-dsDNA, Knight et al. [32] identified 45 patients with both diseases. Patients with suspected SLE who were subsequently diagnosed with DLBCL presented with advanced stage and extra-nodal disease with relatively poor outcomes despite aggressive treatment. Several mechanisms have been proposed to explain the substantially increased risk of NHL, which will be discussed in greater detail in the later sections.

Non-Hematologic Malignancies

Several individual cohort studies have reported that the risk of non-hematologic malignancies such as lung [1-3, 5, 6, 9, 33], liver [2-4, 6, 34], head and neck [3, 5, 10], thyroid [1-3, 35], vaginal/vulvar [1-4, 6], cervical (cancerous and pre-cancerous) [3, 4, 7, 12, 13, 36-42], dermatologic [3-5, 19], bladder or renal [2-4, 14, 43], anal [4, 13], and pancreatic [3, 13] are also increased in SLE.

The SIRs for these malignancies are summarized in Table 1. Several large meta-analyses including between 4 to 30 cohort studies, involving from 416 to 96,578 patients have also reported an increased risk for specific malignancies (summarized in Table 2). In contrast, some studies have reported that patients with SLE have a lower risk of some hormone-associated malignancies, including breast [1, 2, 5, 13], prostate [2, 3], endometrial [1], and ovarian [3, 5]. The mechanisms underlying the increased risk for certain neoplasms, but a decreased risk for others, remain speculative. Each type of malignancy is reviewed below followed by a discussion about potential factors mediating the altered risk.

Lung Malignancy

Among the studies demonstrating an increased risk for lung cancer in SLE, the SIR ranged between 1.23 (95% CI: 1.17–1.29) in a cohort of 11,763 patients and 3.1 (95% CI: 1.3–7.9) in a cohort of 616 patients [1-3, 5, 6, 9, 33]. In a meta-analysis by Wu et al. that included 12 studies and 57,890 patients with SLE, the odds ratio (OR) for lung cancer was 1.60 (95% CI: 1.44–1.77) [44]. In a cohort study by Hemminki et al. [33] involving 7624 patients with SLE, the risk was highest for small cell lung cancer with an SIR of 3.38 (95% CI: 1.89–5.59), followed by squamous cell (SIR 2.97, 95% CI: 1.86–4.50), large cell (SIR 2.55, 95% CI: 1.53–3.99), and adenocarcinoma (SIR 2.12, 95% CI: 1.34–3.18). Bin et al. [45] in their multi-site international cohort of 9,547 patients with SLE found that the most common histological type was adenocarcinoma (26.7%) and most lung cancer patients were smokers (71%).

Hepatobiliary Malignancies

An increased SIR for liver malignancy has also been reported, ranging between 1.83 (95% CI: 1.76–1.90) in a cohort of 11,763 patients and 9.9 (95% CI: 2.5–39.8) in a cohort of 576 patients [2-4, 6, 34]. Castro et al. [34] used large national datasets from Sweden to assess the risk of specific hepatobiliary malignancies. They found an increased risk for primary liver cancer with an SIR of 3.95 (95% CI: 1.57–8.19) after 34,102 person-years of follow-up. The rates of gallbladder cancer were also increased at 3.01 (95% CI: 1.08–6.59) and hepatobiliary tract at 3.25 (95% CI: 1.85–5.29), but extrahepatic bile duct cancer was not.

Head and Neck Malignancies

Chang et al. [10] in a study involving 8,751 Taiwanese patients with SLE reported an incidence rate ratio (IRR) of 2.16 (1.13–4.13) for head and neck malignancies. The incidence of head and neck cancers was highest in the oral cavity (5 of 11 cancers, 45.45%) followed by the nasopharynx (4 of 11, 36.36%). There was also a markedly higher incidence of head and neck malignancies at ages 40–49 years compared with age-matched controls with an IRR of 12.03 (95% CI: 4.36–33.17), highlighting the particular importance of head and neck cancer surveillance in patients with SLE of that age group. Bjorndal et al. [5] in a cohort study of 5,715 patients reported an increased risk for laryngeal malignancy (SIR 3.42, 95% CI: 1.26–7.45) and Chen et al. [3] in a study of 11,763 patients reported an increased risk for malignancies of the oropharynx and larynx (SIR 2.03, 95% CI: 1.90–2.17) and nasopharynx (SIR 4.18, 95% CI: 3.93–4.45).

Thyroid Malignancies

A recent meta-analysis by Zhang et al. [46], including seven cohort studies and 66,093 patients with SLE, reported a pooled SIR for thyroid cancer of 2.22 (95% CI: 2.11–2.34). This meta-analysis did not include a cohort study by Antonelli et al. [35], which included 153 patients and showed a RR of 14.5 (95% CI: 2.3–93.6) for papillary thyroid cancer. Antonelli et al. [35] also found that 80% of patients with SLE with thyroid cancer had concomitant autoimmune thyroid disease compared to 31% of patients with SLE without thyroid malignancy ($p=0.02$). Hence, they suggest thyroid autoimmunity may be a

predisposing condition for papillary thyroid cancer and recommended careful surveillance in these patients. Cancer surveillance will be discussed in further detail later.

Vaginal, Vulvar, and Cervical Malignancies

The SIR for vaginal and/or vulvar malignancies has also been reported to be increased in many studies, ranging between 3.27 (95% CI: 2.41–4.31) in a cohort of 30,478 patients and 9.10 (95% CI: 2.3–36.5) in a cohort of 576 patients [1-4, 6, 47]. The risks of both cervical cancerous and pre-cancerous lesions have been assessed in SLE [3, 4, 7, 13, 36-40]. However, studies assessing cervical cancer incidence using cancer registries may be limited if non-invasive cervical cancer or its precursor lesions are not captured. Further, the SIR could be falsely elevated in studies where the source of cancer ascertainment or the rate of screening differs between cases and controls. In a recent meta-analysis by Zard et al. [48], which included seven cohort studies and 416 patients with SLE, the pooled OR for the risk of high-grade squamous intraepithelial lesions (HSIL) was 8.66 (95% CI: 3.75–20.00). However, several of the studies included in the meta-analysis by Zard et al were from countries where screening is not systematically offered to the entire population at risk. In contrast, in a study from Denmark, a country with high overall screening rates, the OR for HSIL was much lower (1.7, 95% CI: 1.1–2.5) [41] than that reported by Zard (8.66, 95% CI: 3.75–20.00). The Danish group also reported that cervical cancer was not increased (SIR 1.1, 95% CI: 0.6–1.8) [42]. Consistent with these findings, a Swedish study [39] reported an increased risk for cervical intraepithelial neoplasia (CIN 1: hazard ratio (HR) 2.33, 95% CI 1.58, 3.44; CIN 2–3: HR 1.95, 95% CI: 1.43–2.65), but not invasive cervical cancer (HR 1.64, 95% CI: 0.54, 5.02) and an American study reported a marginally increased risk of high-grade cervical dysplasia and cervical cancer (HR: 1.53, 95% CI: 1.07–2.19) [40]. In a systematic review by Santana et al. [49], 15 of 18 cohort studies showed a higher frequency of precancerous cervical lesions in patients with SLE compared to the general population; three of these 15 reported a higher frequency of HSIL in particular. Santana et al., however, did not find a higher frequency of cervical cancer in 14 of 15 studies. One of the cohort studies included, Parikh-Patel et al. [2], which involved 30,478 patients, even reported a reduction in the SIR for cervical cancer (0.55, 95% CI 0.39–0.75). It is hypothesized that data, which show a fairly consistent increase in precancerous cervical lesions, does not necessarily translate into an increased risk of invasive cervical cancer because precancerous lesions are appropriately managed with ablative therapies and thus few precancerous lesions progress. As discussed later in the review, these precancerous lesions may be related to SLE itself, infection with human papilloma virus (HPV), and ISDs.

Dermatologic Malignancies

An increased SIR for non-melanoma skin cancer has been reported, ranging between 1.67 (95% CI: 1.55–1.80) in a cohort of 11,763 patients and 3.08 (95% CI: 1.41–5.85) in a cohort of 5,715 patients [3-5]. The SIR for squamous cell carcinoma has been reported to be 6.43 (95% CI: 1.31–18.5) in a cohort of 238 patients [19]. The meta-analysis by Cao et al. [25] also reported an increased risk of non-melanoma skin cancer with a pooled RR of 1.51 (95% CI: 1.12–2.03), while there was a decreased risk of melanoma with a pooled RR of 0.65 (95% CI: 0.50–0.85). A cohort study by Tarr et al. [15] with 860 patients also reported a lower risk of skin cancers (not including basal cell carcinoma) with an SIR of 0.04 (95% CI:

0.001–0.24). As with non-invasive cervical cancers, ascertainment of non-melanomatous skin cancer through tumor registries is limited as they may not be accurately reported.

Bladder and Renal Malignancies

Several cohort studies have shown an increased risk for bladder cancer with the SIR ranging between 2.28 (95% CI: 1.62–3.12) in a cohort of 7,624 patients and 43.60 (95% CI: 8.21–106.78) in a cohort of 914 patients [4, 14, 43]. Dreyer et al. [4], in a study involving 576 Danish patients, reported an SIR of 3.6 (95% CI: 1.4–9.7) where all of the patients with bladder cancer had received cyclophosphamide. Only one cohort study with 11,763 patients with SLE demonstrated a decreased risk of bladder cancer with an SIR of 0.66 (95% CI: 0.57–0.75) [3]. In the meta-analysis by Cao et al. [25], the pooled RR for bladder cancer was elevated at 2.11 (95% CI: 1.12–3.99). An increased SIR for renal malignancy has been reported in several studies, varying between 2.15 (95% CI: 1.52–2.94) in a cohort of 30,478 patients and 3.99 (95% CI: 3.74–4.27) in a cohort of 11,763 patients [2, 3]. The meta-analysis by Mao et al. reported a pooled IR of 2.00 (95% CI: 1.00–3.99).

Prostate Malignancy

The risk of prostate malignancy has been reported to be decreased in SLE with SIRs ranging between 0.69 (95% CI: 0.50–0.93) in a cohort of 30,478 patients and 0.79 (95% CI: 0.68–0.90) [2, 3] in a cohort of 11,763 patients and confirmed by several meta-analyses [24, 50, 51]. The largest meta-analysis by Huang et al. [51], involving 12 cohort studies and 68,366 patients, reported a pooled SIR of 0.77 (95% CI: 0.69–0.87). In contrast, smaller cohort studies [18, 22] have reported a small increase in risk but with wide CIs, ranging from a hazard ratio (HR) for developing prostate cancer of 3.78 (95% CI: 1.30–11.0) in a cohort of 2,150 patients to a standardized morbidity rate of 6.41 (95% CI: 1.3–18.7) in a cohort of 116 patients. The very high rates may potentially be related to difficulty in accurately identifying early prostate cancers in cancer registries as well as a relatively small sample size.

Breast Malignancies

The risk of breast cancer has also been reported to be decreased, with SIRs ranging between 0.48 (95% CI: 0.35–0.64) in a cohort of 595 patients to 0.76 (95% CI: 0.67–0.86) in a cohort of 30,478 patients [1, 2, 5, 13]. A large meta-analysis of 47,325 patients with SLE from 5 cohort studies reported an SIR of 0.76 (95% CI: 0.69–0.85) [52]. The histological type and receptor status may also differ between breast cancer cases in SLE compared to the general population. A study of 180 breast cancers in an SLE cohort revealed that ductal carcinoma was the most common type, but it was still less common than expected in the general population (66% in SLE versus 80% in the general population) [53]. In a recent study examining receptor status of breast cancers in 63 patients with SLE, there was a higher proportion of triple-negative breast cancers in SLE (27%) versus the general population (15%) [54]. However, this may reflect the young age of patients with SLE in this sample as another cohort study (discussed later in this review) involving older women with SLE suggested a decreased incidence of estrogen receptor (ER)-negative breast cancer [55] versus the general population.

Risk of Malignancy in Pediatric-Onset SLE

In contrast to adults, malignancy in pediatric-onset patients with SLE has been less extensively studied. In a cohort study involving 12 pediatric rheumatology clinics in Canada and the USA enrolling 1,168 patients followed for almost 11 years, fourteen invasive cancers occurred, producing an SIR of 4.13 (95% CI: 2.26–6.93) [56]. Three of these were NHL, yielding an SIR for hematologic cancers of 4.68 (95% CI: 0.96–13.67).

There have been several case reports of hematologic malignancies occurring in pediatric-onset SLE [57–61]. These studies suggest there may be a bimodal pattern to the onset of hematologic malignancies in pediatric-onset SLE with younger children having a higher risk of leukemia and older children of lymphoma [62]. In a recent large meta-analysis of 96,578 subjects from 25 adult-case series and 5 pediatric-case series comparing malignancy rates in adult and childhood-onset SLE [27], cancer incidence was lower in childhood-onset SLE (0.5%, 95% CI: 0.03%–1.5%) versus adult-onset SLE (4.2%, 95% CI: 3.2%–5.3%). However, the analysis was limited in that the duration of follow up does not appear to have been considered in calculating the pooled incidence rates, i.e., the denominator should be expressed as person-years of follow up rather than as the cohort size. Further, although all pediatric series were included, the pediatric sample was quite small.

Risk of Mortality

The risk of mortality from malignancy in adult SLE has also been examined [63–66]. Bernatsky et al. [63], in a cohort study that included 9,547 patients with SLE from 23 sites worldwide, reported an overall (all-cause) standardized mortality ratio (SMR) of 2.4 (95% CI: 2.3–2.5). Although the SMR for cancer overall was not elevated (SMR 0.8, 95% CI: 0.6–1.0), there was a significant increase in the SMR for all hematologic cancers (2.1, 95% CI: 1.2–3.4), NHL (2.8, 95% CI: 1.2–5.6), and lung cancer (2.3, 95% CI: 1.6–3.0). Hemminki et al. [33], in a study involving 7,624 patients with SLE, also reported an increased SMR for small cell lung cancer (2.69, 95% CI: 2.11–3.38). Castro et al. [34], in a study involving 402,462 patients with various autoimmune disorders, also found an increased HR due to hepatobiliary (1.54, 95% CI: 1.07–2.22), gallbladder (2.08, 95% CI: 1.03–4.21), and extrahepatic bile duct cancers (9.24, 95% CI: 2.31–36.94) in patients with SLE.

Most recently, a meta-analysis by Yurkovich et al. [64], involving 12 studies and 27,123 patients with SLE (including 4,993 observed deaths), generated a pooled SMR of 1.19 for overall malignancy in SLE, but the 95% CI around the estimate (0.89–1.59) was wide and included the null value. Thomas et al. [65], in a study that identified 1,593 deceased patients with SLE, reported an even lower SMR for malignancy overall (0.40, 95% CI: 0.34–0.48), which they attributed to premature death associated with other causes of mortality such as cardiovascular and/or infectious diseases. That is, they hypothesize that due to competing risks with other causes of death, no increased risk of malignancy was documented. A decreased SMR was seen mainly for the solid neoplasms (0.34, 95% CI: 0.28–0.42), while the SMR for hematologic malignancies did not differ from the general population (1.08, 95% CI: 0.73–1.56).

B. Factors Potentially Mediating Risk:

Immunosuppressive therapy and SLE disease activity

It remains unclear whether ISDs influence susceptibility to malignancy in patients with SLE. Mechanistically, ISDs may theoretically lead to the development of cancer by causing direct mutagenesis and cytotoxicity and by increasing susceptibility to or decreasing clearance of oncogenic viruses. The evidence on the risk of overall and site-specific malignancies, notably hematological and cervical neoplasia, with ISD exposure is summarized in Table 3.

As the use of ISDs is highly correlated with SLE disease activity, it is difficult to examine the independent effect of each on the risk of malignancy. Bernatsky et al. [67] did so in a case-cohort study nested within their multicenter SLICC cohort study which controlled for SLE disease damage. Disease damage is not a measure of disease activity, but has been shown to reflect cumulative disease activity and disease severity. Two hundred and forty-six SLE patients with cancer (of which 46 had a hematologic malignancy) were compared to 538 SLE patients without cancer and a HR for cancer after exposure to ISDs was calculated, in models that controlled for demographics, smoking status, SLE duration, and SLE disease damage. The reported adjusted HR for any ISD was 0.82 (95% CI: 0.50–1.36). However, there was an association between risk of hematologic malignancies and ISD use, especially when lagged by a period of five years (adjusted HR 2.29, 95% CI: 1.02–5.15). Cyclophosphamide contributed the most to this risk, although this result included the null value (adjusted drug-specific HR 3.55, 95% CI: 0.94–13.37). The adjusted HRs for azathioprine and methotrexate were 1.02 (95% CI: 0.34–3.03) and 2.57 (95% CI: 0.80–8.27), respectively.

In a subsequent case-cohort study, Bernatsky et al. [68] examined the independent effect of ISDs and disease activity on lymphoma risk. Seventy-five SLE patients with lymphoma were compared to 4961 cancer-free SLE controls and the HR for lymphoma related to ISDs was calculated in models that controlled for demographics, secondary Sjogren's syndrome, and disease activity. In the partially adjusted model, there was a suggestion of a slightly greater exposure to cyclophosphamide (HR 1.90, 95% CI: 1.02–3.53) and steroids (HR 1.94, 95% CI: 1.11–3.39) in the lymphoma cases. Higher disease activity was not associated with lymphoma (HR 0.65, 95% CI: 0.35–1.22). The authors suggested that the association between greater cumulative steroid exposure and lymphoma may reflect steroid exposure acting as a surrogate for elements of disease activity that are not captured by the disease activity measure. While disease activity in other autoimmune rheumatic diseases such as rheumatoid arthritis has been linked to a higher risk of lymphoma [69], this has not clearly been observed in SLE. Of additional interest in the Bernatsky case-cohort study, secondary Sjogren's syndrome was associated with lymphoma (in the partially adjusted model: HR 1.94, 95% CI: 1.04–3.61). The link between primary Sjogren's syndrome and lymphoma, primarily of the mucous associated lymphoid tissue (MALT) subtype, is well known [70]. However, in SLE, the DLBCL subtype predominates.

Hsu et al. [71] conducted a nested case-control study within an SLE population identified through the Taiwanese National Health Insurance Research Database. The authors compared 330 cancer cases with 1320 matched cancer-free controls and calculated OR for ISDs in

conditional Cox proportional regression models after propensity score matching. Cyclophosphamide exposure was associated with a dose dependent increased risk of cancer overall (OR 1.09, 95% CI: 1.04–1.13). In contrast, hydroxychloroquine was associated with a small protective effect (OR 0.93, 95% CI: 0.90–0.97), also in a dose-dependent manner. Azathioprine, methotrexate, and systemic glucocorticoids were not clearly associated with cancer risk. However, the authors were unable to adjust for SLE disease activity and damage as this information is not available in administrative databases, and they did not adjust for the concomitant use of other ISDs or stratify their results by specific malignancies.

Wadstrom et al. [39] assessed the risk of cervical neoplasia in women with SLE, overall and stratified by exposure to ISDs, compared with women from the general population. Using Swedish national registries, they assembled a cohort of 4,976 women with SLE and 29,703 general population comparators. Among the women with SLE, 1,942 had been exposed to antimalarials and 2,175 had been exposed to other ISDs, including azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil (MMF), or rituximab. Hazard ratios were calculated for the entire SLE population versus the general population and for the ISD subgroup versus the antimalarial subgroup, adjusting for relevant covariates although there was no data on SLE disease activity or severity. Patients with SLE had a >2-fold increased risk of cervical neoplasia (i.e., CIN or invasive cancer) (HR 2.12, 95% CI: 1.65–2.71). When considered separately, the HR for CIN was significantly increased (CIN 1: HR 2.33, 95% CI 1.58–3.44; CIN 2/3: HR 1.95, 95% CI 1.43–2.65), but not so for invasive cervical cancer (HR 1.64, 95% CI: 0.54–5.02). The increased risk for precancerous lesions, but not for invasive cervical cancer, has been observed by others and discussed earlier in this review [49]. ISD exposure was associated with a 1.8-fold higher risk for cervical neoplasia (HR 1.83, 95% CI: 1.15–2.91) compared with those treated with antimalarials.

In a somewhat similar study design, Kim et al. [40] assessed the risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases, including SLE, compared with those not having a systemic inflammatory disease. Using US insurance data, they identified 14,513 patients with SLE and 533,332 controls. Hazard ratios were then calculated for each inflammatory disease population versus the control population and for those women exposed to ISDs versus controls, adjusting for relevant covariates, but not SLE disease activity. Patients with SLE had an increased risk of cervical neoplasia (HR 1.53, 95% CI: 1.07–2.19). Among those with SLE on ISDs at baseline, the HR was not significantly increased (HR 1.52, 95% CI: 0.64–3.61), but only 3,046 patients with SLE were included in this subgroup analysis (21% of the entire SLE population).

The same authors further investigated the association of ISDs with the risk of high-grade cervical dysplasia and cervical cancer in patients with SLE by comparing the risk between new users of ISDs versus hydroxychloroquine [72]. Among 2451 matched pairs (based on propensity scoring) of ISD and hydroxychloroquine initiators in a commercial health plan, the HR was 2.47 (95% CI: 0.89–6.85) and among 7690 matched pairs in Medicaid, the HR was 1.24 (95% CI: 0.78–1.98). The authors concluded that ISDs may be associated with a greater risk of cervical dysplasia and cancer, albeit not statistically significant.

In a small case-control study nested within a national Swedish cohort of 6,438 patients with SLE, 16 patients with NHL, predominantly DLBCL, were compared to 26 matched SLE controls without malignancy [73]. Lymphoma was not associated with exposure to cyclophosphamide or azathioprine and the authors were unable to examine the effect of disease activity. Using the same national Swedish SLE cohort, 8 patients with myeloid leukemia were matched to 18 SLE cancer-free controls [74]. The exposure to cytotoxic drugs did not differ between the SLE cases and controls. However, both studies are limited by the very small sample size.

Several cohort studies have examined the association of cyclophosphamide and malignancy [14, 38, 75]. In a Korean cohort study involving 914 patients with SLE, 16 cancers were identified [14]. Three of the 16 were bladder cancers and these patients had received more than 6g of cyclophosphamide. Cyclophosphamide exposure was found to be more common in SLE patients with cancer ($p=0.02$) and there was an increased risk of cancer with a higher cumulative dose of cyclophosphamide ($p=0.017$). Ognenovski et al. [38] also found a dose dependent risk of CIN with intravenous cyclophosphamide. Sixty-one patients with SLE with normal baseline cervical smears were assessed at baseline and at 3 and 7 years. For each gram increase of cumulative cyclophosphamide exposure, the risk of developing CIN increased by 13% (risk ratio 1.13, $p=0.04$). Bernatsky et al., in a study of 1015 SLE patients, of whom 74 self-reported an abnormal Pap smear after the diagnosis of SLE, reported that ISD exposure was associated with the occurrence of an abnormal Pap smear (adjusted OR 1.6 (95% CI: 1.0–2.7) [76]. The adjusted ORs for each specific ISD was not significant likely due to the small sample size: cyclophosphamide OR 1.3 (95% CI: 0.8–2.1), azathioprine OR 1.2 (95% CI: 0.8–2.0) and methotrexate OR 1.1 (95% CI: 0.5–2.2).

In summary, there is data suggesting that cyclophosphamide is associated with an increased risk of overall and hematologic malignancies and that ISDs in general are associated with cervical neoplasia. However, several of these studies were based on administrative data and were therefore unable to examine the independent effect of SLE disease activity/severity and ISDs on malignancy risk; the increased risk reported in some of these studies with ISDs may potentially be attributable to increased SLE activity. The risk-to-benefit ratio for ISD use should be evaluated on an individual basis, with the key caveat being that, although the relative risk for malignancy may be slightly increased with ISD exposure, the absolute risk is changed only marginally. We do not believe that concerns about malignancy should result in the withholding of ISDs for SLE manifestations where they are clinically indicated. Future studies are needed to establish evidence-based guidelines on the use of ISDs in SLE patients with a history of malignancy.

Autoantibodies

There is evidence to suggest that SLE-related autoantibodies can impair DNA repair leading to the accumulation of DNA damage that increases the risk of cancer in patients with SLE [77]. Several mechanisms by which membrane-penetrating autoantibodies cross into cells to affect various intracellular functions are summarized by Nobel et al. [77], including Fc-receptor-mediated endocytosis by immune cells and also involvement of cellular structures, such as cell-surface myosin, caveolae and nuclear pores, and nucleoside transporters, to

enter the nucleus. Anti-3E10 is an anti-DNA antibody that was isolated from a mouse model of SLE and is thought to contribute to DNA damage [78]. It preferentially binds to DNA substrates with free single-strand tails extracellularly and then crosses the plasma membrane via a nucleoside transporter [equilibrative nucleoside transporter 2 (ENT2)] and translocates into the nucleus. It can inhibit key DNA repair pathways of base-excision repair and homology-directed repair of DNA double-strand breaks. Furthermore, it has been shown that this antibody can increase the sensitivity of cells to ionizing radiation in *in vivo* mouse experiments. Originally thought to be a potential targeted molecular therapy in SLE and cancer because of its ability to penetrate live cell nuclei “without harming” normal cells, instead now anti-3E10 is believed to increase the risk of malignancy through increased DNA damage. Other SLE-related autoantibodies to enzymes that have key roles in DNA repair such as poly(ADP-RIBOSE) polymerase (PARP) and DNA ligase IV-XRCC4 complex might therefore also contribute to higher malignancy risk.

Studies have also suggested that SLE-related autoantibodies may paradoxically contribute to the decreased risk of certain hormone-sensitive malignancies such as breast, ovarian, and prostate cancer. 5C6, a nucleolytic lupus autoantibody capable of penetrating nuclei, is associated with single-stranded and ds-DNA degradation [79]. In a study of matched pairs of *BRCA2*-proficient and *BRCA2*-deficient human colon cancer cells, 5C6 selectively suppressed the growth of *BRCA2*-deficient cells by inducing cell senescence while having minimal effect on *BRCA2*-proficient cells with intact DNA repair [79]. This provides further support that SLE-related antibodies can penetrate cell nuclei and damage DNA, and that cancer cells with pre-existing defects in DNA repair, such as *BRCA2*-deficient cells, are more prone to this damage. It is hypothesized that since cells with intrinsic deficiencies in DNA repair are particularly susceptible to lupus antibodies that inhibit DNA repair, these *BRCA2*-deficient cancers (such as triple-negative breast cancer) would occur less frequently in SLE than the general population. Some data indirectly support this reasoning. Gadalla et al. [55], in a population based case-control study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, reported an OR of 0.49 (95% CI: 0.26–0.94) for ER-negative breast cancers versus 1.08 (95% CI: 0.85–1.40) for ER-positive breast cancers in older women with SLE. While it is possible that the lower prevalence of ER-negative cancers was due to the older age of the population, the large multisite SLICC cohort of 16,409 patients [53] also reported findings similar to Gadalla et. al; the ductal subtype of breast cancer, which is by definition ER-negative and predominantly triple-negative was less prevalent among breast cancers in the SLE cohort (66%) than would be expected in the general population (80%).

Antiphospholipid antibodies (aPL), which are present in approximately 30% of patients with SLE, have also been suggested to be a risk factor for cancer development, especially hematologic subtypes (reviewed in [80]). Finazzi et al. [81] reported in their study of the natural history of aPL healthy carriers, that hematological malignancies were a major cause of morbidity and mortality, particularly NHL. This finding was recently supported by another study that found that 26% of patients with aPL developed a hematologic cancer [82]. Further studies are needed to validate these findings in SLE patients with aPL.

Chronic Immune Dysregulation

Chronic immune stimulation and immune dysregulation from autoimmunity are also believed to contribute to the formation of organized lymphoid tissue. Both SLE and NHL have been found to individually overexpress cytokines that are normally essential to the survival and proliferation of B cells: B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) [83]. Aberrant expression of these cytokines can lead to overstimulation and defective apoptosis of B-cells and ultimately lymphomagenesis. Knowledge of the role of B cells in autoimmune rheumatic diseases and lymphomas has led to the development of therapies that target these cells including monoclonal antibodies against B-cell specific antigens CD20 (e.g. rituximab) and CD22, BAFF (e.g. belimumab), and APRIL (e.g. atacicept). Only belimumab is currently approved for the treatment of SLE for various reasons, including inconsistent results due to differences in trial design and patient heterogeneity (reviewed in [84]).

Dysregulated immune proliferation can also promote the development of hematologic malignancies, particularly NHL, by promoting translocation and juxtaposition of an oncogene beside a gene regulating immune function with malignant transformation [85]. Further, the most common type of NHL in SLE is DLBCL, which can be further categorized into germinal center B (GCB) cell-like and non-GCB (or activated B) cell-like lymphoma [86]. Preliminary evidence suggests that the non-GCB cell-of-origin DLBCL is more common in SLE versus the GCB cell-of-origin in the general population [87]. The predominance of this DLBCL subtype in SLE suggests that these lymphomas arise from activated lymphocytes and are related to the chronic immune stimulation underlying the pathogenesis of SLE.

Environmental exposures

It is possible that the increased prevalence of certain cancers in patients with SLE is due to increased exposure to known environmental risk factors. Bernatsky et al. [88] conducted a nested case-cohort study to evaluate risk factors associated with lung cancer, including demographics, smoking status, medication exposure, and disease activity. Forty-nine SLE patients with lung cancer were compared to 4,938 SLE patients without lung cancer. The majority (84.2%) of SLE lung cancer cases were ever-smokers at baseline, compared to 40.1% of those without lung cancer. In adjusted Cox proportional hazard regression models, the principal factor associated with lung cancer development was smoking exposure (HR 6.35, 95% CI: 2.4 –16.6). There was no association observed between exposure to ISDs and lung cancer. Bernatsky et al. demonstrated similar findings in an earlier case-cohort study involving 35 lung cancers [67]. Therefore, as in the general population, smoking is the strongest modifiable risk associated with lung cancer in SLE.

In the hormone-sensitive cancers, such as breast and prostate, it is possible that the decreased endogenous and/or exogenous exposure to hormones is partially responsible for the decreased risk. Women with SLE may have an earlier menopause [89], although there is some inconsistency in the literature [90]. Further, they are also potentially less likely to be prescribed oral contraceptives or hormonal replacement therapy because of concerns

regarding thrombosis and exacerbation of SLE disease activity. Men with SLE are known to be hypoandrogenic [91-94].

Oncogenic viruses are another risk factor that could contribute to malignancy risk. Dreyer et al. [4] in a Danish cohort including 576 patients with SLE reported a SIR of 2.9 (95% CI: 2.0–4.1) for all virus-associated malignancies. Malignancies traditionally associated with HPV were particularly increased, with SIRs of 26.9 (95% CI: 8.7–83.4) for anal carcinoma and 9.1 (95% CI: 2.3–36.5) for vaginal/vulvar malignancies [4]. However, there was no actual measurement of HPV status in this cohort. Many other cohort studies have also reported an increased frequency of HPV-associated malignancies [1-7, 10, 13, 36-40], without actually measuring HPV as a risk factor. An increased rate of HPV infection could also be responsible for the increased frequency of cervical dysplasia in women with SLE. In women with normal Pap smears, patients with SLE are more likely than healthy subjects to have an HPV infection [95]. Additionally, patients with SLE are more likely to develop infections with multiple HPV strains as well as infections with high-risk HPV subtypes [96]. Increased susceptibility and/or difficulty clearing HPV infections may stem from immune dysfunction secondary to SLE or impaired immune surveillance due to ISDs [36].

Infection with Epstein Barr virus (EBV) may increase the risk of developing SLE [97] and some authors have suggested that EBV infection may also play a role in the pathogenesis of certain types of lymphoma in SLE [6]. However, to date there are no data directly supporting this association. In a small Swedish study involving only 15 patients with SLE, only two had EBV detectable by in situ hybridization in their lymphoma tissue [73]. The role of EBV in lymphoma and Hepatitis B and C viruses in the development of liver malignancy in SLE remains unclear.

Shared genetic susceptibility to SLE and malignancy

Like SLE itself, it is unlikely that malignancy in SLE is driven by one gene. Rather, it is an expression of the sum of genetic variability that occurs at the level of various single nucleotide polymorphisms (SNPs) throughout the genome [98] as well as gene-environment interactions and recombination events at the time of conception. In 2012, Bernatsky et al. [98] examined whether SNPs associated with SLE might be protective against breast cancer. The frequency of 10 SLE-related SNPs was compared between 3,659 breast cancer cases and 4,897 controls identified from a large breast cancer genome-wide association study (GWAS). SLE-related SNPs did not occur less frequently in those with breast cancer, but there was a weak inverse association between a cytosine(C) nucleotide substitution at rs9888739 (on chromosome 16p11.2) with breast cancer (OR 0.907551, $p = 0.0499$) compared to controls. Future studies are needed to examine more SNPs and stratify patients based on other factors such as menopausal status.

Using a similar study design, Bernatsky et al. [99] examined whether SLE-related SNPs may increase the risk of DLBCL. The frequency of 28 SLE-related SNPs was compared between 3,857 DLBCL cases and 7,666 controls identified from a DLBCL GWAS conducted by the International Lymphoma Epidemiology Consortium (InterLymph). Two of the 28 SNPs that are independently associated with SLE in European Caucasians were possibly associated with DLBCL: CD40 SLE risk allele rs4810485 on chromosome 20q13 (OR per risk allele

1.09, 95% CI: 1.02–1.16) and the HLA SLE risk allele *rs1270942* on chromosome 6p21.33 (OR per risk allele 1.17, 95% CI: 1.01–1.36). CD40 is expressed on several B-cell neoplasms including DLBCL and is part of the tumor necrosis superfamily thought to be involved in the pathology of malignant lymphomas [100]. HLA polymorphisms on their own have been shown to influence the risk of DLBCL [101]. Future studies are needed to confirm these potential pathways linking SLE and DLBCL.

Recent advances in our understanding of lymphoma risk and other tumors in autoimmune rheumatic diseases have been centered upon germline polymorphisms of tumor necrosis factor α induced protein-3 (*TNFAIP3*) or A20. A20 is an immunoregulatory gene responsible for regulating negative feedback of nuclear factor kappa B (NF- κ B) activation in response to multiple stimuli including BAFF and APRIL. NF- κ B is an important regulator of cell proliferation and cell survival [102]. Inability to downregulate NF- κ B signaling can therefore lead to tumorigenesis. Although there is currently very limited published research on *TNFAIP3* in SLE, in primary Sjögren's syndrome, the majority of patients with MALT lymphoma have either germline polymorphisms of *TNFAIP3* or somatic alterations of the gene within the lymphoma tissue [103]. Okada et al. found that polymorphisms of *TNFAIP3* were common to both rheumatoid arthritis and Hodgkin's lymphoma [104]. In the only study examining *TNFAIP3* in SLE, Zhu and Zhou [105] reported that two of 37 patients with SLE were heterozygous for an A20 gene polymorphism (*rs77191406*); one developed bladder cancer with liver metastases while the other had severe SLE, including central nervous system and renal involvement. Hence, *rs77191406* may be an important prognostic marker for malignancy risk and SLE severity. The InterLymph analyses described in the preceding paragraph did not confirm a strong relationship with the lupus-related *TNFAIP3* SNP *rs7749323* specifically for DLBCL, but this may be a power issue, or may reflect the importance of different pathways for different hematologic risk profiles across different autoimmune rheumatic diseases.

A recent meta-analysis using data from seven gene-set analysis (GSA) studies identified a specific genetic pathway in SLE that may be implicated in lung cancer called the KEGG pathway *hsa05322* (p=0.0306) [106]. Several SLE-related genes (*HIST1-H4L*, *-1BN*, *-2BN*, *-H2AK*, *-H4K*, and *C2/C4A/C4B*) and markers (*rs13194781*) located within *HIST12BN* and *rs1270942* located between *C2 and C4A* on chromosome 6p21–22 were the most strongly associated with lung cancer. The association was most prominent in patients with adenocarcinoma (p=0.0030) and in women (p=0.0112) and older cases (p=0.0002).

Heat shock protein 27 (HSP-27) has also been implicated in the pathogenesis of prostate and breast cancer. HSP-27, which has anti-apoptotic properties, has been associated with aggressive cancer progression and metastases and poor clinical outcome [107]. Grzegorzolka et al. [108] have shown that 92% of cases of invasive ductal carcinoma expressed HSP-27 and that increased HSP-27 levels correlated with higher breast cancer grade and human epidermal growth factor receptor 2 (HER)-2 positivity. In ENA-positive patients with SLE, there was decreased levels of HSP-27 expression [109]. Therefore, lower levels of HSP-27 expression in patients with SLE may explain the lower rate of prostate cancer and aggressive invasive ductal carcinomas. However, this remains speculative as the expression of HSP-27 in SLE patients with malignancy has not been studied.

C. Malignancy screening and HPV vaccination in SLE

Tessier-Cloutier et al. [110] recently reviewed the evidence regarding malignancy screening in SLE. Of the 25 research articles that suggested some form of screening strategy, most recommendations were rudimentary and based on cancer incidence data from observational cohort studies or a case-control design and none compared the value of alternative screening strategies. Eleven of these 25 studies promoted following the general population cancer screening guidelines, while the remaining 14 studies recommended more specific or enhanced strategies, focusing primarily on cervical dysplasia. The Canadian expert panel who are developing guidelines for diagnosing and monitoring of SLE in Canada (currently only published in abstract form [111]) believed there was currently only sufficient evidence (albeit low quality) to provide a recommendation regarding cervical cancer screening. They conditionally recommended that all patients with SLE who are or have been sexually active, regardless of sexual orientation, undergo annual cervical cancer screening rather than screening every three years at least up to the age of 69 years. This is of particular importance in those with ISD exposure. The European League Against Rheumatism (EULAR) has recommended adhering to general population guidelines and acknowledged the importance of future development of SLE-specific malignancy guidelines [112].

While there are currently no guidelines addressing lung cancer screening specifically in SLE, it may be reasonable to consider the US Preventive Service Task Force recommendations of annual low-dose computed tomography of the chest for those 55 to 80 years who have a 30-pack year history and currently smoke or have quit within the past 15 years [113, 114]. At a minimum, regular chest radiographs, especially in heavy smokers, should be considered [115]. Further, additional targeted screening, such as annual urine cytology in those with previous cyclophosphamide exposure and thyroid function tests, anti-thyroid peroxidase antibodies, and ultrasonography in those with pre-existing thyroid autoimmunity [35] could be considered, but have not yet been formalized in SLE cancer screening guidelines.

Of note, a study by Bernatsky et al. [116] suggested that patients with SLE may be less likely to complete recommended cancer screening compared to the general population. They found that patients with SLE were less likely to undergo age-appropriate screening for malignancies compared to the general population including for breast (53% versus 74%), colorectal (18% versus 48%), and cervical cancer (33% versus 56%). Patients with SLE who were non-white and with lower education and higher disease damage were less likely to undergo cervical Pap testing. One possible hypothesis for low malignancy screening rates in patients with SLE is that they seek care primarily from specialists who are focused specifically on SLE-related issues. Therefore, lupus specialists need to encourage patients to continue seeing their family physician regarding accessing appropriate malignancy screening or offer it directly.

HPV Vaccination in Patients with SLE

The introduction of the HPV vaccine provides an opportunity to prevent the development of HPV infections. This is a potentially important consideration as HPV infections are known to be more prevalent in patients with SLE [7, 48, 49, 75, 117, 118]. The risk of cervical

dysplasia and pre-malignant lesions is also increased, as discussed in a prior section of this review [4, 36-40, 48, 49]. In the last decade, three non-live protein subunit vaccines for HPV have been approved for the prevention of HPV infection and pre-malignant cervical lesions: bivalent (aimed against serotypes 16 and 18), quadrivalent (qHPV, aimed against serotypes 6, 11, 16, and 18), and most recently, 9-valent (aimed against serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58). Current EULAR recommendations are that HPV vaccinations should be considered for women with SLE until the age of 25 years (grade of evidence III; strength of recommendation C-D) [119].

The safety and efficacy of the HPV vaccine has been demonstrated in a few small SLE cohort studies [120-123]. One of the concerns with this vaccine is that patients with SLE might not develop an adequate response because of immune dysfunction secondary to SLE itself and concomitant ISDs. Mok et al. [120], in a case-control study of 50 patients with SLE and 50 healthy controls, found that the seroconversion rates 12 months after the first vaccination with the qHPV vaccine were reasonably similar between the two groups (for anti-HPV serotypes 6, 11, 16 and 18 in patients and controls, seroconversions rates were 82%, 89%, 95%, 76% and 98%, 98%, 98%, 80%, respectively). The other concern is possible reactivation of SLE triggered by viral antigens or adjuvants contained in the vaccine. In the same study, there was no significant change in disease activity (i.e. titres of anti-dsDNA, complements, anti-C1q and SLE Disease Activity Index (SLEDAI) scores) from baseline to months 2, 7 and 12 [120]. The frequency of disease flares in vaccinated patients with SLE compared to non-vaccinated patients with SLE (who were not part of the study but followed in the investigator's clinic) was comparable (0.22/patient/year versus 0.20/patient/year, $p=0.81$). The frequency of adverse events was similar compared to healthy controls, the most common being injection site reaction (5%). Another prospective, open label study of 27 patients with SLE demonstrated similar findings in terms of good seropositive rate (>94%) post-vaccine and tolerability of the qHPV vaccine [121]. There was no increase in mean SLEDAI scores pre- versus post-vaccination (6.14 vs. 4.49, $p=0.01$). These small studies demonstrate that the HPV vaccine is well tolerated and effective, but studies with larger sample sizes and longer duration of follow-up are needed.

However, the administration of the HPV vaccine is not without controversy as highlighted by recent epidemiological assessments using the national vaccine adverse event reporting system (VAERS) database in the US. Geier et al. [124] evaluated the association of the qHPV vaccine with SLE using the serious autoimmune adverse events (SAAEs) reported to the VAERS database following qHPV vaccinations. They reported that there were 28 cases of SLE self-reported to have occurred post-vaccination among 15,384 individuals vaccinated with HPV versus 8 cases among 33,468 non-vaccinated individuals, yielding an OR of 7.626 (95 % CI: 3.385–19.366). However, it is not possible to conclude if there was a causal relationship between SLE and HPV because individuals may potentially report a diagnosis of SLE that actually antedated the vaccine and there was no attempt to adjust for potential differences between vaccinated and non-vaccinated individuals in their risk for developing SLE.

Based on two case series, eight patients with no prior diagnosis of SLE have also been reported to develop SLE or SLE-like disease following HPV vaccination [125, 126]. All of

these women had either a personal or familial history of autoimmunity. The suggested mechanism behind this association is that of immune cross-reactivity between SLE and HPV [127]. Therefore, a possible solution would be to develop HPV vaccines that bear no homology to the human proteome to avoid potential cross-reaction [127]. Slade et al. [128] also reported an association between the qHPV vaccine and venous thromboembolic events through the VAERS database (RR of 0.2 case per 100,000 doses of qHPV vaccine). Ninety percent of the 31 reported cases had a known risk factor for thrombosis including two cases of antiphospholipid syndrome. It is unclear whether any of these patients had SLE. Additional studies are needed to further evaluate the long-term clinical consequences of the HPV vaccine in patients with SLE.

Summary

There is increasing evidence supporting the association between malignancy and adult-onset SLE. There is an increased risk for malignancy overall as well as for lung, liver, head and neck, thyroid, vulvar/vaginal, and anal malignancies and cervical dysplasia; a substantially increased risk for hematologic malignancies, particularly NHL, has been consistently observed. In contrast, a decreased risk of hormone-sensitive cancers such as breast and prostate has also been reported. Little is known about malignancy in pediatric-onset SLE owing to the small number of studies, but the risk for hematologic cancers also appears to be increased.

Our current understanding of the relationship between malignancy and SLE is limited due to the complexity of both conditions and the multiple pathways implicated in their pathogenesis. The heightened risk of lymphoma in SLE may be partially attributable to exposure to ISDs, chronic immune dysregulation, or shared genetic susceptibility. The increased risk of head and neck, vulvar/vaginal, anal, and cervical malignancies may be due to an increased frequency of HPV infection in SLE. As anticipated, lung cancer in SLE is strongly associated with smoking. The lower risk of hormone-sensitive malignancies may be related to the presence of certain nuclear-penetrating autoantibodies (e.g., 5C6) which are particularly lethal to cells with intrinsic defects in DNA repair. The mechanisms underlying the altered risk of other malignancies, such as hepatobiliary, thyroid, prostate, and endometrial remain poorly understood. Future research should focus on the risk of malignancy associated with: 1) long-term exposure to ISDs, particularly newer therapies such as MMF and belimumab, 2) high cumulative SLE disease activity and specific types of organ involvement, 3) SLE-associated autoantibodies, cytokines, and proteins, 4) oncogenic viruses such as EBV and Hepatitis B and C, and 5) genetic polymorphisms. Further, there is a pressing need to develop evidence-based guidelines regarding malignancy screening, HPV vaccination, and use of ISDs in those with a previous malignancy.

Management of concomitant SLE and malignancy may lie in identifying genetic and antibody pathways common to both diseases. A better understanding of these pathways as well as delineation of risk factors involved in SLE and malignancy may revolutionize the approach to treating and preventing malignant diseases in SLE in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

(AML)	Acute myeloid leukemia
(APRIL)	A proliferation-inducing ligand
(BAFF)	B cell activating factor
(CI)	Confidence interval
(CIN)	Cervical intraepithelial neoplasia
(DLBCL)	Diffuse large B cell lymphoma
(dsDNA)	Double stranded-DNA
(EBV)	Epstein-Barr virus
(ENT2)	Equilibrative nucleoside transporter 2
(EULAR)	European League Against Rheumatism
(GWAS)	Genome-wide association study
(GSA)	Gene-set analysis
(HR)	Hazard ratio
(HSP-27)	Heat shock protein 27
(HSIL)	High-grade squamous intraepithelial lesions
(HL)	Hodgkin's Lymphoma
(HPV)	Human papilloma virus
(ISDs)	Immunosuppressant drugs
(IR)	Incidence rate
(IRR)	Incidence rate ratio
(MMF)	Mycophenolate mofetil

(MDS)	Myelodysplastic syndrome
(NHL)	Non-Hodgkin's Lymphoma
(OR)	Odds ratio
(PTEN)	Phosphatase and tensin homolog
(PARP)	Poly(ADP-ribose) polymerase
(PCNSL)	Primary central nervous system lymphoma
(qHPV) vaccine	Quadrivalent human papilloma virus
(RR)	Relative risk
(SLEDAI)	SLE Disease Activity Index
(SNPs)	Single nucleotide polymorphisms
(SEER)	Surveillance, Epidemiology and End Results
(SIR)	Standardized incidence ratio
(SMR)	Standardized mortality ratio
(SLICC)	Systemic International Collaborating Clinics
(SLE)	Systemic lupus erythematosus
(TNFAIP3)	Tumor necrosis factor α induced protein-3
(USPSTF)	U.S. Preventive Service Task Force

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Important studies (10) are indicated by **

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Practice Points

- There is an increased risk for malignancy overall as well as for lung, liver, head and neck, thyroid, vulvar/vaginal, and anal malignancies as well as cervical dysplasia in SLE. A substantially increased risk (approximately 3-fold) for hematologic malignancies has been consistently observed. In contrast, there is a decreased risk of hormone-sensitive cancers such as breast and prostate.
- Factors potentially mediating malignancy risk in patients with SLE include the use of immunosuppressant drugs, presence of certain SLE-related autoantibodies, chronic immune dysregulation, environmental factors, and shared genetic susceptibility.
- As there is no literature comparing enhanced cancer screening versus general population screening guidelines in patients with SLE, it is currently recommended that patients with SLE follow general population recommendations, with potentially enhanced screening for cervical cancer.

Research Agenda

- A better understanding of potential risks factors including exposure to newer immunosuppressive drugs, SLE-associated autoantibodies, cytokines, and proteins, oncogenic viruses, and genetic polymorphisms is needed.
- Future studies should explore genetic and immune pathways that link SLE and malignancy as they may help elucidate more effective therapeutic approaches to concomitant disease.
- There is a pressing need to develop evidence-based guidelines regarding malignancy screening, vaccination for human papilloma virus, and use of immunosuppressive drugs in those with a previous malignancy.

Table 1.

Adult SLE cohort studies reporting overall risk of malignancy and/or increased or decreased risk of site-specific malignancies¹

Author, yr (reference)	SLE sample size	SIR ² (95% CI) for overall risk of malignancy	SIR ² (95% CI) for higher risk site-specific malignancies	SIR ² (95% CI) for lower risk site-specific malignancies
Abu-Shakra et al. 1996 [23]	724	1.08 (0.70–1.62)	Hematologic (all) 4.12 (1.52–9.01) NHL 5.38 (1.11–15.70)	NR
Antonelli et al. 2010 [35]	153	NR	Thyroid RR 14.5 (2.3–93.6)	NR
Bernatsky et al. 2013 [1]	16, 409	1.14 (1.05–1.23)	Hematologic (all) 3.02 (2.48–3.63) Leukemia 1.75 (1.04–2.76) Lung 1.30 (1.04–1.60) NHL 4.39 (3.46–5.49) Thyroid 1.76 (1.13–2.61) Vulva 3.78 (1.52–7.78)	Breast 0.73 (0.61–0.88) Endometrial 0.44 (0.23–0.77)
Bjornadal et al. 2002 [5]	5,715	1.25 (1.14–1.37)	Hematologic (all) 2.32 (1.78–2.96) HL 4.34 (1.59–9.45) Larynx 3.42 (1.26–7.45) Leukemia 1.98 (1.18–3.13) Lung 1.73 (1.25–2.32) NHL 2.86 (1.96–4.04) Non-melanoma skin 3.08 (1.41–5.85) Unspecified female reproductive system 2.70 (1.09–5.57)	Breast 0.72 (0.54–0.95) Ovarian 0.48 (0.19–0.99)
Black et al. 1982 [21]	39	1.85 (0.05–10.28)	NR	NR
Blumenfeld et al. 1994 [37]	39	NR	Cervical atypia vs. control (35.9% vs. 5%, P<0.01)	NR
Castro et al. (2014) [34]	34,102 (person years after 10 years of follow up)	NR	Hepatobiliary tract 3.25 (1.85–5.29) Gallbladder 3.01 (1.08–6.59) Liver 3.95 (1.57–8.19)	NR
Chang et al. 2012 [12]	1,052	1.555 (1.137–1.974)	Cervical 4.282 (1.722–8.824) NHL 7.408 (2.405–17.287)	NR
Chang et al. 2013 [10]	8,751	IRR 1.56 (1.32–1.85)	Head and neck IRR 2.16 (1.13–4.13)	NR
Chen et al. 2010 [3]	11, 763	1.76 (1.74–1.79)	Kidney 3.99 (3.74–4.27) Leukemia 2.64 (2.45–2.84) Lung or mediastinum 1.23 (1.17–1.29) Nasopharynx, sinus, ears 4.18 (3.93–4.45) NHL and others ³ 7.27 (6.98–7.57) Vagina/vulva 4.76 (4.24–5.33) Others not shown ⁴	Colorectal 0.82 (0.78–0.86) Ovarian 0.72 (0.64–0.80) Prostate 0.79 (0.68–0.90) Bladder 0.66 (0.57–0.75)
Chun et al. 2005 [20]	466	1.04 (0.21–3.03)	NR	NR
Cibere et al. 2001 [7]	297	1.59 (1.05–2.32)	Cervical cancer 8.15 (1.63–23.81) NHL 7.01 (1.88–17.96)	NR
Dey et al. 2013 [13]	595	1.05 (0.52–1.58)	Anal 1.80 (1.48–2.12) Cervical cancer 4.00 (3.50–4.50) Pancreatic 1.43 (1.32–1.54) Prostate 4.29 (1.09–10.24)	Breast 0.48 (0.35–0.64) NHL 0.91 (0.87–0.95)
Dreyer et al. 2011 [4]	576	1.6 (1.14–1.20)	Anal 26.9 (8.7–83.4) Cervical dysplasia/CIS 1.8 (1.2–2.7) Liver 9.9 (2.5–39.8) Bladder 3.6 (1.4–9.7) NHL 5.0 (1.9–13.3)	NR

Author, yr (reference)	SLE sample size	SIR ² (95% CI) for overall risk of malignancy	SIR ² (95% CI) for higher risk site-specific malignancies	SIR ² (95% CI) for lower risk site-specific malignancies
			Non-melanoma skin 2.0 (1.2–3.6) Vaginal/vulvar 9.1 (2.3–36.5)	
Dugue et al. 2014 [41]	2,497	NR	HSIL OR 1.7 (95% CI: 1.1–2.5).	NR
Fallah et al. 2014 [29]	12,207	NR	NHL 4.4 (3.6–5.3)	NR
Hemminki et al. 2012 [33]	7624	NR	Lung 2.47 (1.97–3.05)	NR
Hemminki et al. 2012 [47]	86,627 (patient years)	NR	NR	Other female genital cancers ⁵ 2.97 (1.41–5.48)
Hidalgo-Conde et al. 2013 [11]	175	3.6 (1.5–8.6)	NR	NR
Kang et al. 2010 [14]	914	1.45 (0.74–2.16)	NHL 15.4 (2.9–37.7) Bladder 43.6 (8.2–106.8)	NR
Kim et al. 2015 [40]	14,513	NR	Cervical dysplasia and cancer HR 1.53 (1.07 - 2.19)	NR
Liang et al. 2012 [22]	2,150	HR 1.26 (0.99–1.59)	Prostate HR 3.78 (1.30–11.0)	NR
Lin et al. 2012 [28]	9,349	NR	Hematologic (all) 3.41 (2.41–4.82) Lymphoid 3.30 (2.20–4.93) Myeloid 2.86 (1.49–5.09)	NR
Liu et al. 2013 [43]	7,624	NR	Bladder 2.28 (1.62–3.12)	NR
Mellemkjaer et al. 1997 [6]	1,585	RR 1.30 (1.06–1.58)	Liver RR 8.0 (2.6–18.6) Lung RR 1.9 (1.1–3.1) NHL RR 5.2 (2.2–10.3) Vagina/vulva RR 5.7 (1.2–16.6)	NR
Nived et al. 2001 [18]	116	SMR 2.24 (0.6–5.7) for males, 1.02 (0.4–2.1) for females	NHL SMR 11.63 (1.4–42.0) Prostate SMR 6.41 (1.3–18.7)	NR
Parikh-Patel et al. 2008 [2]	30,478	1.14 (1.07–1.20)	Follicular lymphoma 2.89 (1.88–4.22) HL 3.02 (1.60–5.13) Kidney 2.15 (1.52–2.94) Large B-cell lymphoma 3.26 (2.33–4.39) Leukemia 2.13 (1.49–2.77) Liver 2.70 (1.54–4.24) Lung 1.66 (1.45–1.90) Myeloid 2.96 (1.99–4.26) NHL 2.74 (2.22–3.34) Thyroid 1.83 (1.24–2.62) Vagina/vulva 3.27 (2.41–4.31)	Breast 0.76 (0.67–0.86) Cervix 0.55 (0.39–0.75) Prostate 0.69 (0.50–0.93) Uterus 0.60 (0.40–0.87)
Pettersson et al. 1992 [8]	205	RR 2.6 (1.5–4.4)	NHL RR 44 (11.9–111) Soft tissue sarcomas RR 49 (6.0–177)	NR
Ragnarsson et al. 2003 [19]	238	1.38 (0.89–1.87)	CML 88.95 (2.37–450) Hematological 8.89 (2.45–22.4) Squamous cell skin 6.43 (1.31–18.5)	NR
Ramsey-Goldman et al. 1998 [9]	616	2.00 (1.4–2.9)	Lung 3.1 (1.3–7.9)	NR
Sweeney et al. 1995 [16]	219	1.36 (0.50–2.96)	NR	NR
Sultan et al. 2000 [17]	276	1.16 (0.55–2.13)	NR	NR
Tarr et al. 2007 [15]	860	0.89 (0.63–1.23)	NR	Skin ⁶ 0.04 (0.001–0.24)

Author, yr (reference)	SLE sample size	SIR ² (95% CI) for overall risk of malignancy	SIR ² (95% CI) for higher risk site-specific malignancies	SIR ² (95% CI) for lower risk site-specific malignancies
Wadstrom et al. 2017 [39]	4,976	NR	Cervical neoplasia HR 2.12 (1.65–2.71)	NR

¹ Studies were excluded if they did not report an overall risk of malignancy or an increased or decreased risk of any site-specific malignancy including [36, 42, 129].

² SIR standardized incidence ratio, unless otherwise specified in the table.

³ Others include lymphosarcoma, reticulosarcoma, multiple myeloma, and other immunoproliferative neoplasms.

⁴ Others include: hepatobiliary, breast, uterus, cervix, skin, oropharynx/larynx, stomach, esophagus, pancreas, cancer of ill-defined sites, brain, and thyroid

⁵ Other female genital cancer included vagina, vulva (largest case numbers) and other parts, not including cervical, ovarian, endometrial

⁶ Not including basal cell carcinoma

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; CML, chronic myeloid leukemia; HL, Hodgkin's lymphoma; HR, hazard ratio; IR, incidence risk; IRR, incidence rate ratio; NHL, Non-Hodgkin's Lymphoma; NR, none reported; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized morbidity rates; yr, year

Table 2.
Meta-analyses on Risk of Overall and Site-specific Malignancies in SLE Adult Patients

Author, yr (reference)	Studies included	Calendar period	Number of studies	SLE sample size	Patient Years	Pooled SIR ^I (95% CI) for overall risk of malignancy	Pooled SIR ^I (95% CI) for higher risk site-specific malignancies	Pooled SIR ^I (95% CI) for lower risk site-specific malignancies
Apor et al. 2014 [31]	[1-3, 5, 6, 8, 14, 15]	1958-2009	8	67,929	NR	NR	Hematologic 2.9 (2.0-4.4) HL 3.1 (2.1-4.4) Leukemia 2.3 (1.9-2.7) MM 1.5 (1.0-2.0) NHL 5.7 (3.6-9.1)	NR
Bernatsky et al. 2011a [50]	[2, 5, 6, 130]	1958-2002	4	6,068	38,186	NR	NR	Prostate 0.72 (0.57-0.89)
Bernatsky et al. 2011b [52]	[2, 5, 6, 14, 130, 131]	1958-2002	5 unique studies	47,325	282,553	NR	NR	Breast 0.76 (0.69-0.85) Endometrial 0.71 (0.55-0.91) Ovarian 0.66 (0.49-0.90)
Cao et al. 2015 [25]	[1, 2, 4-9, 14-20, 23]	1951-2009	16	59,662	NR	RR 1.28 (1.17-1.41)	Bladder RR 2.11 (1.12-3.99) Esophageal RR 1.86 (1.21-2.88) HL RR 3.26 (2.17-4.88) Laryngeal RR 4.19 (1.98-8.87) Leukemia RR 2.01 (1.61-2.52) Liver RR 3.21 (1.70-6.05) Lung RR 1.59 (1.44-1.76) MM RR 1.45 (1.04-2.03) NHL RR 5.40 (3.75-7.77) Non-melanoma skin RR 1.51 (1.12-2.03) Thyroid RR 1.78 (1.35-2.33) Vaginal/vulvar cancer RR 3.67 (2.80-4.81)	Skin melanoma RR 0.65 (0.50-0.85)
da Silva Aoki et al. 2017 [27]	[1-4, 7, 8, 11, 13, 45, 68, 129, 132-150]	1958-2009	30	96,578 (adult and pediatric)	NR	Adult rate 4.2% (0.0318-0.0531) Pediatric rate 0.5% (0.0003-0.0154)	NR	NR
Huang et al. 2014 [51]	[1-5, 7, 14, 15, 18, 19, 23]	1951-2009	12	68,366	NR	NR	Kidney 2.29 (1.25-4.18)	Prostate 0.77 (0.69-0.87)
Mao et al. 2016 [26]	[1-3, 5-8, 10, 11, 13-15, 17, 22, 23, 33, 35]	1958-2009	18	86,069	NR	IR 1.44 (1.23-1.69)	Anal IR 1.79 (1.50-2.14) Cervical IR 1.72 (1.02-2.93) Esophagus IR 1.64 (1.43-1.88) Head and neck IR 2.31 (1.54-3.47) Hematological (all) IR 3.36 (1.66-6.80) Kidney IR 2.00 (1.00-3.99) Leukemia IR 2.12 (1.59-2.84) Liver/Gallbladder IR 2.01 (1.52-2.65)	Colon/rectum IR 0.83 (0.79-0.87) Ovary IR 0.72 (0.65-0.80)

Author, yr (reference)	Studies included	Calendar period	Number of studies	SLE sample size	Patient Years	Pooled SIR ^I (95% CI) for overall risk of malignancy	Pooled SIR ^I (95% CI) for higher risk site-specific malignancies	Pooled SIR ^I (95% CI) for lower risk site-specific malignancies
							Lung IR 1.59 (1.30–1.93) NHL IR 5.15 (2.18–12.14) Pancreas IR 1.47 (1.14–1.88) Thyroid IR 2.04 (1.50–2.77) Vagina/vulva IR 4.04 (3.00–5.43)	
Ni et al. 2014 [24]	[2, 5, 6, 14, 15, 33, 68]	1958–2009	7	63,585	360,211	1.16 (1.12–1.21)	Liver 2.44 (1.46–4.05) Lung 1.68 (1.33–2.13)	Prostate 0.71 (0.57–0.89)
Wu et al. 2016 [44]	[1, 2, 4-7, 9, 15, 17-19, 23]	1958–2009	12	57,890	NR	NR	Lung OR 1.60 (1.44–1.77)	NR
Zard et al. 2014 [48]	[151-157]	2001–2012	7	416	NR	NR	Cervical dysplasia OR 8.66 (3.75–20.00)	NR
Zhang et al. 2014 [46]	[1-5, 14, 19]	1958–2009	7	66,093	NR	NR	Thyroid 2.22 (2.11–2.34)	NR

^ISIR standardized incidence ratio, unless otherwise specified in the table.

Abbreviations: CI, confidence interval; HL, Hodgkin's lymphoma; IR, incidence rates; NHL, Non-Hodgkin's lymphoma; OR, odds ratio; MM, multiple myeloma; NR, none reported; SIR, standardized incidence ratio; SMR, standardized morbidity rates; yr, year

Table 3.Potential risk factors¹ mediating the development of malignancy in SLE

Risk Factor	Adjusted HR ² (95% CI) for risk of malignancy	References
Immunosuppressive therapies (excluding antimalarials and steroids)	Cervical neoplasia 1.83 (1.15-2.91) ³ Hematologic 2.29 (1.02-5.15) ⁴	[39] [67]
Cyclophosphamide	Hematologic 3.55 (0.94-13.37) ⁴ Lymphoma 1.90 (1.02 – 3.53) ⁵ Overall OR 1.09 (1.04-1.13) ⁶	[67] [68] [71]
Antimalarials	Overall OR 0.93 (0.90-0.97) ⁶	[71]
Steroids	Lymphoma 1.94 (1.11 – 3.39) ⁵	[68]
Clinical		
Disease damage	Overall 3.07 (1.97 – 4.81)	[67]
Sjögren's Syndrome	Lymphoma 1.94 (1.04-3.61) ⁵	[68]
Antibodies and Immune Dysregulation		
3E10 antibody	Overall (potentially increased risk)	[78]
5C6 antibody	Breast (potentially decreased risk)	[79]
Anti-phospholipid antibodies	Hematologic (potentially increased risk)	[80]
BAFF	Hematologic (potentially increased risk)	[83]
APRIL	Hematologic (potentially increased risk)	[83]
Environment		
Tobacco use	Lung 3.60 (1.32-9.83) 6.35 (2.43 - 16.6)	[67] [88]
Low levels of hormones	Breast and prostate (potentially decreased risk)	[91]
HPV	Anal SIR 26.9 (8.7 – 83.4) Cervical dysplasia Vaginal/vulvar SIR 9.1 (2.3 – 36.5)	[4] [95] [4]
Genetics		
rs9888739 (chromosome 16p11.2)	Breast OR 0.91, p <0.05	[98]
CD40 allele rs4810485 (chromosome 20q13)	DLBCL OR 1.09 (1.02-1.16)	[99]
HLA allele rs1270942 (chromosome 6p21.33)	DLBCL OR 1.17 (1.01-1.36)	[99]
TNFAIP3 or A20 rs77191406 polymorphism	Hematologic/bladder (potentially increased risk)	[105]
rs13194781 and rs1270942 (chromosome 6p21-22)	Lung (potentially increased risk)	[106]
Low levels of heat shock protein 27	Breast and prostate (potentially decreased risk)	[109]

¹ Studies were excluded if they did not report a significantly increased or decreased risk of overall or any site-specific malignancy including [6, 40, 73, 95].

² Hazard Ratio unless otherwise specified in the table

³ The reference group is antimalarial users

⁴ Risk when immunosuppressant exposures were lagged by 5 year periods.

⁵ Partially adjusted model

⁶ Associated with dose dependent effect. Did not adjust for disease activity or damage

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; HPV, human papilloma virus; NR, none reported; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio

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