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Updated insights into cancer risk and pathogenesis in systemic lupus erythematosus; a nephrology viewpoint on recent evidence

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ABSTRACT

Patients with systemic lupus erythematosus (SLE) exhibit a distinct cancer risk profile characterized by increased susceptibility to hematologic malignancies such as non-Hodgkin lymphoma (NHL), as well as certain solid tumors like lung, thyroid, and hepatobiliary cancers. Conversely, they also demonstrate a reduced risk for some cancers including breast, melanoma, and prostate cancer. This unique pattern is influenced by a combination of disease-related immune dysregulation and treatment-related factors. Additionally, immunosuppressive therapy administered in SLE management, including agents like cyclophosphamide, is known to contribute to an elevated risk of malignancies such as cervical dysplasia and certain hematologic cancers. However, specific immunosuppressants like calcineurin inhibitors have shown no significant increase in cancer incidence in some cohorts, suggesting that cancer risk is multifactorial and may depend on the type and duration of immunosuppression. However, in SLE patients, screening practices for cancers like cervical cancer are suboptimal despite their increased risk. However, some studies have found lower cervical cancer screening rates in women with SLE compared to control subjects, which influenced by factors like age, income, and comorbidities. Improved screening uptake is crucial for early cancer detection and better outcomes in this vulnerable population. Moreover, lupus nephritis enhances cancer risk and progression through complex interplay of chronic inflammation, immune dysregulation, treatment effects, and molecular pathway alterations. Inflammation-induced oxidative stress and impaired autophagy, combined with immunosuppressive therapies, provide a background for malignant transformation and decreased tumor immune surveillance.

Review

Implication for health policy/practice/research/medical education:
Several factors are thought to contribute to the altered cancer risk in systemic lupus erythematosus, including chronic inflammation, immune disorders, certain therapies, overlap syndromes of connective tissue diseases, viral infections, and traditional cancer risk factors. Lymphomagenesis in systemic lupus erythematosus (SLE) has been linked to increased activity of multiple inflammatory cytokines and potential viral diseases. The decreased rates of hormone-sensitive cancers like breast and prostate are speculated to be related to the presence of lupus autoantibodies and down-regulation of specific proteins in SLE. Smoking is also identified as a significant etiologic parameter for malignancy development in SLE, with lung cancer risk in SLE patients who smoke increasing approximately fourfold. The risk of breast tumors in SLE may also be influenced by autoantibodies or drugs like antimalarial agents. Cancer development in SLE is correlated with longer disease duration and older age of SLE onset. Patients with SLE who are exposed to immunosuppressive drugs are at higher risk for human papillomavirus (HPV)-related cervical cancer too.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by loss of immune tolerance, production of autoantibodies, immune complex deposition, and subsequent inflammation and tissue damage affecting virtually any organ system (1). Over the past two decades, substantial advances in understanding the immunopathogenesis of SLE have been made, revealing intricate interactions among genetic, epigenetic, hormonal, and environmental factors that contribute to disease onset and flares (1). Concurrently, epidemiological and clinical research has increasingly highlighted a complex and nuanced relationship between SLE and cancer risk. Historically, SLE has been associated with both increased and decreased risks of specific malignancies, but the mechanisms underlying these associations have remained incompletely understood (2). Recent evidence, however, has begun to clarify the biological plausibility of these epidemiological observations, linking chronic immune dysregulation, persistent inflammation, immunosuppressive therapies, and viral co-infections to altered oncogenic pathways (1, 3). This narrative review considers updated insights into cancer risk and pathogenesis in SLE.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords like lupus nephritis, cancer risk, oxidative stress, systemic lupus erythematosus and inflammation

Cancer risk in SLE

The overall cancer risk in SLE appears modestly elevated compared to the general population, with standardized incidence ratios (SIRs) typically ranging from 1.1 to 1.5 in most population-based studies (4). However, this aggregate figure masks substantial heterogeneity across specific cancer types (4). Hematologic malignancies, particularly non-Hodgkin lymphoma (NHL), consistently demonstrate the highest relative risk among SLE patients (5). A previous meta-analysis by Pego-Reigosa et al, reported SIRs for NHL in SLE ranging from 3.0 to 5.0, with some individual cohorts reporting even higher risks, especially in the first few years following SLE diagnosis (6). Pego-Reigosa et al also found that, the elevated risk is not merely an artifact of surveillance bias (6); rather, it reflects shared pathogenic mechanisms between autoimmunity and lymphomagenesis (6). Chronic B-cell activation, a hallmark of SLE, creates a permissive environment for malignant transformation (7). Persistent antigenic stimulation, whether from self-antigens, immune complexes, or viral triggers such as Epstein-Barr virus (EBV) drives B-cell proliferation and somatic hypermutation (8). Over time, this condition can lead to the accumulation of genetic aberrations, including translocations involving immunoglobulin loci and oncogenes like BCL2 or MYC, which are commonly observed in NHL subtypes such as diffuse large B-cell lymphoma (9). Moreover, defects in immune surveillance, particularly impaired natural killer cell and cytotoxic T-cell function, which are well-documented in SLE, may further compromise the body's ability to eliminate nascent malignant clones (10,11). The role of EBV in this context warrants particular attention (12). Nearly all adults are seropositive for EBV, but in SLE, viral reactivation is more frequent due to immune dysregulation and immunosuppressive therapy (13). Epstein–Barr virus encodes latent proteins that can inhibit apoptosis, promote cell cycle progression, and interfere with DNA repair mechanisms, all of which are conducive to oncogenesis (14). Recent studies using high-throughput sequencing have identified clonal EBV integration in lymphoma tissue from SLE patients, suggesting a direct oncogenic role (15). Also, the cytokine milieu in SLE, rich in B-cell activating factor (BAFF), interleukin-6 and type I interferons, provides a fertile ground for B-cell survival and expansion (16). BAFF, in particular, is often markedly elevated in SLE serum and correlates with disease activity (17); transgenic mouse models overexpressing BAFF develop both lupus-like autoimmunity and B-cell lymphomas, underscoring its dual pathogenic role (18). Beyond NHL, other hematologic cancers also show elevated incidence in SLE, albeit to a lesser extent (2,19). Hodgkin lymphoma risk is increased approximately twofold, though the data are less consistent than for NHL (19). On the other hand, multiple myeloma and leukemia also appear modestly elevated in some studies, but sample sizes are often too small to draw definitive conclusions (4,20). The shared immunological underpinnings of chronic inflammation, impaired tumor surveillance, and therapy-related mutagenesis likely contribute to this broader hematologic cancer susceptibility (2,19). In contrast to hematologic malignancies, the risk of solid tumors in SLE is more variable and, in some cases, paradoxically reduced (21). Lung cancer, for instance, shows a consistent and significant increase in risk across multiple cohorts. This elevation persists even after adjusting for smoking, suggesting that SLE-related factors independently contribute to pulmonary carcinogenesis (22). Chronic lung inflammation, whether from pleuritis, interstitial lung disease, or recurrent infections, may promote a pro-tumorigenic microenvironment through oxidative stress, DNA damage, and the release of growth factors (23). Furthermore, long-term administration of cyclophosphamide as a known bladder and lung carcinogen, has been implicated in this association, although recent

studies indicate that the increased lung cancer risk remains significant even among patients not exposed to this agent, pointing to disease-related mechanisms as primary drivers (24). Cervical cancer risk is also notably elevated in SLE, which is largely attributed to persistent high-risk human papillomavirus (HPV) infection, which is more common and less effectively cleared in SLE patients due to impaired cell-mediated immunity (25). Immunosuppressive therapies, particularly long-term corticosteroid and mycophenolate use, further dampen antiviral immune responses, facilitating HPV integration into host DNA and progression to high-grade dysplasia and invasive carcinoma (26). Importantly, despite widespread availability of HPV vaccination and cervical screening programs, adherence among SLE patients remains suboptimal in many regions, exacerbating this risk (27). Recent guidelines now strongly recommend HPV vaccination for all SLE patients before initiation of immunosuppression and emphasize the need for rigorous cervical surveillance (27). Likewise, liver cancer, particularly hepatocellular carcinoma, is another malignancy with increased incidence in SLE (28). While hepatitis B and C co-infections contribute to this risk (28), emerging evidence suggests that SLE-related chronic inflammation and metabolic dysfunction, such as non-alcoholic fatty liver disease, which is more prevalent in SLE due to corticosteroid use and disease activity may independently promote hepatic carcinogenesis (29, 30). Furthermore, some immunomodulatory drugs used in SLE, including azathioprine, have been associated with hepatotoxicity and potential genotoxic effects, although causality remains uncertain (31). Conversely, certain solid tumors demonstrate reduced incidence in SLE (32). The reasons for this protective effect are multifactorial. Hormonal influences are paramount: SLE predominantly affects women of reproductive age, yet many experience menstrual irregularities, premature ovarian insufficiency, or early menopause due to disease activity or cyclophosphamide exposure (33). Lower cumulative estrogen exposure may reduce the risk of hormone-sensitive cancers (34,35). In addition, frequent use of hydroxychloroquine (HCQ), as a cornerstone of SLE therapy has been linked to anti-neoplastic properties (36). Previous studies found that, HCQ inhibits autophagy, a cellular recycling process that can support tumor cell survival under stress, and modulates signaling pathways such as PI3K/AKT/mTOR, which are frequently dysregulated in breast cancer (37). Observational studies suggest that long-term HCQ use is associated with a slight reduction in breast cancer incidence among SLE patients, though randomized controlled trials are lacking (38). Furthermore, prostate cancer appears less common in SLE, though data are limited given the lower prevalence of SLE in men (39). The mechanisms may involve altered androgen metabolism or immune-mediated tumor surveillance, but this finding remains speculative (39). Similarly, colorectal cancer risk is generally neutral or slightly reduced in most large cohorts, possibly due to anti-inflammatory effects of HCQ or other SLE treatments, though findings are inconsistent (40,41).

Immunosuppressive therapy and cancer risk

The impact of immunosuppressive therapy on cancer risk in SLE is a critical and evolving area of research (41). Historically, concerns centered on alkylating agents like cyclophosphamide, which unequivocally increase the risk of bladder cancer and possibly the hematologic malignancies. However, contemporary SLE management favors lower cumulative doses and shorter durations of cyclophosphamide, mitigating but not eliminating this risk (42,43). Azathioprine, another commonly used agent, has been associated with increased skin cancer risk, particularly squamous cell carcinoma, likely due to its photosensitizing and DNA-damaging properties (44). Likewise, mycophenolate mofetil (MMF), now widely administered as a steroid-sparing agent, appears to have a more favorable oncologic profile (45); large registry studies have not shown a significant increase in overall cancer risk with MMF, though long-term data are still maturing (46). Biologic therapies, particularly B-cell–targeted agents like rituximab and belimumab, have raised theoretical concerns about lymphoma risk given their mechanism of action (47,48). However, real-world evidence to date is reassuring. Besides, rituximab, as a CD20-depleting monoclonal antibody has not been linked to increased NHL incidence in SLE cohorts (49,50); in fact, by reducing chronic B-cell activation, it may lower long-term lymphoma risk (50). Likewise, belimumab, which inhibits BAFF, similarly shows no signal for increased malignancy in post-marketing surveillance (51). Nevertheless, vigilance remains warranted, especially as these agents are used earlier in the disease course and for longer durations (52). Corticosteroids, while indispensable in SLE management, present a double-edged sword in cancer risk (53). High-dose, long-term glucocorticoid use is associated with increased infection-related cancers (e.g., cervical, liver) due to immunosuppression, but may exert anti-inflammatory and anti-proliferative effects that reduce risk for other cancers (54). The net effect likely depends on dose, duration, and cancer type, complicating risk stratification (54). Beyond pharmacologic factors, intrinsic disease characteristics significantly modulate cancer risk (55). Higher SLE disease activity, as measured by indices like SLEDAI (systemic lupus erythematosus disease activity index), is independently associated with increased overall cancer risk, particularly for NHL and lung cancer (56). This finding accentuates the importance

of achieving and maintaining remission not only for organ protection but also for cancer prevention (2). Conversely, damage accrual, as captured by the SLICC/ACR damage index may reflect cumulative exposure to both disease and treatment-related carcinogenic factors, further elevating risk (57).

Genetic overlap between SLE and cancer

Recent advances in molecular epidemiology have begun to unravel the genetic overlap between SLE and cancer (32). Genome-wide association studies have identified shared susceptibility loci, such as those in the HLA region, STAT4, and TNFAIP3, which influence both autoimmune dysregulation and tumor suppression or oncogenesis (58). For example, TNFAIP3 encodes A20, a negative regulator of NF-κB (nuclear factor-κB) signaling; loss-of-function variants predispose to SLE and are also found in various lymphomas, where they promote cell survival and proliferation (59). Correspondingly, polymorphisms in DNA repair genes like ATM and BRCA1/2, traditionally linked to hereditary cancer syndromes, have been associated with increased SLE risk, suggesting a common pathway of genomic instability (60). Meanwhile, epigenetic modifications, particularly DNA hypomethylation, are central to SLE pathogenesis and may also contribute to oncogenesis (61). Global hypomethylation in T cells and other immune cells leads to overexpression of normally silenced genes, including proto-oncogenes and endogenous retroviral elements, fostering autoimmunity and potentially malignant transformation (62,63). MicroRNA dysregulation, another epigenetic hallmark of SLE, affects key oncogenic and tumor-suppressor pathways (64); for instance, miR-146a, which is often downregulated in SLE, normally suppresses NF-κB signaling and is also a tumor suppressor in several cancers (65).

The concept of tumor microenvironment in SLE

The tumor microenvironment in SLE patients may also be uniquely permissive to cancer development (66). Chronic type I interferon signaling, a defining feature of SLE, can have paradoxical effects (67); while it strengthens antiviral immunity, it may also promote angiogenesis, epithelial-mesenchymal transition, and immune evasion in established tumors (68). In addition, the abundance of regulatory T cells (Tregs) and myeloid-derived suppressor cells in SLE, initially compensatory to curb autoimmunity can inadvertently suppress antitumor immunity, facilitating cancer progression (69). Emerging data also highlight the role of the microbiome in modulating cancer risk in SLE (70). Dysbiosis of the gut microbiota, commonly observed in SLE, can influence systemic inflammation, metabolite production (e.g., short-chain fatty acids), and immune cell function, potentially affecting carcinogenesis (71). For example, reduced microbial diversity and overrepresentation of pathobionts may increase intestinal permeability, allowing bacterial translocation and chronic endotoxin exposure, which can drive hepatic and colonic inflammation and neoplasia (72).

Cancer enhancement effect of lupus nephritis

Lupus nephritis as a severe manifestation of SLE, is primarily characterized by immune complex deposition and immune-mediated injury to the kidneys (73). This disease chiefly affects renal function (74); however, much attention has increasingly directed toward a concerning association between lupus nephritis and cancer risk, with evidence pointing to mechanisms that may enhance cancer development and progression in this autoimmune context (32,75). As like SLE, patients with lupus nephritis display chronic systemic inflammation, immune dysregulation, and persistent tissue damage that can create a microenvironment conducive to oncogenesis (76). Chronic inflammation, a hallmark of lupus nephritis, contributes to increased oxidative stress, DNA damage, and impaired apoptosis, all of which are established cancer-promoting factors (77). The sustained production of inflammatory cytokines and chemokines incites a pro-tumorigenic milieu by promoting mutagenic lesions, supporting tumor cell survival, and enhancing angiogenesis (78). Specifically, kidney inflammation induces local and systemic immune responses, potentially facilitating malignant transformation in renal tissues or other organ sites (79). In addition to inflammation, immunosuppressive therapies commonly employed in lupus nephritis patients, such as cyclophosphamide, corticosteroids, and calcineurin inhibitors, may elevate cancer risk (80). Though these treatments are necessary to control autoimmune activity (81); nevertheless, they can impair immunosurveillance allowing pre-malignant or malignant cells to evade detection and elimination by the immune system (1). Previous authors found that, prolonged cyclophosphamide administration has been linked to increased risks of bladder cancer and hematologic malignancies (42). Conversely, recent investigations suggest that calcineurin inhibitors may not significantly raise cancer risk, though findings are not fully consistent across studies (82). Similarly, genetic and molecular alterations underlying lupus nephritis also intersect with pathways implicated in cancer biology (83). Dysregulation of signaling cascades such as AMPK/mTOR, which govern cell growth, autophagy, and metabolic homeostasis, have been observed in lupus nephritis and are well-known contributors to tumor development when aberrantly modulated (84). Previous

studies found that, lupus nephritis has been associated with enhanced mTOR activation and reduced autophagic activity, mechanisms that can foster cell proliferation and resistance to cell death, thereby potentially promoting malignancy (76). Moreover, transcription factors like HDAC6, MAFF, and KLF5, which are dysregulated in renal fibrosis and inflammation, relate mechanistically to processes of cellular transformation and tumor progression (85). Accordingly, the immunological milieu in lupus nephritis further alters T cell subsets, including expansions of dysfunctional PD-1+CD8+ T cells that exhibit exhausted phenotypes (76). While the T cell exhaustion may impede effective anti-tumor immunity, it also represents a complex regulatory node in the balance between autoimmunity and cancer (76). Additionally, autoantibodies, immune complexes, and complement activation characteristic of lupus nephritis may induce tissue remodeling and damage that disrupt normal cellular environments, potentially facilitating oncogenic processes (86,87). As mentioned above, epidemiologically, patients with SLE and lupus nephritis have been found to have an overall increased risk of several malignancies, particularly hematologic cancers (such as NHL) and certain solid tumors including lung, liver, and colon cancers (32,88). Preliminary studies have reported that cancer occurs more frequently in lupus nephritis patients than in those with SLE without nephritis, possibly reflecting the severity of immune dysregulation and cumulative immunosuppressive exposure (88). The mechanisms linking lupus nephritis to cancer risk remain only partially understood, but the combination of chronic immune activation, renal injury, altered immune surveillance, and treatment-related factors constitutes a plausible multifactorial basis (1).

Cancer screening in SLE

From a clinical perspective, these insights necessitate a paradigm shift in the long-term management of SLE (89). Cancer screening should be individualized based on SLE-specific risk factors, not merely general population guidelines (90). For instance, SLE patients should undergo more vigilant cervical screening, consider low-dose CT for lung cancer if additional risk factors (e.g., smoking, interstitial lung disease) are present, and receive counseling on HPV vaccination (27,91). Minimizing cumulative exposure to high-risk immunosuppressants, prioritizing HCQ use, and aggressively controlling disease activity are key strategies to mitigate cancer risk (92). Furthermore, patient education about lifestyle modifications smoking cessation, sun protection, healthy diet remains essential (93).

Conclusion

This narrative review found that the relationship between SLE and cancer is complex, dynamic, and shaped by a confluence of immunological, therapeutic, genetic, and environmental factors. While the absolute increase in cancer risk for most SLE patients remains modest, the relative risks for specific malignancies, particularly NHL, lung, cervical, and liver cancers, are substantial and clinically significant. Conversely, the reduced risk of certain hormone-related cancers offers intriguing insights into shared pathogenic pathways. As our understanding of the molecular links between autoimmunity and oncogenesis deepens, so too does our ability to tailor SLE management to not only control disease activity but also optimize long-term oncologic outcomes. Hence, continued vigilance, personalized risk assessment, and multidisciplinary care are necessary in navigating this intricate intersection of autoimmunity and cancer.

Authors' contribution

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Writing–original draft: All authors.
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Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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