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Cancer and Autoimmunity: Harnessing Longitudinal Cohorts to Probe the Link

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Abstract

In many autoimmune rheumatic diseases, there is an increased risk of cancer compared to the general population. While reasons for this increased risk have not been elucidated, it has been hypothesized that the link between cancer and autoimmunity may be bidirectional. For instance, chronic inflammation and damage from the rheumatic disease or its therapies may trigger malignant transformation; conversely, anti-tumor immune responses targeting cancers may become cross-reactive resulting in autoimmunity. In rare rheumatic diseases, longitudinal observational studies can play a critical role in studying these complex relationships, enabling investigators to quantify the extent of cancer risk, identify unique clinical phenotypes that associate with cancer, investigate the biological link between these conditions, and define optimal strategies to screen for and treat underlying cancer. In this review, we discuss recent data on cancer in the rheumatic diseases, and suggest a research agenda to address the many gaps in our current knowledge base.

Keywords

Cancer; autoimmunity; observational cohorts; epidemiology

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Introduction

Autoimmune conditions have long been associated with an increased risk of malignancy. While the pathogenic mechanisms underlying an increased cancer risk are not fully understood, the link between cancer and autoimmunity is likely dynamic and bidirectional in nature [1*]. Multiple immune and inflammatory pathways may activate tumorigenesis, and data suggest that active, inflammatory rheumatic disease may contribute to cancer initiation and promotion. Similarly, anti-tumor immune responses that limit tumor growth may become cross-reactive with self-tissue resulting in autoimmunity. Given the difficulty in measuring relatively rare outcomes such as cancer in the rheumatic diseases, large longitudinal epidemiological studies provide a rich opportunity to understand the relationships between malignancy and autoimmunity. In this review, we discuss recent data on cancer in the rheumatic diseases, and suggest a research agenda to address the many gaps in our current knowledge base.

Mechanisms that may explain the increased risk of cancer in the autoimmune rheumatic diseases

An increased risk of cancer has been demonstrated across the broad spectrum of autoimmune rheumatic diseases. While it is beyond the scope of this article to review cancer risk in detail for all of the rheumatic diseases, Table 1 describes the magnitude of risk and specific tumor sites of concern based on recently published meta-analyses for select diseases. A wide array of cancer types is observed, with an increased risk of both solid organ and hematologic malignancies.

The relationship between cancer and the autoimmune rheumatic diseases is complex with many potential mechanisms linking the two disease states (Table 2). Malignancy may develop secondary to the rheumatic disease and its therapies. For instance, it has been proposed that chronic inflammation and tissue damage may stimulate cytokines and chemokines that further the development of malignancies through multiple mechanisms, including inducing DNA damage, inactivating tumor suppressor genes, stimulating enhanced cellular growth and survival, triggering angiogenesis, and enhancing invasion [8]. Within the rheumatic diseases, a model of inflammation-induced cancer may be particularly important in SLE (detailed below), but there are also data to suggest this mechanism could be relevant in Sjogren's syndrome, rheumatoid arthritis and systemic sclerosis (SSc). In Sjogren's syndrome, studies have demonstrated that salivary gland enlargement, hypocomplementemia, neutropenia, cryoglobulinemia, splenomegaly, lymphadenopathy, longer disease duration, and lymphoid organization in labial salivary gland biopsies at diagnosis are predictive of lymphoma risk [9–11]. In rheumatoid arthritis, an increased risk of cancer and greater cancer mortality has been observed in patients who have elevated inflammatory markers [12]. Additionally a case control study examining RA patients with lymphoma compared to RA controls suggested that longer duration corticosteroid therapy, and intra-articular steroids used to treat acute flares, were associated with a lower risk of lymphoma [13]. In SSc, multiple studies have demonstrated an increased risk of lung cancer in patients with interstitial lung disease, although this has not been found consistently across

all studies [14, 15]. However, data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, which enrolled over 65,000 individuals, has demonstrated that baseline pulmonary scar is associated with future ipsilateral lung cancer, suggesting that this mechanism may also apply in patients with SSs [16, 17].

In addition to disease activity and damage, anti-rheumatic disease therapies may increase the risk of subsequent malignancy. In particular, cyclophosphamide is an alkylating agent that causes crosslinking of DNA strands, thereby impeding cell division and resulting in apoptosis [18]. Acrolein, a metabolite of cyclophosphamide, is excreted by the kidneys and concentrated in the urine. This is thought to cause bladder toxicity including cystitis and cancer. Additional data on cancer risk with cyclophosphamide use is mixed due to varying diseases under study, route of drug administration, dosing and duration of therapy [18]. However, studies have demonstrated that higher cumulative doses, an oral route of administration, and current or former smoking all associate with a higher risk of subsequent cancer [18, 19]. Data on cancer risk with mycophenolate mofetil is less clear as most of the available data stem from the transplant literature where patients are on multiple concomitant immunosuppressive therapies [20–23]. Some studies suggest an increased risk of non-melanoma skin cancers and lymphomas, whereas others do not. Recent data suggest that primary CNS lymphoma risk may be increased in particular with mycophenolate use [24]. The risk of non-melanoma skin cancer is likely increased in patients with rheumatoid arthritis who are treated with TNF inhibitors, and some studies suggest the risk may also be increased for melanoma [25–28]. Annual total body skin examination and counseling about sunscreen use is recommended in this patient population.

Immune dysregulation from the disease or immunosuppressive therapies could also impact the ability to clear oncogenic infections. In a large study of 576 SLE patients, the risk of virus associated cancers was elevated (SIR 2.9), and this was noted in particular with human papillomavirus (HPV) associated malignancies including anal cancer (SIR 26.9), vaginal/vulvar cancer (SIR 9.1), cervical dysplasia/CIS (SIR 1.8) and non-melanoma skin cancers (SIR 2.0) [29]. The risk was also elevated for other potential virally associated cancers, including liver cancer (hepatitis B and C viruses), bladder cancer (polyoma virus), and non-Hodgkin's lymphoma (Epstein-Barr virus, EBV) [29].

While the focus of most research on the link between rheumatic diseases and cancer have focused on malignancies developing after rheumatic disease onset, it is important to note that some patients develop clinical manifestations of autoimmunity shortly after a diagnosis of cancer. This raises the question of whether anti-cancer therapies increase the risk of developing autoimmune diseases. For example, bleomycin and gemcitabine have been reported as potential triggers of skin sclerosis and development or exacerbation of Raynaud's phenomenon and ischemic digits [30–34]. Chemotherapeutic agents may cause direct vascular toxicity and neurotoxicity, potentially resulting in endothelial dysfunction and aberrant sympathetic arterial vasoconstriction [35]. Arthralgias, myalgias, lupus or RA-like syndromes, and reactive arthritis may also develop with various anti-cancer therapies [35]. Increasingly a wide array of immunotherapies, such as IL-2 therapy used for malignant melanoma and renal cell carcinoma, anti-tumor T cell infusions, cancer vaccines, and immune checkpoint inhibitors, are being deployed to treat cancer. These agents prime and

amplify the host immune response to destroy neoplastic cells, and there are reports of new autoimmune diseases developing and disease exacerbations in patients with previously quiescent rheumatic disease after exposure to immunotherapy agents [36–41]. As these drugs are increasingly being studied in clinical trials, it is likely that rheumatologists will see more patients where this mechanism of action is a concern. Lastly, radiation therapy may trigger severe skin thickening in patients with pre-existing SSc or new development of localized scleroderma [42, 43].

A subset of patients may have cancer-induced autoimmunity with diagnosis of cancer shortly preceding or following the first signs of the rheumatic illness [1*]. The two best examples of this are dermatomyositis and SSc (latter example discussed in detail below). In both diseases, patients have (i) an increased risk of cancer, (ii) a striking temporal relationship between cancer diagnosis and rheumatic disease onset, (iii) particular autoantibody subsets that associate with cancer at the time of rheumatic disease onset (e.g. anti-RNA polymerase III in SSc and anti-NXP2 and anti-TIF1 gamma in dermatomyositis), and (iv) an increased expression of disease-associated antigens in cancer tissues [1*, 44*–48*]. In dermatomyositis, the course of the disease also parallels the course of the cancer, with remission of dermatomyositis following effective cancer therapy and relapse of dermatomyositis heralding cancer relapse. Case reports of patients with concurrent cancer and SSc also suggest that cancer therapy may be effective anti-rheumatic disease therapy [49, 50].

In addition to these possibilities, patients may have a shared genetic susceptibility to develop both cancer and autoimmune disease, or a common inciting exposure could trigger both diseases [51]. Further study is required to define the role of genetics and environmental exposures in the link between cancer and autoimmunity.

Recent investigations have provided compelling evidence that the link between cancer and autoimmune rheumatic diseases may indeed be bidirectional in nature. Here we review more detailed data on two of these potential mechanisms, development of inflammation-induced cancer and cancer-induced autoimmunity, through the lens of SLE and SSc.

Inflammation-induced cancer: the example of SLE

Inflammation-induced malignancy has been appreciated for many years. However, the precise pathways underlying the transformation from benign inflammation to malignancy are not fully understood. Recent data have suggested that there is a slight but significant increased risk of overall malignancy in individuals with SLE compared to healthy controls [3*]. Altered cancer risk profiles in SLE are possibly due to both environmental and intrinsic dysregulation of immunity. From both epidemiologic and epigenetic data, a clear link exists between the presence of inflammatory cytokines and malignancy [8, 52]. Drawing from multiple clinical examples, we now know that uncontrolled hepatic inflammation from viral hepatitis clearly increases the risk of hepatocellular carcinoma, just as persistent *H. Pylori* gastritis increases the risk of gastric cancer [53]. In the case of SLE, hematologic malignancies represent the greatest incident malignancy risk [3*, 54*].

Using a large, multi-center and international cohort, Bernatsky *et al.* observed that the incidence and mortality of all hematologic malignancies was significantly elevated in SLE patients compared to the general population (standardized incidence ratio, SIR 3.02; 95% confidence interval, CI 2.48–3.63 and standardized mortality ratio, SMR 2.8; 95% CI, 1.2–5.6) [3*]. Similarly, a meta-analysis of five prospective cohort studies published between 2002 and 2013 also showed an increased risk of hematologic malignancy in SLE patients with a pooled SIR of 2.9 (95% CI, 2.0–4.4) [55]. Of the hematologic malignancies, the association was greatest for non-Hodgkin lymphoma, NHL (SIR 5.7; 95% CI, 3.6–9.1) [55]. The most common type of NHL in SLE is diffuse large B cell lymphoma (DLBCL), which can be further divided into germinal centre B-cell-like (GCB) and non-GCB (or activated B-cell-like) [56]. Preliminary evidence suggests that the non-GCB cell-of-origin DLBCL is more common in SLE, implying that lymphoma development in SLE and other autoimmune diseases may be secondary to chronic inflammatory stimulation [57]. Given that the incidence of malignancy is relatively rare, and in the context of long lead time, epidemiologic studies represent an interesting modality to study malignancy in autoimmune disease. In addition to the studies mentioned above, longitudinal epidemiologic studies have also been able to identify an increased risk of pulmonary, hepatic, and thyroid cancers in SLE, while the risk of breast and prostate cancers is reduced [58].

The precise pathways linking inflammation and malignancy in SLE are not completely understood. However, an important candidate pathway in the development of hematologic malignancy in SLE includes B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), inflammatory cytokines which promote B cell activation and contribute to disease activity in SLE [59, 60]. This same pathway may also be implicated in the pathophysiology of hematologic malignancies. BAFF and APRIL (which are part of the tumor necrosis factor [TNF] superfamily) are associated with activation of nuclear-factor kappaB (NF-κB). NF-κB is a group of nuclear transcription factors which control many cellular processes, including inhibition of cellular apoptosis and maintenance of cell survival [61]. Over the years, NF-κB has been implicated in the tumorigenesis of many cancer types, including hematologic, breast and gastric cancers [53, 61]. After staining for APRIL expression in lymphoma biopsies from individuals with RA, SLE and control cases, Lofstrom *et al.* were able to demonstrate a high expression of APRIL only in SLE-associated lymphoma cases (OR 23.6, 95% CI 2.4–231.2) [62*]. In addition, Epstein-Barr virus (EBV) in the lymphoma tissue was significantly associated with elevated APRIL expression [62*]. The identification of EBV in SLE-associated lymphomas also underlines the potential environmental risk factors which may contribute to malignancy development in inflammatory states. In particular, Epstein Barr virus (EBV), which is known to be implicated in the etiology of various hematologic malignancies, has been repeatedly investigated in SLE patients [63, 64]. In a recent meta-analysis, EBV antiviral capsid antigen was significantly associated with SLE, supporting the hypothesis that EBV infection may predispose to the development of SLE [65] and potentially explain some of the increased lymphoma risk in SLE patients. However, despite certain case-reports citing an association between immunosuppression and EBV in autoimmune conditions [66], larger population-based studies have failed to demonstrate a clear link between lymphoma and EBV in inflammatory diseases [67], and this remains an active area of research.

Cancer-induced autoimmunity: the example of systemic sclerosis

In many rheumatic diseases, subsets of patients are diagnosed with a malignancy around the time of clinical onset of the rheumatic disease, raising the question of whether autoimmunity is triggered by an underlying cancer. While this has been most notable in dermatomyositis [68–70], a similar pattern of contemporaneous cancer has been observed in SSc, particularly in patients with breast cancer although other tumor types may be observed [46, 71]. In an initial study of 23 patients with SSc and cancer from the Johns Hopkins Scleroderma Center cohort, patients with RNA polymerase III autoantibodies were found to have a striking clustering of cancer around the time of SSc onset, and this temporal relationship was not detected in patients with anti-centromere or anti-topoisomerase 1 antibodies [48*]. These patients had unique nucleolar RNA polymerase III expression in their cancerous tissues, suggesting that tumor autoantigen expression and SSc-specific immune responses were associated [48*]. The increased risk of cancer within a short interval of SSc onset among patients with RNA polymerase III autoantibodies has now been confirmed in multiple international SSc cohorts [46, 47, 72, 73]. In an Australian SSc cohort of 451 patients (64 (14.2%) with cancer), patients with RNA polymerase III autoantibodies had a 4.2-fold (95% CI 1.3, 13.4) increased risk of cancer within 5 years of SSc onset [73]. A UK SSc cohort of 2177 patients (154 (7.1%) with cancer) identified a 5.83-fold (95% CI 3.11, 10.92) increased risk of cancer within 3 years of SSc onset in patients with RNA polymerase III autoantibodies compared to those negative for these antibodies [46]. Similarly, in a study of 1044 patients at the Johns Hopkins Scleroderma Center (168 (16.1%) with cancer), a 5.08-fold (95% CI 1.60, 16.1) increased risk of cancer within 2 years of SSc onset was confirmed in patients with RNA polymerase III autoantibodies [47]. Each of these studies demonstrates the power of large observational cohort studies with long-term follow up data to probe the complex relationship between cancer and autoimmunity in rare rheumatic diseases.

In addition to investigating the epidemiologic associations between cancer and autoimmunity, these cohorts provide rich resources to study the biological links between cancer and autoimmunity. In the Johns Hopkins cohort, cancer tissue specimens and blood samples (including serum, DNA and peripheral blood mononuclear cells) were coupled with comprehensive clinical data to perform mechanistic studies based on the initial epidemiologic findings. This work demonstrated that genetic abnormalities (either somatic mutations and/or loss of heterozygosity) in *POLR3A*, the gene that encodes for RNA polymerase III, were uniquely present in cancers from patients with SSc and RNA polymerase III antibodies [74*]. Patients with somatic mutations in *POLR3A* had mutation-specific T cell immune responses and the development of cross-reactive RNA polymerase III autoantibodies [74*]. These data suggest that altered RNA polymerase III proteins in cancers can serve as immunogens that trigger an initial anti-tumor immune response that then becomes cross-reactive, resulting in the development of autoimmunity in SSc [1*]. Data in dermatomyositis suggest that a similar mechanism may be observed in other rheumatic diseases. In one investigation, myositis autoantigens were highly expressed in cancer types associated with myositis and in regenerating myoblasts in myositis muscle [44*]. Therefore, while malignancies may serve as an antigen source that initiates the immune response,

regenerating cells in target tissues may be an antigen source that propagates and sustains autoimmunity [1*].

Longitudinal observational studies provide the framework and foundation to study the links between cancer and autoimmunity

As rheumatologists, we are confronted with the challenges of identifying and treating patients with concomitant cancer and autoimmunity. Cancer screening is often in the purview of the rheumatologist for patients with autoimmune rheumatic diseases, but may be neglected in the context of managing complex, multiorgan disease. Furthermore, once a cancer is identified, there are limited data to guide how the presence of a rheumatic disease should alter cancer management, or how a cancer diagnosis should modify anti-rheumatic therapy. Longitudinal cohort studies can play a critical role in investigating these intertwined relationships between malignancy and autoimmunity in rare rheumatic diseases.

Thus far, observational cohorts have enabled investigators to define whether specific rheumatic diseases associate with an increased risk of individual tumor sites by comparing these data to that of regional cancer registries. While the majority of these studies have been conducted based on patient-reported cancer diagnoses, substantial misclassification and underestimation of cancer risk may occur. In one study of SSc patients, the sensitivity of self-reported cancer diagnoses was only 35% [75]. While patient reported cancer diagnosis may aid in data capture, it is important to validate all cancer diagnoses with careful review of pathology reports or oncology records. Collecting information about histology also enables one to probe more deeply than is possible with only tumor site, as there is substantial heterogeneity in tumor characteristics and prognosis within an individual cancer site (i.e. outcomes in breast invasive ductal carcinoma versus ductal carcinoma in situ differ). Careful planning in study design and statistical analysis is also required to address potential bias. For instance, survival bias may be a concern in patients with concurrent malignancy and onset of autoimmune disease, as patients must survive to presentation at a tertiary referral center and cohort entry. Factors such as left truncation, where someone is at risk but not yet seen, should be accounted for in statistical analyses.

In addition to identifying specific tumor sites of risk, it is critical to define unique rheumatic clinical phenotypes and serologic profiles that may be markers of cancer risk, as these types of epidemiologic studies lay the foundation for study of risk stratification and targeted cancer screening. While cancer screening algorithms have been proposed in some of the rheumatic diseases [51], there is a major unmet need for the development of evidence-based cancer screening recommendations that factor in disease-specific phenotypic risk factors for particular tumor sites. For example, in SLE patients exposed to cyclophosphamide, there may be a role for more frequent pap smears or, as suggested by Tessier-Cloutier *et al.*, there may be a role for urine cytology screening [76]. In addition, given an increased incidence of lung cancer in many of the rheumatic diseases, low-dose CT screening for lung cancer, such as that employed in patients with a significant smoking history, is another concept which may eventually be considered [77]. In patients with SSc and dermatomyositis who make unique immune responses that associate with cancer at the time of disease onset, more

aggressive cancer screening may be warranted [51]. In addition to the direct inflammatory consequences of these diseases, part of a patient's screening and treatment should also include consideration of his/her individual cancer risk profile, including age, gender, environmental exposures and family history. As with all cancer screening, care will be needed to ensure that proposed interventions result in meaningful risk reduction while minimizing harm.

In addition to the study of these critically important clinical questions, large prospective cohorts that capture detailed clinical data coupled with blood, cancer and target tissue samples also provide a rich resource to study potential mechanisms linking cancer with autoimmunity. For patient subsets where cancer-induced autoimmunity is suspected based on this biological work, it will be important to define whether early cancer detection improves both cancer and rheumatic disease outcomes, and in particular, whether cancer therapies may be effective anti-rheumatic therapies also.

Summary

Studying the bidirectional relationship between cancer and relatively infrequent autoimmune rheumatic diseases is complex given the heterogeneity in rheumatic clinical phenotypes, cancer sites at risk, and oncology and rheumatology treatment exposures. In the coming years, it will be important to harness longitudinal cohorts to define patient subsets who would benefit from targeted cancer screening and risk factor modification, and to identify appropriate oncologic and rheumatic treatment approaches when these diseases coexist. It is an exciting time to investigate shared biological mechanisms between cancer and autoimmunity, which may provide critical insights into the optimal treatment of both malignancy and the rheumatic diseases.

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Practice Points

- In many autoimmune rheumatic diseases, there is an increased risk of cancer compared to the general population. While reasons for this increased risk have not been elucidated, it is believed that chronic inflammation and damage from the rheumatic disease or its therapies may trigger malignant transformation; conversely, anti-tumor immune responses targeting cancers may become cross-reactive resulting in autoimmunity.
- Longitudinal observational studies have helped quantify the extent of cancer risk in autoimmune rheumatic disease populations. Certain cancers, including hematological malignancies like lymphoma, are more common in several distinct autoimmune rheumatic diseases (such as rheumatoid arthritis and systemic lupus), suggesting the possibility of shared biological links.
- Some work has been done to define optimal strategies to screen for and treat underlying cancer in autoimmune rheumatic diseases, but knowledge gaps remain.

Research Agenda

- The identification of patient subsets at heightened risk for malignancy has created a need for the development of evidence-based cancer screening algorithms that factor in tumor sites at risk, unique rheumatic clinical phenotypes that may be markers of cancer, and individual cancer risk profiles based on age, gender, family history and environmental exposures.
- Further study is required to define whether early cancer detection and treatment improves not only cancer, but also rheumatic diseases outcomes.
- Coupling biological samples with careful phenotyping of patients with systemic inflammatory rheumatic illness will enable investigators to probe mechanisms linking cancer and autoimmunity.

Table 1

Cancer risk in the autoimmune rheumatic diseases reported in recent meta-analyses

Disease	Author (Year)	Pooled SIR or RR for all cancers	Tumor types with increased risk
Rheumatoid arthritis	Simon (2015) [2]	1.09 (1.06, 1.13)	Lymphoma (Hodgkin, non-Hodgkin), lung, melanoma
Systemic lupus erythematosus	Bernatsky (2013) [3*]	1.14, (1.05, 1.23)	Lymphoma (non-Hodgkin), lung, leukemia, thyroid
Systemic sclerosis	Onishi (2013) [4]	1.41 (1.18, 1.68)	Lung, liver, hematologic, bladder
Myositis Polymyositis	Yang (2015) [5]	1.62 (1.19, 2.04)	Lung, kidney, breast, lymphoma, bladder, endometrial, cervical, thyroid, brain
Dermatomyositis		5.50 (4.31, 6.70)	Ovary, breast, lung, colorectal, cervical, bladder, nasopharyngeal, esophagus, pancreas, kidney
Sjogren's syndrome	Liang (2014) [6]	1.53 (1.17, 1.88)	Non-Hodgkin lymphoma, thyroid
ANCA-associated vasculitis	Shang (2015) [7]	1.74 (1.37, 2.21)	Non-melanoma skin, leukemia, bladder, lymphoma, liver, lung

Table 2

Potential mechanisms linking cancer and the autoimmune rheumatic diseases.

Proposed mechanism	Example(s)	
<i>Cancer secondary to rheumatic disease</i>		
Chronic inflammation and damage from rheumatic disease	1	Sjogren's: disease activity, severity, duration predictive of non-Hogkin's lymphoma risk
	2	RA: elevated ESR and CRP associated with increased cancer risk; longer duration corticosteroid therapy associated with lower lymphoma risk
	3	SSc: pulmonary scar associated with lung cancer
Cytotoxic or biologic therapies	1	Cyclophosphamide: higher cumulative doses associated with increased risk of lymphoproliferative and bladder cancers
	2	Mycophenolate: Possible increase in non-melanoma skin cancer and CNS lymphoma
	3	TNF inhibitors: increased risk of non-melanoma and possibly melanoma skin cancer
Inability to clear oncogenic infections	SLE: risk higher for virus-associated cancers (e.g. cervical, vaginal/vulvar, anal cancers associated with HPV)	
<i>Rheumatic disease secondary to cancer</i>		
Cancer-induced autoimmunity	1	SSc: increased risk of cancer at disease onset among patients with RNA polymerase III autoantibodies; genetic abnormalities of <i>POLR3A</i> in cancers associated with mutation-specific T cell immune responses and cross-reactive autoantibodies
	2	Dermatomyositis: striking clustering of cancer diagnosis with disease onset; increased risk of CAM in patients with unique autoantibodies (NXP-2, TIF-1 gamma); clinical improvement in DM with cancer therapy
Immunotherapy or chemotherapy	1	IL-2 therapy or immune checkpoint inhibitors: inflammatory arthritis and other autoimmune phenomena have been reported
	2	Bleomycin and gemcitabine: associated with skin sclerosis, development of exacerbation of Raynaud's and ischemic digits
Radiation therapy	Localized scleroderma may develop in radiation port	
<i>Shared etiology</i>		
Common inciting exposure	Silica, solvents, organic chemicals, pesticides, smoking, infections, hormonal state	
Shared genetic susceptibility	Increased risks of Hodgkin's lymphoma in patients with a personal or family history of multiple autoimmune conditions	