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Environmental Exposures and the Development of Systemic Lupus Erythematosus

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Abstract

Purpose of Review—This review examines evidence relating environmental factors to the development of systemic lupus erythematosus (SLE).

Recent findings—The strongest epidemiologic evidence exists for the associations of silica, cigarette smoking, oral contraceptives, postmenopausal hormone therapy, and endometriosis, with SLE incidence. Recent studies have also provided robust evidence of the association between alcohol consumption and *decreased* SLE risk. There are preliminary, conflicting or unsubstantiated data that other factors, including air pollution, ultraviolet light, infections, vaccinations, solvents, pesticides, and heavy metals such as mercury, are related to SLE risk. Biologic mechanisms linking environmental exposures and SLE risk include increased oxidative stress, systemic inflammation and inflammatory cytokine upregulation, and hormonal triggers, as well as epigenetic modifications resulting from exposure that could lead to SLE.

Summary—Identifying the environmental risk factors related to risk of SLE is essential as it will lead to increased understanding of pathogenesis of this complex disease and will also make risk factor modification possible for those at increased risk.

Keywords

systemic lupus erythematosus; SLE; environment; risk factor; exposure; pathogenesis

Introduction

Systemic lupus erythematosus (SLE) is a complex multisystem, autoimmune disease likely resulting from an interaction between genetic and environmental risk factors. Approximately 90% of patients with SLE are female, and the incidence of SLE among African Americans is increased 3–4-fold compared with that among Caucasians(1, 2). Recent genome-wide association studies have identified more than 40 single nucleotide polymorphisms involved in SLE pathogenesis and demonstrated that certain genes influence the age of disease onset and observed clinical manifestations(3–6**). However, the relatively low penetrance of the

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Conflicts of Interest:

None

disease suggests that environmental factors and gene–environment interactions play important roles in the etiology of SLE(7). Studies of SLE in monozygotic twins only show a concordance rate of 11 to 57%, underscoring that both genetic and environmental factors are important in the susceptibility to SLE(8–11). Furthermore, the genes identified to date do not adequately explain the excess SLE risk observed among African Americans

There is strong epidemiologic evidence linking environmental factors, including current cigarette smoking(12–14), crystalline silica exposure (15–17), alcohol consumption (decreased risk) (18, 19), oral contraceptives and postmenopausal hormones with the development of SLE(20–23). Other exposures, including infections such as Epstein-Barr virus(24–28), dietary factors(29, 30), pollution(31**, 32*,33*), and other occupational exposures, such as trichloroethylene(34), solvents(17, 35), mercury(35), and pesticides(35, 36) are hypothesized to increase risk of SLE, but these have not been definitively proven. Considerable knowledge gaps remain regarding potential mechanisms by which these environmental factors may be involved in the pathogenesis of SLE. Epigenetic regulation, whereby environmental stimuli may lead to biochemical epigenetic modifications, may be a potential link. Recent studies have revealed strong associations of differential DNA methylation patterns with twin discordance in SLE (37, 38). Studies in syngeneic mice have shown that injecting demethylated DNA into CD4+ T cells with can precipitate a lupus-like syndrome(39, 40). The role of underlying metabolic mechanisms in modifying gene expression in SLE is also proposed (41). Oxidative stress likely also contributes to SLE pathogenesis, and has been shown to inhibit ERK pathway signaling in T cells leading to DNA demethylation, upregulation of immune genes and autoreactivity (42*).

The aim of this article is to review the latest epidemiologic evidence concerning environmental exposures and SLE risk, to highlight some potential biologic mechanisms that may explain these associations, and to demonstrate the need for prospective and basic science studies to further elucidate the role of environmental stimuli in the development of SLE.

Lifestyle and Behavioral Factors

Cigarette Smoking

Mechanistic evidence exists implicating smoking in SLE pathogenesis. Exposure to toxic components from cigarette smoke (e.g. tars, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons and free radicals) can induce oxidative stress and directly damage endogenous proteins and DNA, leading to genetic mutations and gene activation, which could be involved in development of SLE(43). Cigarette smoking stimulates the expression of CD95 on B and CD4 T cell surfaces, potentially inducing autoimmunity(44), and also augments production of pro-inflammatory cytokines(45). In a retrospective case-control study of SLE patients, current smokers were significantly more likely to have anti-double stranded DNA antibodies compared to never smokers (OR 4.0, 95%CI 1.6–10.4)(46). Additionally, smoking leads to the formation of immunogenic DNA adducts with a half-life of 9 to 13 weeks, which may explain why current smoking has been more strongly associated with increased SLE risk(46). Furthermore, a metabolic-polymorphism-smoking interaction has been suggested by a Japanese case-control study in which smoking, along with the

cytochrome P450 1A1 rs4646903 genotype alone or in combination with the glutathione S-transferase M1 deletion genotype, was associated with greatly increased SLE risk(47).

Although epidemiologic studies of smoking and SLE risk had been somewhat conflicting (14, 18, 48, 49), in a meta-analysis of these studies examining smoking as a risk factor for SLE, current smokers had a modestly elevated SLE risk (OR 1.5, 95% CI 1.09–2.08) compared to nonsmokers(50). Past smokers did not have an elevated risk compared to non-smokers in that meta-analysis. However, two additional case-control studies performed since then have demonstrated an elevated risk for both current and former smokers compared to never smokers(49, 51). Long-term, prospective, population-based cohort studies are still needed to establish the association between smoking and incident SLE.

Alcohol consumption

Alcohol contains several compounds (e.g. ethanol and antioxidants) that potentially counteract systemic inflammation. Alcohol diminishes cellular responses to immunogens, and suppresses synthesis of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-6, IL-8, both *in vivo* and *in vitro* in alveolar macrophages and human blood monocytes(52). Increased daily alcohol consumption is associated with a decline in urinary neopterin, a macrophage activation marker and indicator of SLE disease activity(53). Additionally, antioxidants such as resveratrol or humulones in wine and beer influence cytokines such as interferon-gamma *in vitro* and may inhibit key enzymes involved in DNA synthesis (54, 55). Moderate alcohol intake may also reduce serum levels of IgG (56). Finally, alcohol consumption may induce epigenetic changes, resulting in altered gene expression that could affect immune homeostasis(57).

Epidemiologic studies of alcohol consumption and SLE risk again have hadconflicting results(18, 51, 58–60). A subsequent meta-analysis of six case-control studies and one cohort study (including studies of SLE patients treated for <10 years) demonstrated a significantly protective effect of moderate alcohol intake on SLE risk (OR 0.72, 95%CI 0.55–0.95)(19). Recently, we have found a strong inverse relationship between long-term moderate alcohol consumption (≥5 grams or 0.5 drink/day) and incident SLE (HR 0.61, 95%CI 0.41–0.89) among women in the Nurses' Health Study cohorts(61**). As wine was the most common alcoholic beverage consumed by these women, those who drank ≥2 servings of wine/week had significantly decreased SLE risk (HR 0.65; 95%CI 0.45–0.96), compared to women who did not drink wine.

Radiation and Nutritional Factors

Ultraviolet (UV) Radiation

Although UV radiation exposure may exacerbate pre-existing SLE, it remains unclear whether UV exposure plays a role in the pathogenesis of SLE(62). Experimental studies suggest that UV-B radiation results in induction of reactive oxygen species, leading to DNA damage(63), production of novel forms of autoantigens and autoreactive T cells(64, 65), and may have immunomodulatory effects on T cells and cytokines (66, 67), all potentially involved in to SLE pathogenesis. Only a few case-control studies have been able to examine

UV radiation exposure and risk of SLE(68–70), and these have been limited by potential inaccuracy of exposure assessment, and influenced by recall and reverse causation bias, given that photosensitivity due to SLE can be present well before diagnosis. We have recently reviewed this topic in detail elsewhere(71). Large, well-controlled studies are still needed to prospectively assess the relationship of UV-B radiation with incident SLE.

Vitamin D

Further complicating our understanding of the relationship between UV radiation and SLE pathogenesis is the controversial role of Vitamin D. While exposure to solar UV radiation may trigger SLE disease flares, UV light exposure is also the main source of vitamin D production(72). Vitamin D may be immunosuppressive once metabolized to 1α, $25(OH)_2D3$(73), and it has been suggested that UV-B radiation could reduce SLE risk via stimulation of cutaneous vitamin D synthesis(74–76). Many cross-sectional and case-control studies have reported low 25(OH) vitamin D concentrations in SLE patients compared to controls, however, it is not clear whether low vitamin D is a cause or consequence of chronic disease. No protective effect of vitamin D intake from foods or supplements was found amon women in the Nurses' Health Studies (76, 77).

Infections

Epstein-Barr virus (EBV) seropositivity rates are much higher in adults and children with SLE than age-matched controls(24, 25). Potential mechanisms involve EBV RNA/SSB protein complexes inducing type 1 interferon via Toll-like receptor 3 (78) and molecular mimicry between EBV and SLE antigens(28, 79). Additionally, SLE patients have impaired CD8+ cytotoxic T cells, and irregular cytokine production in plasmacytoid dendritic cells and CD69+CD4+ T cells in response to EBV(80, 81). However, no conclusive data have established that EBV infection is linked to future risk of SLE. Notably, in a large population-based Danish cohort, EBV-serologic negative individuals had a sustained increased risk for SLE highest in the 1 to 4 years after testing (standardized incidence rate, 6.6; 95% CI, 3.3–13.2), but this finding may have been due to a surveillance bias as EBV testing is likely to be performed during the work-up for early SLE symptoms(82). In that study, no associations were found with EBV serologic positivity, infectious mononucleosis, or severe infectious mononucleosis requiring hospitalization (82, 83). A recent meta-analysis of twenty-five case control studies demonstrated a statistically significant higher seroprevalence of anti-viral capsid antigen IgG (OR 2.08, 95% CI 1.15 to 3.76, $p = 0.007$) and antibodies to EBV early antigen diffuse, a marker of viral replication, in patients with *existing SLE* patients compared to normal individuals (OR 4.5; 95% CI 3.00 to 11.06, $p < 0.00001$), although the funnel plot examination suggested publication bias. (84). Therefore, the association between EBV and incident SLE, in particular the question of causality, remains to be fully elucidated.

Vaccinations

Vaccinations have been proposed as potential triggers for the onset of SLE given their role in stimulating an antigen-specific immune response. Although few case reports and case series have suggested links between SLE and pneumococcal, tetanus, *Haemophilus influenzae* type b, human papillomavirus, hepatitis B, and influenza vaccinations(85–88), these associations

have not been confirmed in epidemiologic studies(83). A recent international case-control study involving 105 SLE patients demonstrated no association between vaccinations administered within 24 months of SLE index date and the development of SLE(89).

Occupational Factors and Pollutants

Silica and Silicates

Silica exposure has been associated with several autoimmune diseases, most notably scleroderma and rheumatoid arthritis. Crystalline silica is a well-known adjuvant which induces the transcription of pro-inflammatory cytokines, stimulates T cell responses and decreases number of regulatory T cells, increases oxidative stress, and induces apoptosis(90–92). In SLE-prone murine models, silica exposure significantly exacerbates the course of disease, with increased production of autoantibodies, rapid development of high titers of circulating immune complexes, glomerulonephritis, and proteinuria(93). A recent study, in which lupus-prone female NZBWF1 mice were exposed to early repeated short-term crystalline silica and developed SLE-like disease, demonstrated that the lung may serve as the portal of entry for triggering systemic autoimmunity and glomerulonephritis(94*).

The association between silica exposure with incident SLE has been reported in both agricultural and urban settings (95–97). Case-control studies have demonstrated dose-response associations by type of exposure, and by increasing intensity or duration(16, 17, 98). Large population-based studies have confirmed these findings(16, 99, 100). Most recently, a prospective cohort study among male construction workers demonstrated an elevated risk for the development of the combined outcome of rheumatoid arthritis, SLE, systemic sclerosis, and dermatomyositis combined, after adjustment for age and smoking (RR 1.39, 95% CI, 1.17–1.64); however, this study was underpowered to assess for an association among SLE patients independently(101*). Although the evidence supports silica as a likely cause of SLE, questions remain regarding the required dose, and susceptibility factors, and SLE risk due to industrial exposures to other silicates. Asbestos, a long-chain silicate, has been shown to be associated with anti-nuclear antibody development and proteinuria, as well as with increased rheumatoid arthritis risk(102).

Air Pollution

Particulate air pollution has effects similar to those of inhaled cigarette smoke and silica on the immune system and has been linked to asthma, chronic bronchitis, cardiovascular disease, and lung and laryngeal cancers(102–106). Few epidemiologic studies have investigated whether exposure to air pollution is associated with incident SLE. Particulate air pollution has been linked to the development of systemic autoimmune rheumatic diseases (SARD), a term which includes systemic lupus, Sjögren’s syndrome, scleroderma, polymyositis, dermatomyositis, or undifferentiated connective tissue disease in an urban Canadian cohort (33). In that study, after adjusting for demographics, exposure to fine particulate air pollution was associated with an increased risk of SARD, identified from administrative billing databases(33). The odds of being a SARD case increased with increasing air pollution particulate matter level in two other Canadian provinces as well (31). A recent preliminary genome-wide assessment of DNA methylation reported that, among

SLE patients, residing close to a highway was associated with hypomethylation of the *UBE2U* gene, which encodes an enzyme involved in the ubiquitination of proteins and histones, as well as DNA repair (32). Further studies are needed to confirm and expand upon these findings related specifically to SLE patients.

Solvents and Pesticides

Environmental contaminants exist in residential settings and common household products (such as dry cleaning, nail polish removers, paints, perfumes) and hazardous waste sites, in addition to pesticides, all of which may affect oxidative stress and/or sex hormone homeostasis (107). Although increased SLE risk has been found to be associated with jobs and tasks involving solvent exposure in various studies utilizing different study designs(98, 100), other studies assessing solvent exposure based on job history and high-exposure work tasks have found no overall or dose-response associations with SLE(17, 35).

Epidemiologic studies have demonstrated that both recreational and occupational exposure to petroleum distillates, as well as to trichloroethylene and organochlorines, to increase SLE symptoms in those with existing disease(34, 108), however thus far trichloroethylene has not been conclusively linked to development of SLE. Two studies have reported that pesticide exposure, both agricultural and residential, is associated with increased risk for SLE(35, 109): a recent study confirmed these findings using a national cohort of women. More frequent pesticide use (e.g., at least monthly, OR 2.3, 95%CI 1.3, 4.1) and having an early and extended childhood farm residence (OR, 1.8; 95%CI 1.1, 3.0) were strongly associated with SLE (110*). Studies suggesting roles of hair dyes and other cosmetics, including lipstick, remain unconfirmed(111).

Heavy Metals

Data from experimental studies suggest that heavy metals may increase systemic autoimmunity, and that co-exposure to certain heavy metals may increase the risk associated with other exposures(112). Mercury-exposed gold miners were demonstrated to have a higher prevalence of detectable ANA as compared to diamond and emerald miners with no occupational mercury exposure(113) and two case-control studies have shown elevated risk of SLE associated with self-reported exposure to mercury(35, 98).

Sex, Hormonal, and Reproductive Factors

Female sex is a strongly predisposing factor in SLE susceptibility and the overwhelming majority of SLE cases occur among women during childbearing years(114, 115). Both sex hormones and X chromosome factors are thought to be responsible for the striking sex disparity in SLE(116, 117). Epigenetic modification of genes on the “inactive” X chromosome has been proposed as a possible mechanism for the increased female prevalence of SLE(118). Sex steroid hormones, including 17-β-estradiol, testosterone, prolactin, progesterone and dehydroepiandrosterone, influence the regulation of the immune system(119, 120) and the severity of disease in SLE patients(121–123). In a meta-analysis of clinical studies, significantly lower testosterone and dehydroepiandrosterone, and higher estradiol and prolactin, have been demonstrated in women *with existing SLE* compared to

controls (124). Mild or moderate hyperprolactinemia has been demonstrated in 20% to 30% *of SLE patients* and is associated with active disease(125). However, associations between hormonal levels and future risk of developing SLE have not been assessed.

In previous studies, early menarche, exogenous hormone use (including both oral contraceptives [OCPs] and hormone replacement therapy [HRT]), surgical menopause were shown to be associated with risk of SLE(23, 126). However, in a large, prospective study using the Nurses' Health Study cohorts, oral contraceptives and postmenopausal HRT were both associated with increased risk of incident SLE (RR 1.5, 95% CI 1.1–2.1 and RR 1.9, 95% CI 1.2–3.1, respectively)(23). Furthermore, a strong dose-response relationship between the OCP dose of ethinyl estradiol and new onset SLE in a large study using data from the U.K. General Practice Database(127). A separate study demonstrated an inverse (protective) relationship of the progesterone-only pill with SLE (128). Additionally, in the Nurses' Health Study cohorts, surgical menopause and earlier age at natural menopause were associated with increased SLE risk (129). Earlier age at menopause was also found to be a risk factor for SLE among women in the Carolina Lupus Study, but postmenopausal HRT was not associated with risk of SLE in that study(117).

Data on other reproductive factors (e.g. menstrual irregularity, breastfeeding duration, number of ovulatory years, and parity) in relation to SLE have been inconsistent, apart from early age at menarche, which has been associated with increased SLE risk(117, 129, 130). Recently, endometriosis has also been found to be associated with SLE in two large prospective cohort studies. In the Nurses' Health Study II cohort, a two-fold increased risk of SLE was demonstrated among women with laparoscopy-confirmed endometriosis (HR 2.03; 95% CI, 1.17–3.51), but risk was attenuated after adjustment for hysterectomy, oophorectomy and analgesic use (131*). Similarly, a recent population-based case-control study from Sweden demonstrated a positive association between endometriosis and subsequent SLE (OR 1.39, 95% CI1.09–1.78)(132*).

Dietary Factors and Medications

While there are very few prospective studies of dietary intake and SLE, several lines of evidence implicate dietary factors in SLE pathogenesis. First, murine models suggest that dietary exposures can induce epigenetic changes and SLE autoimmunity(133, 134). When genetically-SLE predisposed C57BL/6×SJL mice were fed methyl donor poor diets, they developed lupus nephritis, whereas those fed diets rich in methyl group micronutrients did not(135). As oxidative stress, inflammation and cytokine dysregulation are central to SLE pathogenesis, diet may play an important accelerating role. Prior studies suggest that high intake of certain antioxidants, fish, olive oil and cooked vegetables may confer a protective effect against chronic disease development(136). Women consuming >200 ml of coffee per day had increased inflammation markers, such as interleukin-6 and tumor necrosis factor-α, compared with coffee non-drinkers(137). A prior case-control study suggests a significant increased SLE risk with black tea consumption and borderline increased risk with coffee consumption, but not green tea(138). Previous data suggests that low intake of omega-3 and high intake of carbohydrate among patients with SLE are associated with increased disease

activity (139). Thus far, no well-controlled, prospective studies have assessed associations between dietary factors and incident SLE.

Conclusion

Studies identifying modifiable environmental risk factors for the development of SLE are advancing our understanding of disease pathogenesis and could lead to strategies to prevent disease, in particular for those individuals at high risk. Significant epidemiologic literature exists to support the association between silica, cigarette smoking, oral contraceptives, postmenopausal hormone therapy, and endometriosis with increased risk of incident SLE. Recently, moderate alcohol consumption has been demonstrated to reduce incident SLE risk. Other environmental factors, including air pollution, ultraviolet light, infections, vaccinations, solvents, pesticides, and heavy metals, may increase SLE risk, but further studies are needed to confirm these findings. Biologic mechanisms whereby environmental exposures may contribute to SLE pathogenesis include epigenetic modifications, along with increased oxidative stress, systemic inflammation, inflammatory cytokines, chemokine upregulation, and hormonal triggers. Although data are accumulating, the current literature remains challenging to interpret due to methodological difficulties in assessment of exposures and potential confounders, the heterogenous and relatively rare nature of SLE, and its prolonged disease onset with some features developing prior to clinical diagnosis.

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Key Points

- Substantial literature exists linking environmental factors with the development of systemic lupus erythematosus (SLE).
- Recent studies have provided more robust evidence of this association, particularly related to alcohol consumption, silica, particulate air pollution, endometriosis, and dietary factors.
- Studies identifying the role of modifiable environmental risk factors in the development of SLE will advance our understanding of disease pathogenesis and may lead to strategies to prevent disease.