Chapter

Epidemiology of Systemic Lupus Erythematosus

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Abstract

Epidemiology is the study of the frequency and distribution of diseases and factors related to the development of diseases. Systemic lupus erythematosus (SLE) is a rare, chronic inflammatory autoimmune disease that affects many tissues and organs, whose female-to-male incidence ratio is 6:10 for childbearing age. Its chronic intractable nature has a significant impact on medical care utilization, activities of daily living, and quality of life. However, the etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development. In this chapter, we introduce the incidence and the prevalence of SLE as well as factors related to the development of SLE and discuss how to prevent the development of SLE.

Keywords: SLE, epidemiology, incidence, prevalence, risk factor

1. Introduction

Systemic lupus erythematosus (SLE) is a rare, serious, chronic inflammatory autoimmune disease that affects many tissues and organs [1, 2]. The Japanese Ministry of Health and Welfare designated SLE as an intractable disease because there is no established way to cure or prevent it [3, 4]. Under a nationwide registration system for patients with intractable diseases, 55,021 SLE patients were eligible for financial aid from the Japanese government in 2007 and the prevalence of SLE was estimated to be 44 per 100,000 persons in Japan [5]. Females are 8.2 times more likely to suffer from SLE than males in Japan [5]. Serdula and Rhoads [6] reported that the age-adjusted prevalence of SLE was greater in Japanese (18.2/100,000 persons) than White People (5.8/100,000 persons) in Hawaii, but they could find no reason for the high prevalence of SLE in Japanese ancestry. The etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development [1]. The discrepancies of rates (i.e., higher rates in certain ethnic groups) are in part due to genetic factors as well as due to environmental factors such as smoking and dietary habits [7].

In this chapter, we would like to show the incidence and prevalence of systemic lupus erythematosus (SLE) and the findings from epidemiological studies on the risk/preventive factors for SLE.

2. Diagnosis criterion of SLE (case definition)

The established diagnosis criterion of SLE is needed to estimate the frequency and distribution of the patients with SLE. However, case definition is one of the

important factors, which may influence the results of epidemiological studies. Currently, the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE [8], as modified in 1972 (ACR-97) [9], are widely used for the diagnosis of SLE. The diagnosis of SLE requires the presence of four or more of the following 11 criteria, which are (1) malar rash, (2) discoid rash, (3) photosensitivity, (4) oral ulcer (usually painless, observed by a physician), (5) arthritis (nonerosive arthritis 2 or more peripheral joints), (6) serositis (a. pleuritis or b. pericarditis), (7) renal disorder (a. persistent proteinuria either 0.5 g/day or > 3+ if quantification not performed or b. cellular cast), (8) neurologic disorder (a. seizures or b. psychosis in the absence of offending drugs or metabolic disorders), (9) hematologic disorder (a. hemolytic anemia with reticulocytosis or b. leukopenia <4000/mm^3 or c. lymphopenia <1500 mm^3 or d. thrombocytopenia <100,000 mm^3 in the absence of offending drugs), (10) immunologic disorder (a. antibody to native DNA in abnormal titer or b. presence of antibody to Sm nuclear antibody or c. positive finding of antiphospholipid antibody), and (11) positive antinuclear antibody test result. Although the presence of four or more ACR-97 criteria is required for SLE classification, all other reasonable diagnoses of diseases other than SLE (e.g., neurologic disorder due to uremia, acidosis, or electrolyte imbalance) must be excluded [7]. Among the 11 ACR criteria, positive antinuclear antibody test result, hematologic disorder, immunologic disorder, and arthritis are the four most common criteria seen in SLE patients at the time of diagnosis [10–13] (**Table 1**).

When epidemiological studies are conducted based on the rheumatologist definition, biopsy-proven lupus nephritis patients may be considered to have SLE even though they satisfy fewer than four ACR-97 criteria. In these cases, the rates of SLE will be greater than the rates based on the ACR-97. Recently, the Systemic Lupus International Clinics (SLICC), which is an international group for the clinical research of SLE, presented a new criterion for the classification of SLE in 2012 (SLICC-12) [14]. They also validated the ACR-97 and the SLICC-12. The SLICC-12 resulted in fewer misclassification than the ACR-97 [14]. Compared with the ACR-97, the SLICC-12 had greater sensitivity but less specificity [14, 15]. The SLICC case definition of

	Voss et al. [10]	**Uramoto et al. [11]**	**Lim et al. [12]**	**Izmirly et al. [13]**
Manifestation	**Denmark**	**United States**	**United States**	**United States**
	n = 107	**n = 69**	**n = 267**	**n = 232**
1. Malar rash	52(49)	18(26.1)	55(20.6)	86(37.1)
2. Discoid rash	15(14)	14(20.3)	40(15.0)	32(13.8)
3. Photosensitivity	51(48)	26(37.7)	43(16.01)	74(31.9)
4. Oral ulcer	9(8)	4(5.8)	61(22.8)	81(34.9)
5. Arthritis	62(58)	37(53.6)	167(62.5)	159(68.5)
6. Serositis	47(44)	22(31.9)	91(34.1)	84(36.2)
7. Renal disorder	37(35)	31(44.9)	91(34.1)	81(34.9)
8. Neurologic disorder	14(13)	2(2.9)	24(9.0)	43(18.5)
9. Hematologic disorder	66(62)	55(79.7)	216(80.9)	188(81.0)
10. Immunologic disorder	99(93)	44(63.8)	187(70.0)	170(73.3)
11. Antinuclear antibody	107(100)	46(66.6)	244(90.4)	213(91.8)

Data are expressed as number (%).

Table 1.
Distribution of clinical manifestation and laboratory findings at the diagnosis of SLE.

SLE yielded higher incidence and prevalence estimates than the ACR-97 case definition [15]. Thus, the incidence and prevalence of SLE are influenced by the diagnosis criterion of SLE. Therefore, interpretation of incidence and prevalence of SLE also take into account differences in the methodology used to determine these rates.

3. Incidence and prevalence of SLE

In the United Kingdom, Rees et al. [16] found that the incidence and prevalence of SLE in White People (6.73/100,000 person-years and 134.5/100,000 persons) were smaller than those in other ethnic groups such as Black African (13.78/100,000 person-years and 179.8/100,000 persons), Black Caribbean (31.46/100,000 person-years and 517.5/100,000 persons), and Indian (9.9/100,000 person-years and 193.1/100,000 persons) (**Table 2**). In addition to the United Kingdom, American epidemiologists also reported that the incidence and prevalence of SLE in White

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Rees (2016) [16]	United Kingdom	1999–2012	Clinical Practice Research Datalink (CPRD)	White People	6.73	134.5
				Black African	13.78	179.8
				Black Caribbean	31.46	517.5
				Indian	9.9	193.1
Serdula (1979) [6]	United States (Hawaii)	1970–1975	American Rheumatism Association (ARA)—preliminary criteria	White People	NA	5.8
				Chinese	NA	24.1
				Filipino	NA	19.9
				Hawaiian	NA	20.4
				Japanese	NA	18.2
Lim (2014) [12]	United States (Georgia)	2002–2004	ACR-97 criteria	White People	2.7	32.7
				Black People	8.7	118.5
Somers (2014) [17]	United States (Michigan)	2002–2004	ACR-97 criteria	White People	3.7	47.5
				Black People	7.9	111.6
				Asian/Pacific Islanders	NA	24.9
Dall'Ella (2017) [18]	United States (California)	2007–2009	ACR-97 criteria	White People	2.8	NA
				Black People	15.5	NA
				Asian/Pacific Islanders	4.1	NA

NA, not available.

Table 2.
Incidence and prevalence of SLE by ethnic group in the United Kingdom/the United States.

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Uramoto (1999) [11]	United States (Minnesota)	1950–1979	ACR-82 criteria	Overall	1.51	NA
				Females	2.47	NA
				Males	0.50	NA
	United States (Minnesota)	1980–1992	ACR-82 criteria	Overall	5.56	NA
				Females	9.40	NA
				Males	1.54	NA
Lim (2014) [12]	United States (Georgia)	2002–2004	ACR-97 criteria	All population	5.6	73.0
				Females	9.2	127.6
				Males	1.8	14.7
				White People	2.7	32.7
				Females	4.7	59.0
				Males	0.7	7.5
				Black People	8.7	118.5
				Females	13.4	196.2
				Males	3.2	23.7
Somers (2014) [17]	United States (Michigan)	2002–2004	ACR-97 criteria	All population	5.5	72.8
				Female population	9.3	128.7
				Male population	1.5	12.8
Dall'Ella (2017) [18]	United States (California)	2007–2009	ACR-97 criteria	All population	4.6	NA
				Females	8.6	NA
				Males	0.7	NA
				White People	2.8	NA
				Females	5.3	NA
				Males	0.6	NA
				Black People	15.5	NA
				Females	30.5	NA
				Males	2.1	NA
				Asian /Pacific Americans	4.1	NA
				Females	7.2	NA
				Males	0.6	NA
Izmirly (2017) [13]	United States (New York)	2007–2009	ACR-97 criteria	Overall	4.6	62.2
				Females	7.9	107.4
				Males	1.0	12.5
	United States (New York)	2007–2009	SLICC	Overall	6.2	73.8
				Females	10.3	128.3
				Males	1.7	13.8

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Barnabe (2012) [19]	Canada	1994–2007	Diagnosed in clinical setting (ICD-9, ICD-10)	Females	NA	27.3
				Males	NA	3.2
				First Nations females	NA	32.2
				First Nations males	NA	3.2
				non-First Nations females	NA	27.1
				non-First Nations males	NA	3.2
Somers (2007) [20]	United Kingdom	1990–1999	Clinical Practice Research Datalink (CPRD)	All population	4.87	NA
				Females	8.01	NA
				Males	1.60	NA
Rees (2016) [16]	United Kingdom	1999–2012	Clinical Practice Research Datalink (CPRD)	All population	4.91	64.6–97.0
				Female population	8.34	NA
				Male population	1.44	NA
Arnaud (2014) [21]	France	2010	Diagnosed in clinical setting (ICD10)	All population	3.32	47.0
				Females	5.51	79.1
				Males	0.92	11.8
Zou (2014) [22]	China	2009–2010	Diagnosed by rheumatologists (ACR-97 criteria)	All population	NA	37.6
				Females	NA	70.3
				Males	NA	6.4
Yu (2013) [23]	Taiwan	2000–2008	Diagnosed in clinical setting (ICD9)	All population	8.4	37.0
				Females	15.0	66.6
				Males	1.9	8.5
Shim (2014) [24]	South Korea	2009	Diagnosed (ACR-criteria) (ICD10)	All population	2.8	24.9
				Females	5.1	42.9
				Males	0.6	7.0

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Yamamoto (1986) [25]	Japan	1972–1983	Diagnosed by a rheumatologist (ACR criteria)	All population	2.0	NA
				Females	3.7	NA
				Males	0.25	NA
Ohno (1992) [26]	Japan	1992	Diagnosed in clinical setting (ACR-82 criteria)	All population	NA	29.1
				Females	NA	52.3
				Males	NA	5.0
Iseki (1994) [27]	Japan	1972–1991	ACR-82 criteria	All population	3.0	NA
		1972–1991		Females	1.6–4.7	6.6–68.4
		1973–1991		Males	0.4–0.8	0.8–7.0

NA, not available.

Table 3.
Incidence and prevalence of SLE in females and males in selected countries.

People were smaller than those in other ethnic groups in the United States [6, 12, 17, 18] (**Table 2**). The disease burden of SLE is highest in Black People [17, 18], followed by Asian/Pacific islanders [17] and White People in the United States [17, 18], which may be related to genetic and environmental factors.

As shown in **Table 3**, the incidence and prevalence of SLE are greater in females than in males in all studies regardless of ethnic group or countries [11–13, 16–27]. Age-adjusted incidence of SLE in females was 8.8–14.5 times greater than in males in California, the United States (i.e., 12.3-fold female excess in all population, 8.8-fold female excess in White People, 14.5-fold female excess in Black People, and 12.0-fold female excess in Asian/Pacific islanders) [18], while the age-adjusted incidence of SLE in females was 7.8–14.8 times greater than that in males in East Asia (i.e., 7.8-fold female excess in Taiwan [23], 8.5-fold female excess in South Korea [24], and 14.8-fold female excess in Japan [27]).

SLE is more common in women than men across all age groups, and this female predominance is especially noteworthy in the 15- to 64-year age group, wherein the male-to-female ratios of age-group incidence show a 6- to 10-fold female excess [28], which suggests that female sex hormones may play an important role in the development of SLE [28]. The Nurses' Health Study [29] revealed that oral contraceptive use increased the risk of SLE in the United States, whereas Bernier et al. [30] reported that it was not past use but current use of oral contraceptive pills that increased the risk of SLE in the United Kingdom. These studies [29, 30] also suggest that female sex hormones such as estrogen may play an important role in the development of SLE. In addition to sex hormones, both X-linked and autosomal immune genes are also regulated epigenetically and likely contribute to the sex difference in the incidence of SLE [31].

4. Factors related to the development of SLE

Although genetic factors are suggested to play an important role in the development of SLE, nongenetic factors are also suggested to play a role in the development of SLE [1, 7]. In addition to genetic susceptibility, hormonal and reproductive exposures (e.g., endogenous estrogens, estrogen replacement therapy), occupational and environmental exposures (e.g., silica, ultraviolet light), and infectious exposures (e.g., Epstein-Barr virus) are suggested to influence the risk of SLE [1, 7]. Complex interactions between genetic and environmental factors are thought to play a role in the development and progression of SLE [7].

4.1 Sex hormones and reproductive issues in females

The incidence of SLE is greater in females than in males in all studies regardless of ethnic group or countries [11–13, 16–27]. Although SLE occurs predominantly in females, the incidence of SLE is low before puberty and after menopause (i.e., outside the reproductive ages) [32]. Sex difference in susceptibility is largest during the reproductive ages [33], which suggests that high endogenous estrogen concentrations may increase the risk for the development of SLE. Estrogens enhance B cell activation (e.g., immunoglobulin production including anti-ds-DNA), while they suppress T cell activity (e.g., proliferative response to mitogens and antigens, interleukin 2 production) [32].

Costenbader et al. [29] reported that menarche at a younger age (10 years old or younger vs. 12 years old: RR 2.1, 95% CI = 1.4–3.2) increased the risk for the development of SLE in the NHS 1976–2002 and the NHSII 1989–2003. In addition, they also reported that age at menarche was inversely associated with a risk for the development of SLE (vs. 12 years old: RR = 2.1 for 10 years or younger, RR = 1.2 for 11 years old, RR = 1.0 for 12 years old, 1.1 for 13 years old, and RR = 1.1 for 14 years old, and RR = 1.0 for 14 years old or older, p for trend = 0.02) [29]. These findings suggest that the exposure to high concentrations of endogenous estrogen at early age may increase the risk for the development of SLE.

On the other hand, Bernier et al. [30] reported that current use of combined oral contraceptives increased the risk of SLE (RR 1.54, 95% CI = 1.15–2.07), but past use of combined oral contraceptives did not increase the risk (RR 1.06, 95% CI = 0.85–1.33). In addition, they also reported that the risk of SLE increased with the dose of ethinyl estradiol (vs. nonusers: RR 1.42 for 30 μg or less, RR 1.63 for 31–49 μg, and RR 2.92 for 50 μg), while Costenbader et al. [29] reported that use of oral conceptive (vs. never: RR 1.5, 95% CI = 1.1–2.1) and use of postmenopausal hormones (vs. never: RR 1.9, 95 % CI = 1.2–3.1) increased the risk for development of SLE in the Nurses' Health Study. These findings suggest that use of exogenous estrogens may increase the risk for the development of SLE.

Costenbader et al. [29] also reported that postmenopausal women primary after surgical menopause (vs. premenopausal: RR 2.3, 95% CI = 1.2–4.5) and early age of menopause (younger than 47 years old vs. 53 years old and older: RR 2.2, 95% CI = 0.9–5.4) showed an increased risk for the development of SLE. In their study, most of females who developed SLE after menopause were those with surgical menopause (i.e., bilateral oophorectomy) and were more likely to have taken postmenopausal hormones [29]. The increased risk of developing SLE among postmenopausal females in their study may be partly explained by the use of postmenopausal hormones (RR 1.9, 95% CI = 1.2–3.1) [29] and the surgery (vs. no surgery: surgery without blood transfusion: OR 1.54, 95% CI = 1.05–2.26; surgery with blood transfusion: OR 4.46, 95% CI = 1.99–10.00) [34].

Ulff-Møller et al. [35] reported that live birth showed a decreased risk of SLE among Danish females (RR 0.74, 95% CI = 0.64–0.86), while Washio et al. [34] reported that live birth (OR 0.23, 95% CI = 0.09–0.59) decreased the risk of SLE and found a positive association between the risk of SLE and the number of living children delivered among Japanese females (vs. 0; OR 0.27 for one to two children, and OR 0.14 for three or more children, p for trend <0.01). On the other hand, Cooper et al. [36] could not find any meaningful association between the risk of SLE and number of live births. However, they found that breast-feeding was associated with a decreased risk of SLE (OR 0.6, 95% CI = 0.4–0.9) among females in the United States [36]. These findings suggest that lactation may play an important role in reducing the risk of SLE among women with live-born children because serum estrogen levels are usually at or below the lower range for the early follicular phase of the normal menstrual cycle during the lactation [37].

4.2 Tobacco smoking and alcohol drinking

Several researchers suggested that smoking increased the risk of SLE [38–42]. Ghaussy et al. [39] reported a significantly increased risk of SLE in both current and former smokers compared with never smokers (current smokers: OR 6.69, 95% CI = 2.59–17.28, former smokers: OR 3.62, 95% CI = 1.22–10.70) in the United States. On the other hand, others reported no association with smoking history (i.e., current, former, or never-smoker) and the risk of SLE in the United States [43, 44]. A meta-analysis by Costenbader et al. [45] revealed an increased risk of SLE among current smokers compared with nonsmokers (summary OR 1.50, 95% CI = 1.09–2.08).

The Kyushu Sapporo SLE study (i.e., the KYSS Study) was a hospital-based case-control study to evaluate nongenetic and genetic risk factors for the development of SLE among Japanese females [42]. All SLE patients fulfilled the American College of Rheumatology 1982 revised criteria for SLE [8]. In the KYSS study, Kiyohara et al. [46] reported that (1) compared with nonsmokers, smokers showed an increased risk of SLE (vs. nonsmokers: OR 2.49 for former smokers, and OR 3.06 for current smokers, p for trend <0.01). In addition, the risk of SLE increased with number of cigarettes smoked/day during peak smoking period (vs. 0/day: OR 2.77 for 1–19/day, and OR 3.29 for 20+/day, p for trend<0.01) [46]. Since hydrazine, a drug containing aromatic amines, is a known inducer of SLE [47], aromatic amines in cigarette smoke may partly explain the association between smoking and the risk of SLE.

Some studies suggested that alcohol consumption may decrease the risk of SLE [38, 40, 41]. Hardy et al. [38] reported a dose-response negative association between alcohol drinking and SLE risk (vs. 0 unit of alcohol: OR 0.73 for 1–2 units, OR 0.41 for 3–5 units, OR 0.47 for 6–10 units, and OR 0.30 for more than 10 units, p for trend <0.01). On the other hand, other studies failed to show an inverse association between alcohol drinking and SLE risk [37, 40]. A meta-analysis by Wang et al. [48] demonstrated that moderate alcohol drinking might have a protective effect on the development of SLE (vs. none: summary OR 0.73, 95% CI = 0.547–0.954). In the KYSS study, Kiyohara et al. [46] found a U-shape relationship between alcohol consumption and SLE risk among Japanese females (vs. 0 ml/week: OR 0.52, 95% CI = 0.31–0.86 for 1–70 ml/week, OR 0.38, 95% CI = 0.19–0.76 for 71–210 ml/week, and OR 0.67, 0.31–1.46 for 211 ml/week or more). These findings suggest that light to moderate alcohol consumption may decrease the risk of SLE.

Although there are potential biases associated with retrospective assessment of exposures and selection of cases and controls in a case-control study [49], Kiyohara et al. [46] reported that ever-smokers with drinking alcohol (OR 3.44, 95% CI = 2.03–5.82), nonsmokers without drinking alcohol (OR 2.56, 95% CI = 1.57–4.17), and ever-smokers without drinking alcohol (OR 6.98, 95% CI = 2.87–17.0) showed a greater risk of SLE than nonsmokers with drinking alcohol in Japanese women.

4.3 Occupational exposures and chemicals

Crystalline silica exposure is known to increase the risk of SLE [50, 51]. Finckh et al. [52] reported that exposure to silica for more than 1 year increased the risk of SLE (OR 4.3, 95% CI = 1.7–11.2). They also reported that the risk of SLE was associated with the duration of exposure to silica (vs. less than 1 year: OR 4.0 for 1–5 years, and OR 4.9 for more than 5 years, p for trend = 0.01) [52]. Parks et al. [53] reported a positive relationship between a history of silica exposure and SLE risk (vs. none: OR 1.6 for low, and OR 3.1 for medium or high, p for trend = 0.003).

On the other hand, Cooper et al. [54] reported that occupational silica exposure increased the risk of SLE among never-smokers (vs. no-silica exposure: OR 2.6, 95% CI = 1.2–5.7) but not among ever-smokers (vs. no-silica exposure: OR 0.99, 95% CI = 0.46–2.1), which suggests that smoking may play a more important role in the development of SLE than silica exposure.

Cooper et al. [43] reported that any use of permanent dyes increased the risk of SLE (OR 1.5, 95% CI = 1.0–2.2) in the United States. On the other hand, Sanchez-Guerrero et al. [44] failed to find a positive association between use of permanent hair dye and SLE risk (ever-users vs. never-users: OR 0.96, 95% CI = 0.63–1.47) in the Unites States.

4.4 Ultraviolet radiation exposure

Washio et al. [42] reported that walking increased the risk of SLE in Kyushu, southern Japan with a temperate climate (30 min/day or more vs. less than 30 min/day: OR 2.07, 95% CI = 1.14–3.76) but failed to increase the risk of SLE in Hokkaido, northern Japan with a subarctic climate (30 min/day or more vs. less than 30 min/day: OR 1.13, 95% CI = 0.46–2.79). In this study, walking may be a surrogate of staying outdoors with exposure to strong sunlight [42]. On the other hand, Cooper et al. [54] reported that outdoor work in the 12 months preceding diagnosis (OR 2.0, 95% CI = 1.0–3.8) increased the risk of SLE. In their study, a larger variation in the association between outdoor work and SLE risk was seen when examined within categories of sun reaction to midday sun (vs. none; OR 0.75 for tan or darken without burning, OR 2.7 for sunburn, and OR 7.9 for sunburn with blistering or rash) [54]. However, it is controversial whether ultraviolet (UV) radiation exposure itself plays a role in the development of SLE although UV radiation exposure may exacerbate preexisting SLE [50].

4.5 Family history

Family history of SLE [40, 55] as well as family history of connective tissue diseases/autoimmune diseases [40, 41, 55] is reported to increase the risk of SLE. Alarcón-Segovia et al. [56] reported that there was familial aggregation of SLE and of RA in SLE patients. These findings suggest that predisposing genes of autoimmune diseases as well as environmental risk factors sharing in family members may play a role in the development of autoimmune diseases including SLE.

4.6 Genetic susceptibility

It is widely accepted that SLE development requires environmental factors acting on a genetically predisposed individual. Studies of twin concordance are commonly used in epidemiology to estimate the role of genetics and the influence of environmental factors on disease susceptibility. Disease concordance is much higher in monozygotic twins (24–57%) than in dizygotic twins (2–5%),

suggesting that a genetic factor may play a role in the development of SLE [57, 58]. The genetic basis of SLE is very complex; it has been estimated that over 100 genes may be involved in SLE susceptibility [59], but it is difficult to predict how many genes contribute to SLE susceptibility. Exposure to reactive oxygen species (ROS) via cigarette smoking is thought to contribute to the development of SLE. ROS is considered to promote the autoimmune response [60]. The cytochrome P450 (CYP)1A1 and glutathione S-transferase (GST) M1 enzymes are critical for the functionalization of genotoxic substances in cigarette smoke. The CYP1A1 enzyme contributes to the phase I metabolic activation and formation of ROS, whereas the GSTM1 enzyme plays a critical role for phase II detoxification of activated carcinogens or ROS [61, 62]. Extensive studies have been performed on the possible associations between polymorphisms of *CYP1A1* and *GSTM1* and cancer susceptibility [63–65]. Similarly, the N-acetyltransferase (NAT) enzyme is involved in the metabolism and detoxification of cytotoxic and carcinogenic compounds as well as ROS [66]. It has been suggested that N-acetylation of polycyclic aromatic hydrocarbons (PAHs) by the NAT2 enzyme may be associated with ROS production [67]. ROS increase immunogenicity of DNA, LDL, and IgG, generating ligands for which autoantibodies show higher avidity [60]. Tumor necrosis factor r superfamily member 1B (TNFRSF1B) is a receptor for TNF-α and is considered to mediate various biological effects including generation of ROS and the subsequent intracellular proinflammatory signaling events [68]. Furthermore, cigarette smoking has been suggested to influence TNFRSF1B production [69, 70]. Representative functional polymorphisms of the *CYP1A1*, *GSTM1*, *NAT2*, and *TNFRSF1B* genes are *CYP1A1* rs464903, *GSTM1* deletion, *NAT2* genotypes determined by *NAT2**4, *5B, *6A, or *7B allele and *TNFRSF1B* rs1061622. Considering that exposure to ROS via cigarette smoking may be contributed to the development of SLE, it is important to study the association between SLE and the polymorphisms involved in metabolism of tobacco smoke and ROS production. We conducted candidate gene association studies (hypothesis-driven approach) of SLE in female Japanese subjects with special reference to the interaction between the polymorphisms involved in ROS production and cigarette smoking [71–74]. *CYP1A1* rs4646903 (OR of the CC genotype = 2.47, 95% CI = 1.28–4.78) [71] and *NAT2* genotypes (OR of the intermediate acetylator and slow acetylator genotypes combined = 2.34, 95% CI = 1.36–4.02) were significantly associated with SLE risk [72]. *TNFRSF1B* rs1061622 was marginally associated with an increased risk of SLE (OR of the G allele possession = 1.56, 95% CI = 0.99–2.47) [71]. There were significant additive interactions between smoking and any one of the following: *CYP1A1* rs4646903, *NAT2*, or *TNFRSF1B* rs1061622 [72–74]. Replication of findings is very important before any causal inference can be drawn. Testing replication in different populations is an important step. Future studies involving larger control and case populations, precisely and uniformly defined clinical classification of SLE and better exposure histories, will undoubtedly lead to a more thorough understanding of the role of the genetic polymorphisms involved in ROS production in SLE development.

5. Applications of findings in the epidemiological studies

Descriptive epidemiologic studies of SLE have been conducted not only in the Western countries (e.g., the United Kingdom, France, the United States, Canada) but also in Asian countries (e.g., China, South Korea, Japan). The prevalence of SLE provides useful information for the needs of health services for SLE patients. Information of the age- and sex-specific incidence and prevalence of SLE can be used to estimate the number of newly diagnosed SLE patients and the total number

of SLE patients in a community whose age and sex structure is known. On the other hand, the discrepancies of rates between different groups (e.g., different ethnic groups in the same country, different countries), which may be partly due to genetic factors as well as due to environmental factors [6], may give epidemiologists clues to plan epidemiological studies to determine a risk factor for SLE.

Observational studies such as case-control studies and cohort studies have been conducted to determine factors related to the development of SLE (i.e., risk factors, preventive factors) [49, 75]. After determining risk factors, preventive action will be started to control the level of exposure to a risk factor for SLE (i.e., reducing the risk of SLE) as well as to undergo a medical examination for the early detection of SLE for persons who are at special risk (e.g., silica [50–54]) (i.e., high risk strategy [76]). The size of relative risk/odds ratio indicates the strength of association between an exposure and a risk of SLE. For a public health perspective, however, the attributable risk of SLE is more important than the relative risk. The attributable risk is the difference in the risk of SLE between the exposed and the unexposed persons [49, 75]. The population attributable risk is the incidence of SLE in a population that is associated with an exposure to a risk factor, which is useful for determining the relative importance of exposures for the entire population [49, 75]. When the proportion of exposed persons is large, the population attribute risk is high even if the relative risk is small. More cases of SLE may develop in a large number of persons who are at a small risk than in the small number who are at high risk.

Smoking is an avoidable risk factor for SLE [38–42, 45] as well as for cancer [77] and cardiovascular diseases [78]. Therefore, antismoking education for both smokers and nonsmokers throughout lifetime (i.e., population strategy [76]) is important to reduce the incidence of SLE as well as the incidence of cancer and cardiovascular diseases in the general population.

6. Summary

The incidence and prevalence of SLE vary with sex, age, ethnicity, and the way how to detect SLE patients (e.g., case definition). SLE is more common in women than men across all age groups, and this female predominance is especially noteworthy during the reproductive ages [28], which suggests that female sex hormones may play an important role in the development of SLE.

A lower incidence and prevalence of SLE has been constantly observed in White People than in Black People [12, 17, 18] as well as Asian/Pacific Islanders [6, 17, 18] in the United States, while the incidence and prevalence of SLE is lower in White People than in Black African, Black Caribbean, and Indian [16]. The discrepancies of rates between ethnic groups are in part due to genetic factors as well as due to environmental factors such as smoking and dietary habits [7].

There are worldwide differences in the incidence and prevalence of SLE [79]. In addition to genetic factors and environmental factors, the way to detect SLE patients (e.g., case definition) is an important factor, which influences the incidence and prevalence of SLE. Ighe et al. [15] reported that the SLICC case definition of SLE yielded higher incidence and prevalence estimates than the ACR-97 case definition.

In this chapter, we introduce factors related to the development of SLE as well as incidence and prevalence of SLE. Among the reproductive issues, menarche at a younger age [29], use of contraceptive [29, 30], and use of postmenopausal hormones [29] increase the risk of SLE, while breast-feeding is associated with a decreased risk of SLE. Among environmental factors, tobacco smoking increases the risk of SLE [38–42, 46], while light to moderate alcohol drinking decreases

the risk of SLE [46]. On the other hand, the exposure to crystalline silica [50, 51], silica [52, 53], strong sunlight [42, 54], and ultraviolet radiation [50] increase the risk of SLE. Among genetic factors, *CYP1A1* rs4646903 and *NAT2* genotypes are associated with an increased risk of SLE, while *TNFRSF1B* rs1061622 is suggested to increase the risk of SLE [71–74]. In order to reduce the risk of SLE, we should reduce the exposure to avoidable risk factors such as smoking, contraceptives, crystalline silica, silica, strong sunlight, or ultraviolet radiation.

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