American Journal of Epidemiology

Vol 145, No 5
Printed in U.S.A.

Age-specific Incidence Rates of Myocardial Infarction and Angina in Women with Systemic Lupus Erythematosus: Comparison with the Framingham Study

Susan Manzi,[1] Elaine N Meilahn,[2] Joan E Rairie,[1] Claudia G. Conte,[1] Thomas A. Medsger, Jr.,[1] Linda Jansen-McWilliams,[2] Ralph B. D'Agostino,[3] and Lewis H. Kuller[2]

The authors ascertained cardiovascular events (myocardial infarction and angina pectoris) in 498 women with systemic lupus erythematosus seen at the University of Pittsburgh Medical Center from 1980 to 1993 (3,522 person-years). Subjects were stratified by age, and cardiovascular event incidence rates were determined. The authors compared these rates with cardiovascular event rates occurring over the same time period in 2,208 women of similar age participating in the Framingham Offspring Study (17,519 person-years). Age-specific rate ratios were computed to determine whether the cardiovascular events in the lupus cohort were greater than expected. The risk factors associated with cardiovascular events in women with lupus were determined. There were 33 first events (11 myocardial infarction, 10 angina pectoris, and 12 both angina pectoris and myocardial infarction) after the diagnosis of lupus; two thirds were under the age of 55 years at the time of event. Women with lupus in the 35- to 44-year age group were over 50 times more likely to have a myocardial infarction than were women of similar age in the Framingham Offspring Study (rate ratio = 52.43, 95% confidence interval 21.6–98.5). Older age at lupus diagnosis, longer lupus disease duration, longer duration of corticosteroid use, hypercholesterolemia, and postmenopausal status were more common in the women with lupus who had a cardiovascular event than in those who did not have an event. Premature cardiovascular disease is much more common in young premenopausal women with lupus than in a population sample. With the increased life expectancy of lupus patients due to improved therapy, cardiovascular disease has emerged as a significant threat to the health of these women. The impact of this problem has been underrecognized, with little focus placed on aggressive management of hypercholesterolemia and other possible risk factors. *Am J Epidemiol* 1997;145:408–15.

angina pectoris; lupus erythematosus, systemic; myocardial infarction; women

Although cardiovascular disease is rare among premenopausal women, several conditions appear to increase the risk of vascular disease in this population. Insulin-dependent diabetes mellitus (1), familial hypercholesterolemia (2), and possibly polycystic ovary syndrome (3) are three recognized examples. These conditions are associated with elevated low density lipoprotein cholesterol, reduced high density lipoprotein cholesterol, elevated testosterone, central obesity, and hypertriglyceridemia that are likely to contribute to the increased risk. In addition, women with artificial menopause resulting in low estrogen blood levels and increased low density lipoprotein cholesterol levels may also have an increased risk of vascular disease (4). Another disorder with an unappreciated association with premature cardiovascular disease is systemic lupus erythematosus. Lupus is a chronic inflammatory autoimmune disorder that affects young women much more often than it does men. Cardiovascular disease has been reported to be a major cause of both morbidity and premature mortality in women with lupus (5–12). The pathogenesis of premature cardiovascular disease in women with lupus is likely multifactorial, related to the underlying vascular inflammation and arterial wall injury, adverse effects of corticosteroids, the high prevalence of renal disease and hypertension, and increased thrombosis in the setting of antiphospholipid antibodies.

In this retrospective cohort study, we determined age-specific incidence rates of cardiovascular events, including myocardial infarction and angina pectoris, in

Received for publication January 22, 1996, and accepted for publication October 15, 1996.

Abbreviations: CI, confidence interval; RR, rate ratio.

[1] Department of Medicine, Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA.

[2] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

[3] Department of Mathematics, Boston University, Boston, MA.

Reprint requests to Dr. Susan Manzi, Suite 502, Liliane Kaufmann Building, 3471 5th Avenue, University of Pittsburgh, Pittsburgh, PA 15213.

a large population of women with systemic lupus erythematosus followed at the University of Pittsburgh over a 14-year period. We compared these rates with cardiovascular event rates in women of similar age, followed over the same time period, who were participating in the Framingham Offspring Study (13). We also determined the risk factors associated with cardiovascular events in women with lupus.

MATERIALS AND METHODS

Population surveyed

All consecutive female patients with a diagnosis of systemic lupus erythematosus seen at the University of Pittsburgh Medical Center between January 1, 1980, and December 31, 1993, were eligible for study entry. All patients met the 1982 revised American College of Rheumatology criteria for classification as having definite or probable lupus (14). In order to minimize potential referral bias, the 10 percent of our patients residing outside a 100-mile radius (160 km) of the medical center were excluded.

At the time of the initial evaluation, a standardized data collection form was used to prospectively collect clinical and demographic data on all patients with lupus. These forms are completed by the patient's physician. Approximately 450 variables are included on the form covering demographics, pertinent aspects of present and past medical history, physical examination (including blood pressure, reproductive history, the dates of lupus symptom onset, physician diagnosis of individual organ system manifestations, and all of the American College of Rheumatology revised classification criteria for lupus) (14), and laboratory evaluation (routine and immunologic). At each subsequent clinic visit or rehospitalization, all additional clinical, laboratory, and treatment data are recorded on an abbreviated standardized follow-up form. Treatment data include dose and schedule of corticosteroids and medications taken for comorbid diseases, including antihypertensives, insulin, oral hypoglycemics, and cholesterol-lowering agents.

We maintain updated records of deaths that occur in the University of Pittsburgh lupus cohort. Death certificates are requested routinely along with medical records to determine the most accurate cause of death.

A comparison of cardiovascular incidence rates was made with those of 2,208 women of similar age participating in the Framingham Offspring Study, which is a population-based, prospective investigation to identify cardiovascular disease in the offspring of the 5,209 men and women participating in the original Framingham Heart Study (13).

Recruitment and ascertainment of cardiovascular events in the lupus cohort

Initial patient contact was made at an office visit or via a letter describing the research study and requesting consent for participation. Cardiovascular events were ascertained during routine examination or by telephone interview. Participants were asked to provide information about all physician-diagnosed cardiovascular events, including myocardial infarction or angina pectoris. An authorization for release of medical information was obtained from any participant reporting an event, and all pertinent hospital and outpatient records were reviewed (S. M.). Criteria for defining a myocardial infarction or angina were taken from the Cardiovascular Health Study (15–17). Documentation required a hospital face sheet with diagnosis and procedure codes, discharge summary, admitting history, physical examination, and pertinent laboratory results, as well as diagnostic tests including an electrocardiogram, chest radiograph, treadmill stress test, cardiac catheterization, thallium and multigated acquisition scan, and cardiology consultation reports. Criteria for diagnosing both myocardial infarctions and angina were similar in the Framingham Offspring Study (18).

Cardiovascular events in the deceased patients were obtained by medical record review and records of deaths in the lupus cohort. Death certificates and autopsy reports were requested along with medical records as part of routine follow-up.

We collected information on both "traditional" risk factors and lupus disease-related factors that may be associated with the occurrence of cardiovascular events in these women. Most of the information was prospectively collected during routine surveillance of patients. The risk factor exposure period for the women with lupus was until the diagnosis of cardiovascular event in those women who had an event, until the time of interview in the living participants, or until the last hospital or outpatient visit in the deceased patients.

The "traditional" risk factors were defined as follows. Smoking was defined as ever use of tobacco (yes/no), and the number of pack-years (packs of cigarettes/day times the number of years smoking) was calculated. A family history of cardiovascular disease was defined as a myocardial infarction in a first degree relative before the age of 60 years. Hypertension was defined as a recorded blood pressure of greater than 140/90 mmHg at any patient visit or use of antihypertensive medication. A serum total cholesterol level greater than 240 mg/dl or a physician-diagnosed history of hypercholesterolemia requiring treatment with lipid-lowering agents was considered hypercholester-

olemia. Diabetes was defined by a physician diagnosis requiring either insulin or oral hypoglycemic agents.

The lupus disease-related factors were renal disease defined by the American College of Rheumatology criteria for lupus (14). These include the following: 1) persistent proteinuria (>500 mg/24 hours), 2) greater than 3+ proteinuria on dipstick if 24-hour quantitation was not performed, or 3) cellular casts (red blood cells, granular, tubular, or mixed). Corticosteroid use included the duration of use (total months of corticosteroid usage) and maximum dose standardized by conversion to prednisone equivalents (mg/day).

Current age, race, age at lupus diagnosis, and lupus disease duration from the first physician's diagnosis were documented. In addition, menopausal status (surgical or natural) was carefully determined for all subjects.

Statistical analysis

Chi-square and unpaired *t* tests were used to compare demographic variables and potential risk factors in the women diagnosed with lupus with and without cardiovascular events.

For each participant, the person-time of observation was calculated from the study interval start date, January 1, 1980, or the date of the first visit until death, cardiovascular event date, or the end of the study interval, December 31, 1993. The ages of the women with lupus were stratified into six 10-year intervals ranging from age 15 to age 74 years. The incidence rates of cardiovascular events were calculated by dividing the number of women with an event in each age group by the total person-years of observation contributed by all of the women in that age stratum. Each woman contributed the person-years of observation that she spent in a specific age stratum. For example, if a woman was age 19 years at lupus diagnosis and is currently age 33, she contributed person-years of observation to two different 10-year strata (15–24 and 25–34 years). Age-specific death rates were calculated in the same manner. Ninety-five percent confidence intervals were calculated based on a Poisson distribution.

The incidence rates of cardiovascular events from January 1, 1980, through December 31, 1993, per age stratum were also computed for the women in the Framingham Offspring Study. This allowed the calculation of age-specific rate ratios and 95 percent confidence intervals comparing the women with lupus with women from the Framingham cohort (19, 20).

The differences in frequencies and mean values of the various risk factors in women with lupus with and without cardiovascular events were determined by chi-square analysis and Student's *t* test. To determine the association between potential risk factors and cardiovascular events in the women with lupus, we used a Cox proportional hazards model with BMDP software (BMDP Statistical Software, Inc., Los Angeles, California).

RESULTS

Of the 575 eligible women with lupus, 503 (87 percent) had sufficient cardiovascular event information available (447 living and 56 deceased). Twenty-one (3.7 percent) women were lost to follow-up, 25 (4.3 percent) chose not to participate, and 26 (4.5 percent) are known to be alive but have been unable to complete the interview. We excluded five women 75 years of age or older from the analysis, since there were no women of comparable age in the Framingham Offspring Study. Seventy-six percent of the remaining 498 participants were Caucasian, 22 percent were African American, and the rest were American Indian, Asian American, and Eastern Indian. The mean age at lupus diagnosis was 34 years (range, 7–73 years). Each woman contributed an average of 6.7 years of observation, for a total of 3,522 years of observation.

Of the 54 deceased women whose mean age at the time of death was 49 years, six had a myocardial infarction. Combining the deceased and living patients, 37 (7.4 percent) of 498 women had a documented cardiovascular event. Four of these women had their event prior to lupus diagnosis with three of them having their event within 6 months of the first symptom of lupus. For the purposes of calculating incidence rates, we included as event cases only the 33 women with a verified cardiovascular event after the diagnosis of lupus. Eleven of these 33 women had a myocardial infarction, 10 had angina pectoris, and 12 had both angina pectoris and a myocardial infarction. The mean age of the 33 women at the time of the first cardiovascular event was 48 years (range, 22–72 years), and the median age was 44 years. Twenty-two (60 percent) of the 37 women with a cardiovascular event had either a cardiac catheterization or an autopsy. Eighty-two percent had evidence of significant atherosclerosis of the coronary vessels.

Thirteen additional women reported cardiovascular events that could not be verified. In three cases, a review of the medical record revealed diagnoses other than a cardiovascular event, including pericarditis, mitral valve prolapse, and respiratory arrest. In the remaining 10 cases, we were unable to obtain adequate medical records for verification. Only the cardiovascular events that were verified by a review of the medical records were included in the analysis.

Table 1 shows the age-specific distribution of cardiovascular events in the 498 women with lupus and

TABLE 1. The age-specific distribution of cardiovascular events in 498 women with systemic lupus erythematosus, University of Pittsburgh, 1980–1993, and 2,208 women, Framingham Offspring Heart Study, 1980–1993

Age (years)	Myocardial infarction*		Angina pectoris		Person-years of observation	
	SLE†	Framingham	SLE	Framingham	SLE	Framingham
15–24	1	0	0	0	158	312
25–34	3	0	1	2	820	3,207
35–44	11	1	2	4	1,311	6,143
45–54	3	10	1	8	623	5,125
55–64	3	5	2	6	358	2,516
65–74	2	0	4	0	252	216
Total	23	16	10	20	3,522	17,519

* Note those individuals with either myocardial infarction or both myocardial infarction and angina pectoris were included in the myocardial infarction category. Those who had only angina pectoris but not myocardial infarction are in the angina pectoris category.
† SLE, systemic lupus erythematosus.

the 2,208 Framingham women, respectively. The age-specific rates of cardiovascular events per 1,000 person-years for both the women with lupus and the women from the Framingham Offspring Study are shown in table 2. The rate ratio for myocardial infarction in the 35- to 44-year age group was 52.43 (95 percent confidence interval (CI) 21.6–98.5), indicating that the women with lupus were approximately 52 times more likely to have a myocardial infarction than were women in this population sample.

Table 3 shows the age-specific distribution of deaths from all causes along with death rates and 95 percent confidence intervals in the 498 women with systemic lupus erythematosus.

The comparison of demographic variables and potential risk factors in women with lupus with and without a cardiovascular event is shown in table 4. An older age at lupus diagnosis (39 vs. 34 years, $p = 0.02$), longer lupus disease duration (13 vs. 10 years, $p = 0.01$), hypercholesterolemia (18 percent vs. 4 percent, $p = 0.003$), longer duration of corticosteroid use (11 vs. 7 years, $p = 0.002$), and postmenopausal status (48 percent vs. 29 percent, $p = 0.03$) were more common in the women with lupus who had a cardiovascular event than in those without an event.

In the Cox proportional hazards model controlling for age (table 4), lupus disease duration (rate ratio (RR) = 0.83, 95 percent CI 0.74–0.92), hypercholesterolemia (RR = 3.35, 95 percent CI 1.34–8.36), and older age at lupus diagnosis (RR = 1.21, 95 percent CI 1.09–1.35) were the three variables significantly associated with cardiovascular events.

TABLE 2. Incidence rates of cardiovascular events per 1,000 person-years in the 498 women with systemic lupus erythematosus, University of Pittsburgh, and 2,208 women, Framingham Offspring Heart Study, 1980–1993

Age (years)	SLE*		Framingham		Rate ratio	95% CI
	Rate	95% CI*	Rate	95% CI		
			Myocardial infarction			
15–24	6.33	0.2–35.3	0.00	0.0–11.8	∞	
25–34	3.66	0.8–10.7	0.00	0.0–1.2	∞	
35–44	8.39	4.2–15.0	0.16	0.0–0.9	52.43	21.6–98.5
45–54	4.82	1.0–14.1	1.95	0.9–3 6	2.47	0.8–6.0
55–64	8.38	1.7–24.5	1.99	0.6–4.6	4.21	1.7–7.9
65–74	7.94	1.0–28.7	0.00	0.0–17.1	∞	
			Angina			
15–24	0.00	0.0–23 4	0.00	0.0–11.8	∞	
25–34	1.22	0.0–6.8	0.62	0.1–2.3	1.96	0.0–9.0
35–44	1.53	0.2–5.5	0.65	0.2–1.7	2.35	0.4–11.1
45–54	1.61	0.0–8.9	1.56	0.7–3.1	1.03	0.2–4.6
55–64	5.59	0.7–20.2	2.39	0.9–5.2	2.33	0.9–5.5
65–74	15.87	4.3–40.6	0.00	0.0–17.1	∞	

* SLE, systemic lupus erythematosus, CI, confidence interval.

TABLE 3. Age-specific distribution of deaths and the death rates in 498 women with systemic lupus erythematosus, University of Pittsburgh, 1980–1993

Age (years)	No. of deaths*	No. of person-years	Rate/1,000 person-years	95% CI†
15–24	2	158	12.6	1.5–45.6
25–34	12	820	14.6	7.6–25.5
35–44	13	1,311	9.9	5.3–16.9
45–54	7	623	11.2	4.5–23.1
55–64	14	358	39.1	21.3–65.6
65–74	6	252	23.8	8.7–51.8
Total	54	3,522		

* Deaths due to all causes.
† CI, confidence interval, based on the Poisson distribution

DISCUSSION

The frequency of cardiovascular disease events in women with lupus has been reported to range from 6.1 percent to 8.9 percent in several series (5–7). Thirty-seven (7.3 percent) of the present lupus population had a cardiovascular event, with 33 (6.6 percent) having the event after the diagnosis of lupus. Thus, the overall frequency of cardiovascular events is similar in our lupus population. However, the age-specific incidence rates compared with those of the general population have not been previously reported. Our study emphasizes the disturbingly high frequency of cardiovascular events in young women with lupus.

Although coronary disease is the leading cause of death among women, coronary events occur rarely in women under the age of 55 years (21). In contrast to the general female population, 22 (67 percent) of our 33 women with lupus had their cardiovascular event under the age of 55 years. Eighteen of these 22 women were under the age of 45 years. The incidence of myocardial infarction in women with lupus aged 35–44 years is over 50 times greater than in women of similar age from a population-based sample. We recognize that information regarding myocardial infarction is less susceptible to detection bias than is angina. We likely underestimated the frequency of angina in our women with lupus because of the strict definition requiring a physician diagnosis. This may explain the lack of significant difference in rates of angina between our young women and the Framingham women. From our clinical experience, we find that a considerable number of our patients with lupus report angina-like chest pain that has never been evaluated or rec-

TABLE 4. Comparison of risk factors between women who had systemic lupus erythematosus with and without cardiovascular events, University of Pittsburgh, 1980–1993

Risk factors	Cardiovascular event* (n = 33)		No event (n = 465)		p value†	RR‡	95% CI‡
	No	%	No.	%			
Non-Caucasian	6	18	93	20	0.97	0.57	0.23–1.42
Renal disease	10	30	101	21	0.35	1.51	0.69–3.32
Pericarditis	6	18	51	11	0.33	0.92	0.37–2.25
Hypertension	24	72	295	63	0.37	1.16	0.52–2.57
Hypercholesterolemia	6	18	21	4	0.003	3.35	1.34–8.36
Diabetes	4	12	27	5	0.28	1.98	0.69–5.71
Family history of cardiovascular disease	12	36	150	32	0.76	1.64	0.79–3.39
Postmenopause	16	48	138	29	0.03	0.77	0.24–2.46
Corticosteroid use	29	87	383	82	0.56	0.57	0.19–1.67
Duration of use§					0.002	0.98	0.94–1.03
Maximum dose¶					0.59	1.00	0.99–1.01
Tobacco							
Use	19	57	248	53	0.77	1.33	0.66–2.70
Pack-years#					0.33	1.01	0.99–1.03

	Cardiovascular event (mean years)	No event (mean years)	p value	RR	95% CI
Age at lupus diagnosis	39	34	0.02	1.21	1.09–1.35
Lupus disease duration	13	10	0.01	0.83	0.74–0.92

* Myocardial infarction and angina pectoris.
† Chi square, *t* test.
‡ RR, rate ratio (univariate Cox regression models controlling for age); CI, confidence interval.
§ Eleven- and 7-year durations of use for cardiovascular event and no event, respectively.
¶ Sixty-two- and 58-mg maximum doses for cardiovascular event and no event, respectively.
# Twenty-four and 20 pack-years for cardiovascular event and no event, respectively.

ognized by their primary physicians. This may be due to underreporting by the patient or a low index of suspicion on the part of the physician, since most of these women are young and premenopausal.

We found a small decline in the incidence rates for myocardial infarction in women with lupus aged 45–54 years compared with those having the same diagnosis aged 35–44 years. The reasons for this are unclear and may be a sampling phenomenon. The mortality rates from all causes are not significantly different between the women in these two age strata, thus making differences in overall survival an unlikely explanation. A plausible theory may be the prothrombic effects of estrogen in combination with hypertension, renal disease, and possibly the presence of antiphospholipid antibodies in premenopausal women aged 35–44 years with a relatively protective effect of declining estrogen levels in women aged 45–54 years. As might be expected, the incidence rates for myocardial infarction begin to rise again after the age of 55 years. The role of estrogen in cardiovascular disease is of particular interest in women with lupus. Abnormalities in estrogen metabolism resulting in a relative increase in the estrogen/androgen ratio have been reported in lupus and may explain the higher incidence of disease in women and the increased risk of lupus disease activity during pregnancy and menses (22, 23). Because of the retrospective design of this study, we were unable to obtain accurate information with regard to hormone replacement or birth control use in many of the women; thus, we did not include these data in our analysis. Larger studies evaluating the role of estrogen and cardiovascular disease in lupus are needed.

Premature cardiovascular disease is a major factor in mortality in these young women. Urowitz et al. (8) were the first to suggest that mortality in lupus followed a bimodal pattern. Deaths early in the disease course were most often due to active lupus and/or intercurrent infection, whereas deaths later in the disease course were more frequently attributed to atherosclerotic coronary heart disease and acute myocardial infarction. Thirty percent of 51 deaths from lupus in this series were due to vascular disease. Six deaths occurred in women under the age of 55 years. Spiera and Rothenberg (9) reported two women with lupus in their early twenties who died following a myocardial infarction. Postmortem examination revealed significant atherosclerosis. There have been multiple other case reports and small series confirming premature mortality due to cardiovascular disease in young women with lupus (10, 11).

Our hypothesis is that the pathogenesis of cardiovascular disease in lupus is likely multifactorial, because of an interaction between inflammation-induced and antiphospholipid antibody-related vascular injury/thrombosis from the underlying disease and traditional cardiovascular risk factors. Corticosteroid treatment and renal disease with resulting hypertension may accelerate the atherosclerotic process in women with lupus. In our study, as well as in other series, atherosclerotic heart disease has been a major finding in the women with cardiovascular events. Coronary vasculitis is rare (24). Although vascular inflammation is not the sole etiology of most cardiovascular events in lupus, it may be a major contributor.

The role of inflammation in the development of atherosclerosis in the general population is currently of great interest (25, 26). Cytokines, particularly interleukin-6, have proliferative effects on fibroblasts that may contribute to formation of atherosclerotic plaques (27). Hunt (28) has proposed that an increase in coagulation factors, such as fibrinogen, is induced by interleukin-6 from proliferating smooth muscle cells in atherosclerotic lesions. Fibrinogen is procoagulatory in that it is a precursor to fibrin, which forms the blood clot. Elevated plasma fibrinogen levels have been found among postmenopausal women compared with both premenopausal women and women taking estrogen therapy (29). Elevated fibrinogen levels have been linked to the risk of heart disease prospectively in women (30). Persistent vascular injury may result in a prolonged acute phase response with a decrease in serum albumin level, increase in globulin and other proteins, and possibly an increased risk of thrombosis. The association between inflammatory mediators and cardiovascular disease is of particular interest in women with lupus, since lupus is a disease characterized by inflammation.

Treatment with corticosteroids has been implicated as a risk factor for atherosclerosis. A necropsy study by Bulkley and Roberts (31) was one of the first to suggest an association between long-term corticosteroid therapy and accelerated atherosclerosis in patients with lupus. Eight of 36 (22 percent) young patients with lupus who had been taking corticosteroids for over 1 year had evidence of significant coronary artery atherosclerosis at autopsy. Interestingly, none of the 17 patients with lupus who were taking corticosteroids for less than 1 year had significant coronary atherosclerosis. Other investigators (7, 32) have found that ever use of or longer duration of use of corticosteroids is associated with an increased risk of cardiovascular events in patients with lupus. Whether corticosteroids are directly atherogenic or whether they are causally related to atherosclerosis through the enhancement of cardiovascular disease risk factors such as hyperlipidemia (33), hyperglycemia, hypertension, or obesity

remains unclear. In addition, corticosteroids may be a proxy for severe disease, since patients with severe lupus are more likely to be treated with corticosteroids at higher doses for longer periods of time. We also found that a longer duration of corticosteroid use was more commonly seen in our women with lupus with a cardiovascular event compared with those without an event.

Renal involvement is a serious feature of lupus and has been reported in as high as 50 percent of patients (34). The most common pathologic lesion is immune complex-mediated glomerulonephritis. Endothelial cell damage produced by immune complexes, or other mediators of inflammation, may be responsible for activation of the coagulation system in patients with lupus nephritis, resulting in elevated plasma and urine levels of fibrinogen. Increased fibrinogen, along with the abnormal lipid profiles and hypertension frequently seen in patients with nephritis, may result in an increased risk of cardiovascular disease in women with lupus. We did not find an association between renal disease and cardiovascular events in our study. In part, the failure to identify a relation may be due to our definition of renal disease that was based on the American College of Rheumatology criteria. These criteria emphasize heavy proteinuria and cellular casts; the former may be too restrictive and the latter missed because of the retrospective nature of the study.

Traditional risk factors for cardiovascular disease in the general population include diabetes mellitus, hyperlipidemia, hypertension, obesity, family history of cardiovascular disease, sedentary lifestyle, and smoking. Petri et al. (7) reported that a higher mean serum cholesterol level, hypertension, or previous use of antihypertensive medications was significantly associated with cardiovascular events that occurred in 19 of 229 patients with lupus. We also found that hypercholesterolemia was associated with cardiovascular events.

The limitations of our study are due to its retrospective design. We were limited in some instances in our ascertainment of cardiac events and risk factors by what was available in the medical record. Our cardiac event frequencies may even be higher than reported, considering that 10 women reported events that we were unable to confirm because of the unavailability of adequate medical records for verification. All of the women in the Framingham study are Caucasian and do not represent a similar racial distribution as do our women with lupus. We did not find race to be a risk factor in the development of cardiovascular disease in our lupus cohort and believe that this racial difference cannot explain the strikingly higher frequency of cardiovascular events in our young women with lupus. Because of the retrospective design of this study and inclusion of women seen as remotely as 1980, we did not have adequate information on antiphospholipid antibody status on enough participants to include this potential risk factor. Although these antibodies have been associated with thromboembolic events, including stroke in women with lupus (35, 36), there has not been a clear association reported with myocardial infarction (37). Women with lupus who had a cardiovascular event had a longer mean lupus disease duration than had those women without an event (13 vs. 10 years, $p = 0.01$). However, when we performed the Cox analysis, adjusting for age, a longer lupus disease duration appeared to be protective (RR = 0.83, 95 percent CI 0.74–0.92). Although this seems counterintuitive, defining lupus disease duration is difficult. We measured lupus disease duration from the time of diagnosis. This is an arbitrary time period that is likely dependent on access to medical care and severity of disease (e.g., women with more severe disease are likely to be diagnosed sooner than those with mild disease). Measuring lupus disease duration from the time of the first symptom is theoretically better; however, the first symptom can be very subjective and from our clinical experience much more difficult to determine. For these reasons, we chose to measure disease duration from the time of the first physician diagnosis. Our results in reference to lupus disease duration as a risk factor for a cardiovascular event should be interpreted cautiously. Overt cardiovascular events may underestimate the true frequency of cardiovascular disease in these women. The prevalence of "subclinical disease" is likely much higher (38–40).

Although cardiovascular disease is gaining more recognition as a major health problem in women in the general population, it is largely a disease of postmenopausal women, over the age of 55 years. Nearly half of our young women with lupus were premenopausal at the time of their event. Our study emphasizes the premature nature of vascular disease that leads to overt cardiovascular events in women with lupus. The impact of this problem has been underappreciated, with little focus placed on the aggressive management of hypercholesterolemia and on other correctable risk factors. In addition, the use of hormone replacement therapy in these women has often been avoided because of concern over the role of estrogen in the exacerbation of lupus. The identification of women at highest risk of a cardiovascular event, including those with evidence of early subclinical atherosclerosis by noninvasive testing, will allow targeting of intervention in a cost-effective manner.

ACKNOWLEDGMENTS

This study was supported by grants from the Commonwealth of Pennsylvania (Department of Health); Lupus Foundation of America, Western Pennsylvania Chapter; and Pennsylvania Lupus Foundation, Inc.

The authors thank Joan Neitznick for her clerical assistance.

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