Prevalence of Factors Influencing Cancer Risk in Women with Lupus: Social Habits, Reproductive Issues, and Obesity

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ABSTRACT. ***Objective.*** There is mounting evidence that hematological malignancies are increased in systemic lupus erythematosus (SLE), and the risk of certain solid tumors may also be increased. The pathogenesis may be different for the 2 processes: risk of hematological malignances in SLE may be due to chronic lymphocyte stimulation, while risk of solid tumors may be influenced by factors such as obesity and reproductive habits. We aimed to determine prevalence in a lupus cohort of selected factors that influence the risk of cancer, and to compare this prevalence to that of the general population.

Methods. Subjects were women followed in the Montreal General Hospital Lupus Clinic. We administered a postal survey of factors known to be associated with lung and aerodigestive cancers (smoking, alcohol use) as well as factors associated with breast and gynecologic cancers (nulliparity, use of oral contraceptives, and hormone replacement therapy). For patients who had died or been lost to followup, data were abstracted from clinic records. Information about nonsteroidal antiinflammatory drug (NSAID) use (a potentially protective factor for colorectal cancer) was also collected. Obesity prevalence was established from the clinic database. Comparison figures were obtained from the 1996–1997 National Population Health Survey data for Quebec women and age adjusted, where possible.

Results. Compared to the general population, the lupus population had lower prevalence of current use of oral contraceptives, and greater prevalence of obesity and nulliparity. The average number of pack-years among smokers was also greater in the lupus cohort.

Conclusion. Solid cancer incidence in SLE may be influenced by established cancer risk factors such as smoking, obesity, and reproductive history. (J Rheumatol 2002;29:2551–4)

Key Indexing Terms:
MALIGNANCY   SYSTEMIC LUPUS ERYTHEMATOSUS   CANCER RISK FACTORS

There is mounting evidence that cancer risk is increased in systemic lupus erythematosus (SLE)[1-5], although the conclusions have not been uniform[6–8], likely due to study limitations[2]. The increased risk of hematological malignancies, particularly non-Hodgkin's lymphoma, has been demonstrated in numerous cohort studies[2-8], but an increased risk may also be apparent for certain types of solid tumors[9].

There is evidence that immune system abnormalities in SLE may increase cancer susceptibility, at least for lymphoreticular malignancy[10-15]. However, little is known about how the prevalence of certain cancer risk factors (such as obesity and nulliparity) potentially contributes to an increase in solid tumors. Thus, we investigated the prevalence of selected malignancy risk factors in SLE patients, compared to the general population.

Because the majority of patients with lupus are women, and because many of the risk factors of interest pertain to breast and gynecologic tumors, we focused on female patients only.

MATERIALS AND METHODS

The study population was the Montreal General Hospital (MGH) Lupus Clinic cohort. The periods of observation spanned from January 1977 to December 1998. As of 1998, the cohort numbered 325 individuals, 290 of which were women. Consecutive patients are enrolled in the cohort at the time when they present for their first clinic visit, and data from each visit are entered into a computerized database. All members fulfill the American College of Rheumatology criteria for SLE[16,17].

In 1998, we administered a postal survey of risk factors for lung and aerodigestive (smoking, alcohol use) as well as factors for breast and gynecologic cancers (nulliparity, age at birth of first child, use of oral contra-

ceptives, and hormone replacement therapy). Information about current nonsteroidal antiinflammatory drug (NSAID) use (a potentially protective factor) was collected at the same time. For those who had died (n = 57) or were lost to followup (n = 43) data were abstracted from the database or medical records (this was also done for 23 living patients who consented to participate but who did not wish to complete a questionnaire). Obesity prevalence for the cohort was determined by calculating body mass index using each patient's last recorded weight in the database. To rule out a time trend bias, we repeated the analysis including only those patients for whom we had relevant data during the period 1995–1998. This study was approved by the McGill University Health Centre Research Ethics Committee.

Risk factor prevalence among women members of the cohort was compared to that of the general population, using age adjusted data collected on Quebec women during the 1996–1997 National Population Health Survey (NPHS)[18]. For our analyses, we used the raw data from the women respondents (N = 1401) from surveyed households in Quebec to produce age-standardized population prevalence rates and means for the risk factors under study. As the NPHS contains a single question that combines NSAID and other analgesics, we obtained our age and sex adjusted population figures on NSAID use prevalence from a recently published Canadian study[19].

Proportions and means were calculated for our study subjects. For each risk factor of interest, the population value (for Quebec women) was standardized to the age distribution of our study cohort as it stood at the beginning of 1998. For both the cohort and the population values, approximate 95% confidence intervals (CI) for the prevalences and means were calculated using the large sample inference for a population. The differences between the cohort values and the population values were obtained by subtraction of the latter from the first, and approximate 95% CI were calculated for the differences. The variance for the general population estimate was calculated using a weighted sum of variances of the age group categories (weights for calculating the variance being the square of those for calculating the standardized estimate). In the calculation of the CI for both the general population estimate and for the difference between the 2 groups, the general population standard error used was the square root of this variance.

For both the NPHS and for the lupus cohort, the risk factor of smoking was defined as having ever smoked regularly (i.e., on a daily or weekly basis). Therefore this included both current smokers and former smokers in the same category of "ever smokers." (The data for pack-years includes both current and past smokers.) Similarly, for both populations, alcohol exposure was dichotomized as the consumption of greater than 2 (vs 2 or less) glasses of alcohol per day (current or past)[20].

For both populations, current use of oral contraceptives was determined only for women aged 50 or less, as women over the age of 50 were unlikely to require contraception. In like fashion, we considered only women who were older than 50 to determine the prevalence of hormone replacement use. The population data available were for current use of oral contraceptives and hormone replacement therapy; thus we present data on current use for the cohort.

RESULTS

Table 1 presents the age distribution of the subjects. The majority (76%) were Caucasian; the mean number of years of education was 13 years (standard deviation 2.8). The patients ranged across the spectrum of disease severity, in terms of treatment pattern. At some time in their disease course, 80% had taken prednisone and 79.4% had taken antimalarials (the majority hydroxychloroquine), 12.6 % of the cohort had been exposed to methotrexate, 16.6% had been exposed to cyclophosphamide, and 25.9% to azathioprine.

Table 1. Age distribution for women members of the Montreal General Hospital lupus cohort.

Age*, N	Alive, N (Participants)	Dead, N	Lost, N	Refused, N	
< 25	7	2	5	0	
25–29	11	4	4	1	
30–34	21	7	6	4	
35–39	28	2	7	3	
40–44	23	3	7	0	
45–49	19	5	4	3	
50–54	29	5	5	1	
55–59	14	3	2	0	
60–64	8	5	2	0	
65–69	8	7	0	1	
70–74	3	9	0	0	
75–79	2	3	0	0	
80-plus	3	2	1	1	
Subtotal	176	57	43	14	Total 290

* Age for participants: at time of study; for deceased patients: at time of death; for patients lost to followup: at time of last contact; for patients who refused: at time of study.

Data on alcohol use and tobacco use were missing for 13% and 17% of the total subjects, respectively. (The proportion of data missing did not differ significantly between the group that completed the questionnaires and the group where data were obtained from chart review.)

Table 2 presents the results of the prevalence estimates for each risk factor, both for the women in the McGill General Hospital cohort and the general population. Compared to the general population, the following differences were noted: the lupus population had a lower prevalence of current use of oral contraceptives, and a greater prevalence of nulliparity and obesity. The results were similar when data prior to 1995 were excluded, although CI were wider, and, in the case of obesity, the limits for the point estimates for the 2 populations overlapped. Positive history of smoking (past or current) was similar between the 2 groups; however, the average number of pack-years was greater in the lupus cohort compared to the general population. NSAID use was similar in the 2 populations.

DISCUSSION

Compared to the general population, the lupus population had a distinct profile of risk factors known to be associated with malignancy, with a lower prevalence of current use of oral contraceptives, and a greater prevalence of nulliparity and obesity. These factors might lead to an increased risk of colon, endometrial, ovarian, and possibly breast cancer. In a recent analysis of cancer incidence in the MGH Lupus Cohort, point estimates of the standardized incidence ratio are consistent with increased risk of colon, breast, and ovarian cancers, although because of the low number of events, the CI are wide and include the null value[21]. Interestingly, although the risk factor profile of these

Table 2a: Prevalence of risk factors for malignancy in the Montreal General Hospital (MGH) lupus cohort and the Quebec population.

Risk Factor	Prevalence		Difference, Cohort vs Quebec Population (95% CI)	Predicted Effect on Lupus Cohort Cancer Risk
	MGH Cohort (95% CI)	Quebec Population (95% CI)		
Smoking, ever	0.51 (0.46, 0.56)	0.56 (0.53, 0.60)	–0.05 (–0.11, + 0.01)	
Oral contraceptives	0.04 (0.00, 0.08)	0.10 (0.08, 0.12)	–0.06 (–0.11,–0.02)	Breast ↓ Endometrial ↑ Ovarian ↑ Colorectal ↑ Cervical ↓
HRT	0.22 (0.13, 0.30)	0.15 (0.12, 0.17)	+ 0.07 (–0.01, 0.17)	
Nulliparity	0.26 (0.18, 0.36)	0.08 (0.08, 0.09)	+ 0.18 (0.10, 0.28)	Breast↑ Endometrial ↑ Cervical ↓
Alcohol use	0.04 (0.01, 0.06)	0.02 (0.02, 0.03)	+ 0.02 (0.0, 0.04)	
Obesity	0.30 (0.23, 0.36)	0.22 (0.22, 0.23)	+ 0.07 (0.01, 0.14)	Breast ↑ Endometrial ↑
NSAID use	0.19 (0.14, 0.24)	0.22 (0.17, –0.25)	–0.03 (–0.11, + 0.04)	

↑ : Increased cancer risk due to risk factor; ↓ : decreased cancer risk due to risk factor. HRT: hormone replacement therapy, NSAID: nonsteroidal anti-inflammatory drugs.

Table 2b: Mean of risk factors for malignancy in the Montreal General Hospital (MGH) lupus cohort and the Quebec population.

Risk Factor	MGH Cohort, Mean (95% CI)	Quebec Population, Mean (95% CI)	Difference, Cohort vs Quebec Population	Predicted Effect on Lupus Cohort Cancer Risk
Age at first child, yrs	24.7 (23.9, 25.4)	25.0 (24.7, 25.3)	–0.30 (–0.49, 0.11)	
Smoking, pack-years	16.35 (13.68, 19.02)	13.34 (12.34, 14.34)	+3.01 (0.16, 5.86)	Lung ↑ Aerodigestive ↑ Breast ↑ Colorectal ↑

↑: increased cancer risk due to risk factor; ↓: decreased cancer risk due to risk factor.

patients would suggest a decreased risk of cervical cancer, an increased risk of pre-cancerous cervical lesions has been reported in lupus[22] and an increased incidence of cervical cancers has been suggested in cohort studies[3]. The women in the MGH cohort experienced 4 cervical malignancies, but all were *in-situ*, which makes it difficult to measure their relative risk of cervical cancer compared to the general population, as Quebec rates do not include *in-situ* cancers. It is possible that the risk of cervical malignancies in lupus is influenced by drug exposure[23] or immunologic abnormalities[24] more than by reproductive factors.

The prevalence of current smokers in the cohort (not shown in Table 2) is 0.471 (95% CI 0.402, 0.539). This is similar to the prevalence of smoking estimated in other lupus cohorts[25-29]. It is noteworthy that Bruce, *et al*[29] found that physicians providing care for patients with lupus tended not to provide advice regarding cessation of smoking. Rectification of this would assist in limiting damage to persons with lupus, not only in coronary heart disease but presumably with respect to malignancies as well.

The finding of high prevalence of obesity among patients with SLE has been noted by others[26]. Since obese women are at greater risk of endometrial, breast, and colorectal cancers, obesity in lupus could heighten the danger of other factors (such as decreased use of oral contraceptives) that favor endometrial and other cancers.

We believe we have presented the most thorough assessment to date of risk factor prevalence for malignancies within a cohort of individuals with SLE, at least with respect to social habits, reproductive issues, and obesity. However, we acknowledge limitations in our study related to the difficulties in accurately measuring exposures that change over the lifetime of an individual. As well, we did not focus on other exposures that may be carcinogenic in lupus, such as alkylating agents and immunosuppressive drugs. The magnitude of the effect of these agents in lupus populations is not easy to establish, and a study of the relative importance of this in lupus compared to the general population is difficult to formulate, given the very low incidence of exposure to these agents in the general population. However, an

international collaborative effort is currently under way to determine with precision both the risk of cancer occurrence in SLE and the influence of drugs and other exposures on this risk[30].

In conclusion we note that although risk factor profiles could influence the incidence of certain solid malignancies in SLE, modification of these factors (particularly with respect to reproductive issues) may not be practical. All the same, we should recognize and attempt where possible to minimize the impact of cancer risk factors such as smoking and obesity.

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