Cancer Screening in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To examine whether patients with systemic lupus erythematosus (SLE) undergo cancer screening according to established guidelines, to compare their reported screening practices with information from the general population, and to examine potential predictors of screening within our SLE sample.

Methods. We conducted a patient survey of cancer screening practices within the Montreal General Hospital lupus cohort. We compared self-reported frequency of cancer screening to guidelines suggested for the general population, and to figures for cancer screening reported in the general population. We also developed logistic regression models to establish potential predictors of screening for patients with SLE, with cervical cancer screening being the outcome of interest in our primary analyses.

Results. Of 48 women aged 50-69, 53% (95% confidence interval, CI: 38-68) had had a mammogram in the past 12 months, compared to 74% (95% CI: 73-75) for similarly aged Quebec women. Of 51 subjects aged 50 and older, only 18% (95% CI: 8-34) reported screening (fecal occult blood check with or without endoscopy) within the recommended time frame, compared to 48% (95% CI: 45-51) for colorectal screening for persons > 50 in the general population. Only 9 of 27 patients with SLE aged less than 30 had Pap tests in the past 12 months (33%, 95% CI: 19-52), compared with a general population rate of 56% (95% CI: 53-59) for similarly aged Quebec women. Our logistic regression model suggested that, among the SLE patients, non-whites, those with lower education, and those with higher disease damage scores were less likely to undergo cervical Pap testing.

Conclusion. These data suggest that appropriate cancer screening may be overlooked in patients with SLE. (J Rheumatol 2006; 33:45–9; First Release Dec 1, 2005)

Key Indexing Terms:
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There is evidence that the incidence of cancer among patients with systemic lupus erythematosus (SLE) is increased, compared to the general population[1]. Some might postulate that this is related to a surveillance bias, whereby because they are likely to have regular medical followup, patients with SLE, may get more screening tests for cancer. On the other hand, because of the acute nature of much of the care provided to patients with SLE, screening for other diseases (such as breast and colorectal cancer and cervical dysplasia) may be overlooked. However, no studies to date have examined the frequency of cancer screening in SLE.

Our primary objective was to establish the frequency with which SLE patients undergo cancer screening (mammograms, colorectal cancer screening, and cervical Pap tests). Secondary objectives were to determine if this frequency was in accord with established guidelines, and to compare their cancer screening frequency with available figures for the general population. Finally, we examined whether specific demographic (race, education) and clinical factors (SLE damage scores, medication exposure) were predictors of cancer screening, with our primary outcome of interest being cervical Pap smear testing.

MATERIALS AND METHODS

Study design. We conducted a survey of cancer screening practices reported by patients registered in the Montreal General Hospital (MGH) lupus

cohort. The MGH lupus cohort enrols consecutive patients with American College of Rheumatology (ACR) criteria for SLE[2,3] at the time they present for their first clinic visit. Specific detailed clinical and laboratory data are collected prospectively on an annual basis, including information on disease activity and medication exposures.

Study participants. Our survey was performed between March 2004 and February 2005, using a short self-administered questionnaire given to patients attending a clinic visit. Written consent was obtained prior to administering the survey, and the protocol was approved by our institutional review board. As we created only English and French versions of the questionnaire, knowledge of one or other language was a prerequisite for study entry. Altogether, 166 consecutive clinic attendees were approached and asked to participate in the study and all but one agreed to complete the questionnaire. This patient could not participate because of inadequate knowledge of either English or French.

Data analysis. We compared self-reported frequency (of cancer screening) to guidelines suggested for the general population. Breast cancer screening was assessed according to specific guidelines recommended by the Canadian Task Force on the Periodic Health (annual mammography for women ages 50–69 years)[4]. Colorectal cancer screening was assessed according to the 2001 Canadian Task Force on Preventive Health Care, which recommends yearly fecal occult blood testing or periodic sigmoidoscopy or colonoscopy in individuals aged 50 and older[5]. For cervical Pap tests, we considered guidelines that suggest yearly cytology screening particularly for women younger than 30[6].

Quebec statistics for frequency of mammograms and Pap testing were obtained from Statistics Canada's Health Indicator reports[7]. Data on general population rates for colorectal screening were obtained from the literature[8,9].

We developed logistic regression models to examine potential predictors of screening in the SLE sample. Cervical cancer screening (within the past year) was the outcome of interest in our primary analyses because of numerous studies emphasizing the increased risk of cervical dysplasia in SLE[10-14]. We also performed secondary analyses to examine determinants of (1) mammography within the past year in women of age 50 or older; and (2) colorectal screening in all subjects age 50 or older (limiting the sample to those without family history of colorectal cancer). In these models, we examined for the effects of SLE disease damage (as captured by the total Systemic Lupus International Collaborating Clinics/ACR Damage Index [SLICC/ACR DI] score), previous immunosuppressant exposure (a dichotomous variable indicating whether the patient had previously been exposed to azathioprine, cyclophosphamide, methotrexate, or mycofenolate), race, and education. These covariates were chosen *a priori* because of data suggesting that they may influence screening behavior[15,16]. The estimates from these models were adjusted for age, sex (for colorectal cancer screening), SLE duration, and whether or not the patient indicated they had a regular family doctor, as these were felt to be potential confounders or effect modifiers.

RESULTS

Of the sample of 165 respondents, 146 (89%) were females. The median age of the entire group was 43 years (mean 44.2, standard deviation, SD 14.7). Regarding medication use, the majority (81.4%) had been exposed to prednisone at some point in their treatment; 9.4% had been exposed to methotrexate, 12.1% to mycofenolate, 15% to cyclophosphamide, and 26.6% to azathioprine. Demographic and clinical characteristics are presented in Table 1.

Breast cancer. Among the 146 women, 4 reported a past history of breast cancer, and all of these reported having a mammogram in the past 12 months. In the entire sample, 9 women reported a family history of breast cancer; of these, 7 had had a mammogram in the past 12 months. Of the 48 women aged 50-69, just over 50% (53%, 95% confidence interval, CI: 38–68) had had a mammogram in the past 12 months, compared to 74% (95% CI: 73–75) for similarly aged Quebec women[7].

Table 1. Demographics and characteristics of patients with SLE (n = 165).

Variable	n (%)
Female (%)	146 (88.5)
Caucasian* (%)	121 (73.3)
Has regular family doctor (%)	97 (58.8)
Age, yrs, mean (SD)	44.2 (14.7)
Education, yrs, mean (SD)	12.5 (2.7)
SLE duration, yrs, mean (SD)	13.8 (10.3)
SLE damage score**, mean (SD)	1.8 (2.3)

* The remainder were Asian (n = 16), black/African American (n = 13), or other (n = 15). ** The most recent Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) score; the median value of the SLICC/ACR DI scores was 1.0 (interquartile range 3.0).

Colorectal cancer. None of the respondents had a personal history of past colorectal cancer; 13 had a family history of colorectal cancer. Of these 13, just 6 reported having had appropriate screening in the past 5 years. Of the subjects aged 50 and older (n = 51), only 18% (95% CI: 8–34) reported screening within the recommended time frame, compared to the reported 48% (95% CI: 45–51) for colorectal screening for persons > 50 in the general population[8]. Altogether, 25% of the subjects (95% CI: 19–33) had had screening of any kind for colorectal cancer; corresponding population figures are just over 40% (95% CI: 36–43)[9]. Thirteen percent (95% CI: 8–19) reported ever having had fecal occult blood testing, compared to general population figures of 32% (95% CI: 29–36)[9].

Cervical cancer. Seven women reported a history of cervical dysplasia. Only 5 of these had had a Pap test in the last 12 months. Altogether, just 43.8% (95% CI: 36.1–51.9) of the women with SLE reported having a Pap test in the preceding 12 months compared to a Quebec population rate for reported yearly Pap tests of 52.0% (95% CI: 51.7–52.3). In younger women, for whom recent guidelines emphasize yearly Pap tests, a third (9 of 27 SLE subjects aged less than 30) had Pap tests done in the past 12 months (33.3%, 95% CI: 18.6–52.2). This compares with a general population rate of 55.9% (95% CI: 52.9–58.9) for similarly aged women in Quebec[7].

Screening predictors. Table 2 shows the results for the logistic regression models to establish potential predictors of screening in the SLE sample. We found an increased likelihood for Caucasian women and those with higher education to have cervical Pap testing. The data also suggested that patients with higher SLICC/ACR DI scores were less likely to have regular Pap tests. These effects were not reliably seen for the other 2 cancer screening procedures.

Table 2. Adjusted odds ratios (OR) for undergoing cancer screening, with 95% confidence intervals (CI). Odds were adjusted for sex, age, SLE duration, whether or not the patient reported having a regular family doctor, as well as for the other covariates listed.

	OR	95% CI
Colorectal screening: all patients ≥ 50 years old*, n = 51		
SLE damage score**	1.5	0.2 13.0
Immunosuppressant exposure***	0.8	0.2 3.5
Caucasian	0.8	0.2 4.5
Education, yrs	1.0	0.8 1.3
Mammogram within the past year: women ≥ 50, n = 48		
SLE damage score**	1.2	0.8 1.7
Immunosuppressant exposure	0.5	0.1 2.4
Caucasian	0.2	0.0 1.4
Education, yrs	1.1	0.9 1.4
Cervical Pap smear within the past year, all women, n = 146		
SLE damage score**	0.7	0.6 0.9
Immunosuppressant exposure	1.4	0.6 3.5
Caucasian	2.6	1.1 6.3
Education, yrs	1.1	1.0 1.3

* Excluding those with a family history of colorectal cancer. ** SLICC/ACR scores were treated continuously; models with dichotomizing into low and high damage yielded similar results. *** Previously exposed to azathioprine, cyclophosphamide, methotrexate, or mycofenolate.

As the SLICC/ACR DI contains a damage item for malignancy, we repeated the analyses subtracting this item from the total SLICC/ACR DI scores, but the logistic regression results were unchanged.

DISCUSSION

Breast and cervical cancers are the 2 most common cancers among women worldwide[17], and colorectal cancer is the 4th most frequent cancer worldwide. The availability of screening programs for these common cancers has led to the development of guidelines to optimize efficient application of these measures in the hope of improving outcomes. Of course, adherence to clinical guidelines or recommendations is certainly not uniform, and in certain settings may be far from optimal[18-20]. Observance of clinical care recommendations or guidelines depends on a number of factors, related to the physician, clinic, and patient[21].

To our knowledge, there is only one study of the extent to which guidelines for cancer screening are followed among patients with rheumatic disease. This recent analysis of data from the Nurse's Health Study suggested that the self-reported frequency of mammography and gynecological examinations in women with rheumatoid arthritis was no lower than in the general population[22]. However, the education level and health awareness of women in the Nurse's Health Study is likely to be much higher than in the general population of rheumatic patients. We believe ours is the only study to date regarding cancer screening in SLE.

We note in particular that our sample of women with SLE was less likely than the general population to have had yearly Pap testing. This is especially concerning because of reports consistently suggesting that the risk of cervical dysplasia[10-14] and possibly cancer[23] is increased in SLE. Our results suggest that younger women with SLE specifically may be under-screened in this regard. Our logistic regression model estimated that non-whites, and those with less education, were least likely to have cervical Pap screening. This same phenomenon has been seen in the general population[15].

The data also indicate that patients with higher SLICC/ACR DI scores may be less likely to have cervical Pap testing. This is interesting because of previous work showing that SLE patients with higher damage scores were less likely to undergo monitoring for anti-malarial toxicity[16]. It may be that patients with SLE with more severe disease are, in general, at greater risk of missing routine screening because of the complexity of their medical management. Of course the damage scores themselves do not measure SLE disease activity or severity (there is no accepted tool to measure SLE "severity"), but SLICC/ACR DI scores are a well-validated outcome measure capturing total damage accumulation since SLE onset, and have been shown to reflect the impact of cumulative disease activity[24–25]. We did not see a clear effect on cancer screening procedures other than cervical Pap testing, or for the other variables examined, but our precision was limited and we may not have had sufficient power to detect effects of a small magnitude.

Potential limitations of our study are important to point out. First, we used self-report, which may not be accurate.

However, other similar studies have relied on this methodology[22]. Further, in the Province of Quebec, data on Pap smear tests are not reliably recorded in the physician billing administrative database, which was therefore not an optimal data source. Chart review was not feasible, since the patients in the MGH lupus clinic receive care from a large number of different care providers at different institutions. Finally, the available comparison data from the population was also self-report data. For all these reasons therefore, self-report was chosen as the best means of estimating cancer screening frequency in our sample.

As a second potential limitation, we compared self-reported rates from a hospital-based clinic with community reported rates. However, although the clinic is at a tertiary center, it is drawn from the community, and the MGH lupus clinic encourages referral of SLE patients from the periphery. Second, we considered that self-reported rates from our SLE sample might, if anything, be higher than community reported rates (because patients with SLE tend to have regular medical followup). Therefore, our finding that our sample of SLE patients actually reported a lower frequency of Pap smears is particularly noteworthy.

Finally, we acknowledge that our statistical power was limited for the secondary analyses exploring predictors of mammography and colorectal screening. However, this does not diminish the importance of the significant results that we did find, including the fact that among patients with SLE, non-whites, those with lower education, and those with higher SLICC scores, were less likely to have cervical Pap testing.

APPENDIX Record of Cancer Screening Procedures

Canadian guidelines suggest annual mammography for women aged 50 – 69[a] and yearly fecal occult blood testing or periodic sigmoidoscopy or colonoscopy in individuals older aged 50 and older[b], consult references for specific details regarding persons with high risk of these cancers (based, for example, on personal or family history). For cervical Pap tests, guidelines suggest yearly pap tests in women younger than 30, and that older women with 3 consecutive cytology negative for intraepithelial lesions or malignancy may be screened every 2-3 years[c] although women with suppressed immune systems appear to have higher risk for cervical neoplasia and could be considered for yearly pap testing regardless of age. Country-specific guidelines vary.

Patient Name: ______________________________

Check if ever exposed to immunosuppressive agent ☐

Personal history: ☐breast cancer ☐colon/rectal cancer ☐cervical cancer/dysplasia

Family history: ☐breast cancer ☐colon/rectal cancer ☐cervical cancer/dysplasia

Date of Review		**Abnormal results**
	Date Last Mammogram Exam ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Colorectal Screening ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Cervical Pap testing ________ (Or check if not applicable ☐)	☐ Y ☐ N
Date of Review		**Abnormal results**
	Date Last Mammogram Exam ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Colorectal Screening ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Cervical Pap testing ________ (Or check if not applicable ☐)	☐ Y ☐ N
Date of Review		**Abnormal results**
	Date Last Mammogram Exam ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Colorectal Screening ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Cervical Pap testing ________ (Or check if not applicable ☐)	☐ Y ☐ N
Date of Review		**Abnormal results**
	Date Last Mammogram Exam ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Colorectal Screening ________ (Or check if not applicable ☐)	☐ Y ☐ N
	Date Last Cervical Pap testing ________ (Or check if not applicable ☐)	☐ Y ☐ N

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In summary, our data do not provide evidence of a "surveillance bias" (i.e., increased cancer screening) among SLE patients. Rather, it appears that appropriate screening for cancer may be overlooked in SLE. The results serve as a reminder to both rheumatologists and family physicians regarding the need for attention to this issue in persons with rheumatic disease. Special care should be taken to ensure that recommendations regarding Pap testing are not neglected in SLE patients, particularly those with a history of dysplasia or who are undergoing immunosuppressive therapy, as immunosuppression increases the risk of cervical dysplasia[10,11,13,14]. Our results also draw attention to the need for diligence in SLE patients with more severe disease, who may be more likely to miss out on screening because of the complexity of their medical management.

Combined efforts of both specialists and family doctors may be necessary to recognize patients who are not undergoing routine cancer screening, and to encourage those patients to participate in recommended screening programs. We have designed a simple tool (Appendix) that may be adapted and placed in a patient chart to serve as a physician reminder (please note that country-specific guidelines for cancer screening may vary).

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