

## Concise Report

# Reports of abnormal cervical cancer screening tests in systemic sclerosis

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**Objective.** To assess the prevalence of abnormal cervical cancer screening (Pap tests) reported by women with SSc onset before the age of 50 yrs.

**Methods.** Female members of a Canadian multi-centre SSc cohort completed standardized assessments and were questioned regarding a history of an abnormal Pap test. Potential correlates examined included demographics, reproductive history, smoking, diffuse vs limited SSc type, immunosuppressant exposure and SSc duration.

**Results.** In the 320 women with SSc onset before the age of 50 yrs, the life-time prevalence of an abnormal Pap test (according to self-report) was 25.4% (95% CI 20.9, 30.4%). By comparison, self-reported prevalence of abnormal Pap tests among general population Canadian females was recently reported at 13.8% (95% CI 11.6, 16.4%). Women with diffuse SSc ( $n=142$ ), tended to have a higher prevalence of self-reported cervical dysplasia (31.7%) compared with those with limited disease (20.7%), but the CIs overlapped. A multivariate logistic regression found a significant positive association between self-reported abnormal Pap test and diffuse disease [odds ratio (OR) 1.87; 95% CI 1.01, 3.47]. An independent association of an abnormal Pap test with smoking (OR 2.43; 95% CI 1.23, 4.78) and with younger age at disease onset was also noted.

**Conclusions.** We noted a high prevalence of abnormal Pap tests self-reported in our sample. Increased risk was seen among those with diffuse SSc, and also among smokers and those with a younger age at disease onset. Thus, it seems prudent to ensure that adequate attention is paid to cervical cancer screening for women with SSc.

**KEY WORDS:** Cervical dysplasia, Pap test, Malignancy, Systemic sclerosis, Scleroderma.

## Introduction

An association between SSc and malignancies has been documented [1, 2]. An increased cancer risk is also present in other autoimmune rheumatic disease populations, such as SLE [3]. In SLE, there has been particular interest in cervical dysplasia [4]. To date, there has been no systematic assessment of this issue in SSc. We assessed the self-reported prevalence of abnormal cervical cancer screening (Pap testing) in a large SSc cohort.

## Methods

Our study was approved by ethics board review within the McGill University. The Canadian Scleroderma Research Group maintains a national cohort of subjects with clinically confirmed SSc,

who provided (as per the Declaration of Helsinki) written consent to participate. Cohort members complete a detailed questionnaire at baseline, which includes self-report of a history of an abnormal Pap test. We assessed the self-reported prevalence of abnormal Pap tests in this cohort, using a standardized questionnaire that asked, 'Have you ever had an abnormal Pap test?' Although this approach has not been formally validated, it reflects the methods that have been successfully used by our group, in SLE [5], and others, in the general population [6].

Information was also available on cohort member demographics (age, self-reported race, and marital status) and other relevant covariates, such as smoking history and reproductive history. Data on clinical features included SSc duration, type (diffuse vs limited, as defined by Leroy *et al.* [7]), degree of skin involvement (measured by the modified Rodnan skin score, ranging from 0 to 51) [8], and medication exposures, including ever/never exposure to immunosuppressants (penicillamine, cyclophosphamide, AZA, MTX, cyclosporin, tacrolimus, mycophenolate or LEF).

Multivariate logistic regression was then performed to determine independent predictors of a self-reported abnormal Pap test. In our model, we included as covariates the demographic variables and exposures that, based on the literature, were likely to be potential predictors of cervical dysplasia. These included age and marital status [9], reproductive issues (parity, history of therapeutic abortions and oral contraceptive use) [10], race and smoking [10, 11]. We also considered that duration of SSc would increase the likelihood of a history of an abnormal Pap test, thus we included this in our model. As well, given the evidence that immunosuppressant drugs can increase the risk of cervical dysplasia in SLE [12], we included a history of immunosuppressant use. Finally, given that diffuse disease is said to be a risk factor for malignancies in SSc [13], we also included a variable for diffuse vs limited SSc. For our analyses, we used SAS Version

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TABLE 1. Reported abnormal cervical cancer screening (Pap test) in women with SSc onset before the age of 50 yrs

Covariate	History of abnormal Pap test		Adjusted OR <sup>a</sup>	95% CI
	Yes ( <i>n</i> =81)	No ( <i>n</i> =239)		
	Average (s.d.)			
Age at onset <sup>b</sup>	32.6 (10.3)	35.0 (10.3)	0.94	0.91, 0.98
Number of pregnancies <sup>b</sup>	2.2 (1.6)	2.2 (1.6)	1.07	0.88, 1.29
	<i>n</i> (%; incohort group)		Adjusted OR	95% CI
Current smoker, <i>n</i> =53	21 (25.9)	32 (13.4)	2.43	1.23, 4.78
White, <i>n</i> =280	69 (85.2)	211 (88.7)	1.09	0.48, 2.49
Current oral contraceptive use, <i>n</i> =79	16 (19.7)	63 (26.5)	0.51	0.24, 1.09
History of therapeutic abortion	24 (29.6)	54 (22.6)	1.49	0.78, 2.88
Never married, <i>n</i> =23	5 (6.2)	18 (7.6)	0.30	0.09, 1.02
Divorced or separated, <i>n</i> =68	23 (28.4)	45 (18.9)	1.62	0.84, 3.11
Diffuse disease, <i>n</i> =142 <sup>c</sup>	45 (55.6)	97 (40.8)	1.87	1.01, 3.47
History of immunosuppressant, <sup>c</sup> <i>n</i> =146 <sup>d</sup>	38 (46.9)	108 (45.4)	0.78	0.41, 1.48
	Average (s.d.)		Adjusted OR	95% CI
SSc duration	8.5 (8.0)	10.2 (8.6)	0.96	0.93, 0.99

<sup>a</sup>Adjusted for all variables in table. <sup>b</sup>Continuous variable. <sup>c</sup>Diffuse disease is as defined by Leroy *et al.* [7]. <sup>d</sup>Ever/never exposure to penicillamine, cyclophosphamide, AZA, cyclosporin, tacrolimus, mycophenolate or LEF.

9.1.3 (SAS Institute, Cary, USA), using the PROC LOGISTIC command with the STRATA option specified to account for data clustering by study centres.

## Results

There were 320 women with onset of SSc symptoms before the age of 50; the mean age at time of Raynaud's symptom onset was 34.5 yrs (s.d. 10.4; median 36.4 yrs). The majority (87.8%) of the subjects were of white race. At the time of cohort entry, the mean SSc duration for our sample was 9.7 (s.d. 8.4; median 7.7) yrs. A history of cyclophosphamide exposure was present in 28 patients (13 with limited and 15 with diffuse disease). In addition, 118 patients had been exposed to at least one immunosuppressant other than cyclophosphamide, most commonly MTX (*n*=63), followed by AZA (*n*=30), with a small number exposed to penicillamine, cyclosporin, tacrolimus, mycophenolate or LEF.

In this sample, the prevalence of self-reported abnormal Pap testing was 25.4% (95% CI 20.9, 30.4). In patients with diffuse disease (*n*=142), the prevalence of self-reported cervical dysplasia tended to be somewhat higher (31.7%; 95% CI 24.6, 39.8) than for patients (*n*=178) with limited disease (20.7%; 95% CI 15.3, 27.2), but the CIs overlapped. Our multivariate logistic regression (Table 1) found a significant positive association between self-reported abnormal Pap test and diffuse SSc [odds ratio (OR) 1.87; 95% CI 1.01, 3.47]. Similar results were seen using skin scores, as a continuous variable, in place of the variable for diffuse disease, but with less precision. Also noted was an independent association between an abnormal Pap test and smoking (OR 2.43; 95% CI 1.23, 4.78), and with younger age at disease onset. The results also suggested that reports of an abnormal Pap test were more common in women of relatively short SSc disease duration.

## Discussion

Over a quarter of the women in our sample (25.4%; 95% CI 20.9, 30.4) reported a history of an abnormal Pap test. In comparison, in the general population, the self-reported prevalence of abnormal Pap tests among similarly aged Canadian women was recently documented at 13.8% (95% CI 11.6, 16.4) [9]. Thus, compared with the general population, we found some evidence of increased reporting of abnormal Pap tests in women with SSc whose onset of first symptoms began before the age of 50.

Certainly, it may be that persons with one established chronic illness are more likely to be aware of (or to report) comorbidity,

due to the fact that they have more contact with the medical system than persons in the general population. As well, it is possible that physicians who care for individuals with SSc are aware of the fact that this population may have an increased malignancy risk, and hence enforce rigorous screening, which could create a 'detection' bias. On the other hand, women with SLE (an autoimmune rheumatic condition also known to be associated with malignancies) were shown to be less likely than the general population to undergo Pap testing and other forms of cancer screening [14].

Studying non-incident SSc cases, in a cross-sectional way, can create biases, since a non-inception cohort will exclude some members of the population of interest (i.e. those who die very early on in the disease course). However, since it appeared that women with newer-onset SSc were more likely to report an abnormal Pap test, we suspect that if anything, our findings (in terms of dysplasia prevalence) reflect an underestimate. Another problem of our data set is that we did not have the date of the abnormal Pap test reported by women. Neither did we have dates of first exposures to previous drugs (such as oral contraceptives and immunosuppressives). As a result, there would be some misclassification of time-dependent exposures. This would be expected to occur non-differentially, with the result tending to bias towards the null (for example, this may have masked an effect related to drug exposures). Finally, we acknowledge that self-report of abnormal Pap results is not perfect; one study found that 11% of the women in a general population survey incorrectly stated that their last Pap test was normal [15].

In other populations, specifically SLE, there is evidence that immunosuppressant exposure confers additional risk regarding cervical dysplasia [5]. In fact, the American College of Obstetricians and Gynecologists (ACOG) recommends an increased frequency of Pap tests in individuals with a history of immunosuppression. Thus, though their current guidelines indicate that women over the age of 30 yrs (with no prior history of dysplasia) generally require a Pap test only once every 3 yrs, they recommend that those with a history of immunosuppression have yearly Pap testing regardless of age [16]. Although we were unable to establish an independent association between immunosuppressant use and history of abnormal Pap test, given the limitations of our data set, it would be prudent for women exposed to immunosuppressive therapy to adhere to the ACOG or similar guidelines.

Very possibly, the effect of immunosuppression on cervical dysplasia risk may be mediated by decreased clearance of human papilloma virus (HPV) [17, 18]. We were not able to establish

precisely the independent influence of immunosuppression in our sample, likely related in part to the relatively low number of individuals exposed to immunosuppressives. As well, we grouped all immunosuppressive agents together, which may have misclassified exposure if only some of the agents confer risk. Some work has suggested that, among immunosuppressants, cyclophosphamide confers the greatest risk of cervical dysplasia [12, 19]. However, a total of only 28 patients were exposed to this agent in our sample, and the result was an imprecise estimate for this specific exposure.

Other studies of malignancy in SSc have demonstrated an increase in lung cancer and head and neck tumours, but not necessarily cervical cancers. In fact, though numerous studies have reported an increase in cervical dysplasia in SLE, only one has confirmed an increase in cervical cancer in SLE [3, 20]. This is likely related in part to the difficulties in confirming non-invasive cancers (which are often not captured by cancer registries) and in establishing relevant population controls. As well, although cervical cancer was the leading cause of cancer death in American women as recently as the 1930s, the incidence of cervical cancer has decreased markedly (to 8 cases per 100 000 women), likely as a result of widespread screening [16].

In summary, we noted a high prevalence of self-reported abnormal Pap test in women whose SSc onset occurred prior to the age of 50 yrs, with particular risk suggested for individuals with diffuse disease, for smokers, and for those with an early age at SSc onset. Although the lack of longitudinal data in our cohort preclude definitive conclusions, it seems prudent to ensure adequate attention to cervical cancer screening, as per current guidelines [16], for women with SSc.

#### Rheumatology key messages

- Reports of abnormal Pap tests were frequent in SSc; particular risk factors included diffuse disease, smoking and early age of onset.
- Cervical cancer screening in SSc must not be neglected.

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