Hormonal exposures and breast cancer in a sample of women with systemic lupus erythematosus

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Objectives. To determine if breast cancer risk in women with SLE is modified by a history of exposure to hormone replacement therapy (HRT) or oral contraceptives (OC), after adjusting for other risk factors.

Methods. Data were pooled from SLE cohorts at three centres. For each female cohort member (n = 871), the probability of developing breast cancer was estimated from factors (age, parity, age at first live birth, age of menarche, personal history of benign breast disease, family history) in the Gail model, an established tool for predicting breast cancer risk. From these probabilities, the expected number of breast cancers for the cohort was estimated. Actual occurrence of cases was determined by linkage with regional cancer registries. Standardized incidence ratios (SIRs; ratio of cancers observed to expected) were calculated, with subgroup analyses according to HRT and OC exposure.

Results. In the cohort, 15 breast cancers occurred vs 7.2 predicted [SIR 2.1, 95% confidence interval (CI) 1.1, 3.5]. When controlling for Gail model risk factors, estimates were similar for women never exposed to HRT vs those exposed to HRT. Adjusted SIR estimates appeared similar also for women exposed or not exposed to OC.

Conclusions. Although not definitive, the data suggest that the breast cancer experience in this sample is not completely explained by factors such as reproductive and family history, or by exogenous hormonal exposures. Other determinants, including medication exposures or genetic factors (possibly related to oestrogen receptors or metabolism) may be important. Variations in these factors might explain why an elevated risk of breast cancer has not been apparent in all SLE populations.

KEY WORDS: Systemic lupus erythematosus, Breast cancer risk, Oestrogen.

Evidence of an association between systemic lupus erythematosus (SLE) and malignancy has accumulated over the past several years [1–5]. An increased risk of breast cancer has been reported in at least one SLE cohort study [4] although this is not a uniform finding across all SLE cohorts. Of the previous studies on cancer in SLE, few have made even a brief examination of factors traditionally associated with malignancy, and in particular none have adequately addressed the issues of the reproductive factors and hormonal exposures which are relevant in breast cancer [6]. This shortfall is critical because the prevalence of important breast cancer risk factors, such as nulliparity, may be different in women with SLE compared with the general population [7]. Hormone replacement therapy (HRT) is increasingly recognized as a risk factor for breast cancer in the general population [8–10]. Use of combined oral contraceptives (OC) has been reported to slightly increase women’s breast cancer risk, at least among current users [11]. Accounting for the prevalence of these exposures might explain the increased breast cancer risk seen in some groups of SLE patients. The varying frequency of these exposures might in part explain why an increased risk of breast cancer in SLE has not been uniformly seen across all centres.

We have recently evaluated the experience of breast cancer in women from a combined SLE cohort by adjusting for specific risk factors, such as reproductive and family history [12]. The results suggested that the risk of breast cancer in our SLE sample was not completely explained by these factors. However, it is also important to take into consideration external sources of oestrogen, such as HRT and OC. Thus, our current objective was to determine if the risk of breast cancer in women with SLE differs according to history of HRT exposure or OC use, after accounting for other traditional risk factors. We performed this study in an expanded sample (the previous assessment had included two centres only).

Patients and methods

The study sample consisted of patients from the SLE clinic cohorts at three centres: the Montreal General Hospital, Canada, the Feinberg School of Medicine at Northwestern University in Chicago, IL, USA, and the University of Birmingham Medical School, UK. Consecutive patients with American College of Rheumatology criteria [13, 14] for SLE were enrolled in these clinic cohorts at the time they presented for their first clinic visit. The total number of female subjects in the combined cohort was 890. Subjects’ written consent was obtained according to the Declaration of Helsinki, and the relevant institutional review boards at each site (Montreal General Hospital, Northwestern...
University and the University of Birmingham) provided approval for this work.

For each participating female cohort member, the probability of developing breast cancer during follow-up was estimated based on factors (age, parity, age at first live birth, age of menarche, personal history of benign breast disease, family history) used by the Gail model, a well-established tool developed and used by oncologists to predict breast cancer occurrence [15]. From these probabilities, the expected number of breast cancers for the cohort was estimated. The actual occurrence of cancer cases was determined by linkage with regional cancer registries. Standardized incidence ratios (SIRs; the ratio of cancers observed to cancers expected) were calculated, with subgroup analyses according to the history of HRT and OC exposure. The definition for both HRT use and for OC use was use of any duration.

Information on breast cancer risk factors came from a survey administered at the time of the cancer registry linkage. For patients who had died or been lost to follow-up, data were obtained from information in the clinical database or medical records. This was also done for 23 living Montreal patients who consented to participate but who did not wish to complete a questionnaire. We used a conservative approach with respect to missing risk factor data, by replacing missing values with the higher risk category. This approach maximized the expected number of cancers predicted by the Gail model, thus avoiding overestimation of the SIR.

The calendar period of observation under study spanned from 1984 to 1998 in Montreal, from 1985 to 1995 in Chicago, and from 1980 to 2000 in Birmingham. The observation interval for each subject began at time of enrolment; the end of the interval was marked by the earliest of three dates: death, breast cancer occurrence, or the date of tumour registry linkage. For patients lost to follow-up, vital status was determined by linkage with the vital status registry for Montreal patients; at the Chicago and Birmingham sites a conservative approach was used such that the patients lost to follow-up were considered to have remained alive up to the date of the tumour registry linkage. This maximized the number of person-years and thus the number of expected cancers, again minimizing the possibility of overestimation of the SIRs.

The Gail model is an established model for predicting individualized probabilities of developing breast cancer for females. It can be used to estimate the probability that a woman with a given age and risk factors will develop breast cancer over a specified interval. The logistic regression equation used to estimate the expected probability of the development of breast cancer includes the following major predictors for breast cancer risk, all treated categorically: age, early menarche, breast cancer in a first-degree relative, late age at first childbirth, and history of benign breast disease. It also includes terms for the interactions between age and the number of breast biopsies for benign disease, and between age at which a first live birth occurred and the number of relatives who had breast cancer.

Using the Gail model, we calculated the probability of developing breast cancer for each patient during the observation interval, and these probabilities were summed. This sum reflects the total number of breast cancers that would be expected to occur in our sample, since each patient provides independent information, and each individual probability can be considered to be the expected number of cancer cases in that subject.

We obtained exact 95% confidence limits for the observed: expected ratio (the SIR) using the standard approaches for estimating a Poisson-distributed variable, multiplying the actual number of cancers by the appropriate confidence limit factor [16] which produces upper and lower limits for the observed number of cancers. These were then divided by the expected number of malignancies to produce the limits for the confidence intervals of our SIR estimates.

Results

Fourteen of the 890 female members of the combined cohort declined participation, and five had been diagnosed with breast cancer prior to cohort entry and were excluded. Two-thirds of the remaining 871 subjects were Caucasian, 18.6% were black, just over 10% were East Asian, and the remainder were of other racial origin. The mean age was 41 (s.d. 13) yr. The average SLE duration at the time of breast cancer diagnosis was 11.8 yr; the average SLE duration at the end of the observation interval for the remaining women was 9.1 yr.

Table 1 presents the distribution of Gail model breast cancer risk factors for the 871 subjects. In these women, 15 cases of breast cancer occurred compared with 7.2 predicted by the Gail model [SIR 2.1, 95% confidence interval (CI) 1.1, 3.5]. Thus, after controlling for common risk factors, the incidence of breast cancer appeared to be elevated (Table 2). The breast cancer incidence rate in the SLE female patients over the observation interval was 5.2 cases per 1000 person-years.

Sixty subjects were missing information with respect to HRT exposure and 71 were missing information with respect to OC exposure. In the remaining subjects, 16.3% had been exposed to HRT and 47.2% had been exposed to OC. When controlling for the Gail model risk factors, subgroup analyses revealed that the SIR for women never exposed to HRT (n = 679) remained elevated at 2.3 (95% CI 1.1, 4.2). The SIR point estimate for breast cancer in women exposed to HRT (n = 132) was similar, at 2.2 (95% CI 0.59, 5.6). For women exposed to OC (n = 411) the similarly adjusted SIR point estimate for breast cancer (2.0, 95% CI 0.7, 3.4) did not appear different from that of women (n = 389) not exposed to OC (SIR 2.4, 95% CI 0.8, 4.5).

In sensitivity analyses excluding the subjects with missing data on risk factor information, the SIR estimate for women exposed to HRT was 3.1 (95% CI 1.0, 7.3) and the SIR estimate for women never exposed to HRT was 2.5 (95% CI 0.08, 14). Excluding the subjects with missing data, the SIR estimate for women exposed to OC was 2.0 (95% CI 0.6, 5.1) and the SIR estimate for women never exposed to OC was 0.8 (95% CI 0.02, 4.4).

Discussion

Evidence of an association between SLE and cancer has accumulated over the past several years. Data to date [2–6, 17] confirm an increased risk of malignancy in SLE, particularly for specific subtypes of haematological malignancies, where about a 3-fold

### Table 1. Prevalence of Gail model risk factors for breast cancer in the lupus cohort

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study start (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>689</td>
<td>79</td>
</tr>
<tr>
<td>≥50</td>
<td>182</td>
<td>21</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>177</td>
<td>20</td>
</tr>
<tr>
<td>12–13</td>
<td>290</td>
<td>33</td>
</tr>
<tr>
<td>&lt;12</td>
<td>158</td>
<td>18</td>
</tr>
<tr>
<td>Missing</td>
<td>246</td>
<td>28</td>
</tr>
</tbody>
</table>

Benign breast disease

- No history: 717 (82)
- ≥1 biopsy: 116 (13)
- Missing: 38 (4)
- Nulliparous: 334 (38)

*Combined cohort includes subjects from the Montreal General Hospital (n = 271), Feinberg School of Medicine, Northwestern University (n = 291) and the University of Birmingham (n = 309).

*Missing data on parity in 46 patients (5%).
increased risk of lymphoma has been seen fairly consistently. However, for most specific tumour types, including breast cancer, risk estimates have generally been too imprecise to allow definitive comments. It is possible that there is considerable heterogeneity of risk among different SLE populations for non-haematological malignancies [2–6, 17].

In this work, we present an examination of the role of hormonal and reproductive risk factors in breast cancer in women with SLE. Our estimate of the relative breast cancer risk in this sample might be considered conservative, since our treatment of missing data was conservative. This approach maximized the expected number of cancers predicted by the Gail model, to avoid overestimation of the SIRs. The Gail model may overestimate the expected number of breast cancer cases for certain groups (i.e. non-Caucasians and women younger than 40) [18, 19]. However, the effect would only be to slightly inflate the expected number of breast cancers for the cohort, and produce conservative estimates for the SIRs. Excluding non-Caucasian subjects, the SIR estimate for breast cancer occurrence among female cohort members is 2.2 (95% CI 1.1, 3.8). There were women aged <40 within the cohort; however, these subjects contributed a relatively small amount of observation time to the cohort.

Ours are the first efforts, to date, that have examined cancer risk in SLE considering reproductive factors and exogenous exposures. We acknowledge that the number of breast cancer cases limited our power to establish definitively small differences between exposure groups in our subgroup analyses. Though the conclusions from the study are therefore limited, one interpretation of the results is that the experience of breast cancer in this sample is not completely explained by reproductive or family history, or by exposure to HRT or OC. One explanation for these findings is that there are other factors influencing the development of solid tumours in SLE. These factors may include medications (alkylating agents and immunosuppressive drugs), other environmental exposures, or genetic influences predisposing to both autoimmune diseases and cancer. Alternatively, immune system pathology (i.e. in apoptosis and cell proliferation) may play a role in the emergence of neoplasms following the development of SLE. Within the spectrum of SLE, perhaps there are clinical subsets that are at higher risk of solid tumours; for example, one could hypothesize that SLE patients with scleroderma overlap features may be the ones most likely to manifest increased risk of lung and possibly breast cancers [20, 21].

One may question why the subgroup SIR estimates for breast cancer in the exposed and non-exposed subjects were so similar if oestrogen exposures are known risk factors for breast cancer in the general population. In fact, it is now known that OC exposure is probably only a weak and likely transient risk factor [11, 22]. For HRT, the breast cancer risk has been more firmly established [8, 9, 23], but since this risk is most pronounced in later decades, the effect would be less evident in our relatively young sample. This is, then, a major limitation of our results, which may not adequately reflect the experience of women with SLE in the highest age groups, who are at the greatest risk of breast cancer [24]. Also, we did not have detailed information on duration of use, which influences breast cancer risk among women exposed to HRT in the general population [9]. A more useful evaluation, which we could not do due to limitations in our data, would be to consider the risk among patients that took HRT for defined periods, such as for greater than 5 yr [24]. Our findings thus may in part reflect non-differential misclassification of exposure (e.g. considering ‘ever exposure’ as a risk group, instead of the risk group of those who had HRT exposure for a duration of >5yr), which would bias against finding a difference in breast cancer risk for women with SLE exposed to HRT.

Our results should not be interpreted as indicating that HRT does not confer risk in SLE. We note that there is a decreasing tendency for physicians to prescribe HRT for postmenopausal women in general [25], due to adverse effects with respect not only to cancer but also to thrombotic and other cardiorespiratory events. Concern about the thrombogenic effects of HRT may be amplified in SLE, given the higher risk of SLE patients for thrombotic and atherosclerotic disease [26].

We note that obesity is associated with an increased risk of breast cancer, presumably because of higher oestrogen levels derived from the aromatization of androstenedione in adipose tissue [27]. In previous work done in the Montreal General Hospital lupus cohort, we demonstrated an increased prevalence of obesity [7], which could in part mediate an increased risk of breast cancer in this sample. Also, some women with SLE may also have differences in oestrogen receptors or metabolism [28, 29] that could result in higher breast cancer risk, due to higher endogenous oestrogen levels throughout their reproductive lifetime. This effect could make it difficult to appreciate an increased risk caused by exogenous oestrogens, due to a higher baseline risk. Differences in genetic polymorphisms in oestrogen receptors or metabolism (related to variations in ethnic distributions) might also explain why an elevated risk of breast cancer has not been clearly demonstrated in all SLE populations under study. The patients in our combined cohort were of various ethnic backgrounds, but we obviously could not disect potential effects of genetic polymorphisms in our study.

In concert with members of the SLICC (Systemic Lupus International Collaborating Clinics) and CaNIOS (Canadian Network for Improved Outcomes in Lupus) research networks, we have in progress a large multicentre case-cohort study to evaluate the role of clinical and environmental factors in the

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**Table 2. Standardized incidence rates (observed:expected, SIR) for breast cancer in a lupus cohort**, adjusted for Gail model risk factors and stratified according to history of hormonal exposure

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>132</td>
<td>4</td>
<td>1.8</td>
<td>2.2</td>
<td>0.6, 5.6</td>
</tr>
<tr>
<td>Not exposed</td>
<td>679</td>
<td>10</td>
<td>4.4</td>
<td>2.3</td>
<td>1.1, 4.2</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>389</td>
<td>6</td>
<td>3.0</td>
<td>2.0</td>
<td>0.7, 3.4</td>
</tr>
<tr>
<td>Not exposed</td>
<td>411</td>
<td>7</td>
<td>2.9</td>
<td>2.4</td>
<td>0.8, 4.5</td>
</tr>
</tbody>
</table>

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*aCombined cohort includes subjects from the Montreal General Hospital (n = 271), Feinberg School of Medicine, Northwestern University (n = 291) and the University of Birmingham (n = 299).

*bAdjusted for age, nulliparity, age at first childbirth, early menarche, personal history of benign breast disease, and history of breast cancer in a first-degree relative.

*cSixty subjects were missing information with respect to hormone replacement therapy, and 71 were missing information with respect to oral contraceptive exposure.*
development of cancer in SLE [17]. These efforts, we hope, will further elucidate the factors contributing to the association between cancer and autoimmunity.

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References