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Breast Cancer in Systemic Lupus Erythematosus

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Abstract

Objective—Evidence points to a decreased breast cancer risk in systemic lupus erythematosus (SLE). We analyzed data from a large multisite SLE cohort, linked to cancer registries.

Methods—Information on age, SLE duration, cancer date, and histology was available. We analyzed information on histological type and performed multivariate logistic regression analyses of histological types according to age, SLE duration, and calendar year.

Results—We studied 180 breast cancers in the SLE cohort. Of the 155 cases with histology information, 11 were referred to simply as ‘carcinoma not otherwise specified’. In the remaining 144 breast cancers, the most common histological type was ductal carcinoma (n = 95; 66%) followed by lobular adenocarcinoma (n = 11; 8%), 15 cancers were of mixed histology, and the remaining ones were special types. In our regression analyses, the independent risk factors for lobular versus ductal carcinoma was age [odds ratio (OR) 1.07, 95% confidence interval (CI) 1.01–1.14] and for the ‘special’ subtypes it was age (OR 1.06, 95% CI 1.01–1.10) and SLE duration (OR 1.05, 95% CI 1.00–1.11).

Conclusions—Generally, up to 80% of breast cancers are ductal carcinomas. Though our results are not definitive, in the breast cancers that occur in SLE, there may be a slight decrease in the ductal histological type. In our analyses, age and SLE duration were independent predictors of histological status.

Keywords

Breast cancer; Systemic lupus erythematosus; Histopathology; Epidemiology

Introduction

Evidence of possible links between systemic lupus erythematosus (SLE) and cancer has generated much interest. Recent studies have shown an increased risk of hematological malignancies and a decreased risk of some reproductive malignancies (breast, ovary, and endometrial). However, the underlying pathophysiologic mechanisms of those observations are still not fully understood. In particular, there have been no investigations of the distribution of the histological subtypes of breast cancers in SLE. Our objective is to provide a brief report of the breast cancer cases from an SLE cohort with respect to histopathology.

Methods

Data were obtained from a multisite international cohort study of 16,409 SLE patients from 30 centers [1]. Cancer cases were ascertained through linkage with regional tumor registries. Information on the date of birth, the date of SLE diagnosis, and the cancer date was available, as were the histology reports from the cancer registries where the breast cancer cases had been ascertained. Cancer cases were included if they had occurred any time after SLE diagnosis, and cancers of all stages, including noninvasive lesions, were assessed. We

summarized demographic characteristics, analyzed information on histological type, and compared it to the frequency reported in the general population.

Within the cancer cases that had occurred in SLE, we also performed multivariate logistic regression analyses to determine whether there were independent effects on the histological type of breast cancers in SLE according to age, SLE duration, and calendar year. Here, we modeled the prevalence odds ratio (OR) for two different sets of histological outcomes. The first multivariate regression assessed the OR for the histological type of lobular versus ductal cancer (the two most common histological types of breast cancer), and the second regression assessed the OR for 'special' histological subtypes versus ductal cancer (the most common histological type). Given the potential for a high correlation between age and SLE duration if both are treated as continuous variables, we modeled age as a continuous variable but SLE duration categorically (less than 5 years', 5–10 years', and >10 years' duration). The calendar year period was dichotomized (up to 1990 vs. 1990 and beyond). This represents an 'early' and more 'recent' period, in an attempt to reflect changes in drug use (as clinicians have increasingly been using drugs like hydroxycholorquine and mycophenolate).

We have previously published cancer incidence data including 114 breast cancers [1] (excluding in situ lesions) in the lupus cohort, but for this report, we extended our observation window to 2011 and included in situ cancers.

Results

Of the 30 centers involved in the initial cohort study, 16 reported breast cancer cases (180 cases). Of these 16 centers, 3 (from Denmark, Germany, and Sweden) did not provide histology information. As a result, the histological type was unavailable for 25 breast cancer cases. At the time of cancer diagnosis of these 180 breast cancers, the average age of the SLE patients was 54 years [median 53, standard deviation 11.5], and the average SLE duration was 14 years (median 13, standard deviation 9.5). Of the 155 breast cancers with histology information (including 30 in situ lesions), 11 were referred to simply as 'carcinoma not otherwise specified'. In the remaining 144 breast cancers, the most common histological type reported was ductal adenocarcinoma [n = 95; 66%, 95% confidence interval (CI) 64–72%] followed by infiltrative lobular adenocarcinoma (n = 11; 8%, 95% CI 4–13%). In addition, 15 were of mixed histology, and the remaining were special types (tubular, cribiform, medullary, mucinous papillary adenoid cystic, and inflammatory).

Table 1 displays the distribution of histological types, comparing the cases in our SLE sample to the distribution reported in recent literature [2–4]. For comparability with other published literature, the table includes only the 125 invasive breast cancers that occurred in SLE patients, but the distribution was very similar to that of the total 155 patients (including noninvasive lesions, data not shown).

Results from our multivariate regression analyses of the breast cancer cases in SLE are shown in table 2. Of the 155 cases (including in situ lesions), 120 had complete information (age, date of diagnosis, and duration of SLE before cancer diagnosis) and thus could be included in the regression analysis. When the outcome studied was lobular versus ductal breast cancer, the prevalence OR for age (adjusted for SLE duration and calendar year), as a continuous variable, was 1.07 (95% CI 1.01–1.14). In the regression where the outcome was special subtypes versus ductal breast cancer, the adjusted OR for age was 1.06 (95% CI 1.01–1.10). Our logistic regression also suggested that among SLE patients with breast cancer, those with longer SLE duration were more likely to be diagnosed with special

subtypes even after adjusting for age and calendar year (adjusted OR 1.05, 95% CI 1.00–1.11).

Discussion

In the general population, up to 80% of invasive breast cancers are ductal carcinomas, lobular carcinomas represent up to 8%, and the remaining 16% are composed of mixed ductal/lobular and rarer subtypes (mucinous, tubular, or medullary papillary) [3]. Our findings suggest a decreased proportion of ductal subtypes. Interestingly, ductal breast cancers tend to be estrogen receptor (ER)- and progesterone receptor-negative, and a previous study using Veteran Affairs data suggested a decreased incidence of ER-negative breast cancer in SLE patients [5]. In seeking to understand the reduced incidence of ductal and ER-negative breast cancer in SLE, it is important to consider differences between normal and SLE populations related to immune function and, potentially, hormone receptor expression.

Regulatory T cells (Treg) are highly represented in ER-negative breast tumors, and these lymphocytes counter-act helper T cells and have a detrimental effect on the immune system's antitumor response and are associated with a poor prognosis [6]. In SLE patients, however, Treg functions are altered, favoring the beneficial antitumor response from the unopposed helper T cells [7]. Thus, altered Treg functions in SLE may explain in part the decreased incidence of ductal and ER-negative breast cancer in the SLE population.

Another intriguing novel hypothesis to explain the decreased risk of breast cancer in women with SLE is that autoantibodies associated with SLE may be suppressing the emergence of certain types of breast cancer. It has recently been shown that a cell-penetrating lupus-related anti-DNA antibody inhibits DNA repair in cancer cells, particularly those with intrinsic defects in DNA repair [8]. Triple-negative breast cancers are known to harbor defects in DNA repair. Such tumor cells would therefore likely be susceptible to the effects of lupus antibodies that may inhibit DNA repair, and both the reduced incidence of ER-negative breast cancer associated with SLE and our present finding of a reduced incidence of ductal subtypes of breast cancer in SLE are consistent with this hypothesis, because triple negative breast cancer is, by definition, ER-negative and is predominantly of the ductal carcinoma subtype [9]. Additional studies are needed to directly test the association of cell-penetrating lupus antibodies with the suppression of certain types of breast cancer in SLE.

Though we interpret our data as showing a strong trend towards a lower frequency of ductal cancers in SLE patients, the imprecision of our estimates must be noted. SEER (Surveillance, Epidemiology, and End Results) data can provide very precise estimates, being based on the highest number of cases. The percent of SEER breast cancers that were lobular was 70.2%, with a 95% CI of 70.0–70.4%. Our own point estimate for ductal breast cancer was 66.4%, with a 95% CI of 57.7–74.1%. The relatively small number of breast cancers in SLE (compared to SEER) causes a wide CI which includes the null value of potentially no difference between SLE and SEER cases.

National Cancer Institute data state that the median age at the diagnosis of breast cancer is 61 years [10] (which is similar to the mean age reported, i.e. 60 years). The median age at the diagnosis of breast cancer in our SLE patients tended to be lower, i.e. 53 years (mean 54 years) and the 95% CI for our mean age (52–56) is lower than in general population figures. The SEER data estimates for the relative frequency of breast cancer types are a good comparator for our sample, in that SEER estimates are population-based and include a broad range of ages (from 20 years upwards). However, we do not have age-stratified indicators of breast cancer subtype frequency, and given the somewhat younger age distribution of the

breast cancer cases in our SLE sample (compared to the general population), it is possible that differences seen in part relate to age. Published estimates of breast cancer histology in young women are rare, and most evaluation of breast cancer types in young women focus on molecular phenotypes (e.g., a greater proportion of young women have luminal B tumors, and a smaller proportion have luminal A tumors) [11]. Since we did not have information about race/ethnicity distribution and histological type, this could influence results slightly. However, our previous analyses have suggested that all race/ethnicity groups in SLE have a similarly decreased breast cancer risk compared to the general population [12]. Similarly, we have previously reported that the breast cancer risk in SLE is decreased in both young (aged <50) and older (age >50) women.

Our logistic regression looked at prevalent cases of breast cancer, examining histology, and controlling for age, SLE duration, and calendar year, providing estimates of the effects of these variables on the prevalence OR for the outcomes under study. One limitation is the possible correlation between these variables, particularly age and SLE duration. This could make it difficult to examine for independent effects; for this reason, we used age as a continuous variable and SLE duration as a categorical variable. The trend for younger age in SLE patients affected by ductal cancer, compared to lobular carcinoma and other uncommon cancer types, corresponds with demographic trends seen in the current literature [13].

The logistic regression results also suggested that longer SLE duration was more likely to be diagnosed with a special subtype of breast cancer. It may be that this demographic factor contributes to the possible increase in the frequency of special subtypes in SLE compared to the general population figures.

Another potential limitation of our study is that we did not look at medication exposure. Although some have suggested a potential benefit of lupus-related medications such as hydroxychloroquine [14] and nonsteroidal anti-inflammatory drugs [15] for breast carcinoma, these studies did not stratify the different subtypes of cancer and have not been reproduced [16]. Cyclophosphamide exposure is known to cause amenorrhea, which could alter the risk of breast cancer. However, this exposure is relatively uncommon in SLE patients, and in earlier case-cohort analyses we did not find associations between this drug and cancer risk, aside from hematological malignancies [17]. We also did not look at reproductive factors such as parity or stage and receptor status (which was unavailable in the current sample). However, it would be difficult to provide general population comparisons that are stratified by all these elements. Our brief report is of value in that it represents the first published study of breast cancer histology in SLE.

In summary, though not definitive, the results of our study suggest that ductal cancers may be the histological breast cancer type most decreased in SLE. Further work is planned to collect information that will allow us to assess other features of breast cancers in SLE, including treatment history, stage, and receptor status, with a particular interest in the frequency of ‘triple-negative’ cases.

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Table 1

Invasive breast cancer histopathology: SLE versus three general population-based registries

Histological type	NCI SEER, 1988–2001 [4] (n = 260,735), %	Louwman et al. [3] (n = 158,846), %	SLE cohort, 2013 (n = 125), %
Invasive ductal carcinoma	70.2	78.0	66.4
Invasive lobular carcinoma	7.7	11.1	8.0
Tubular carcinoma	1.4	2.2	0.8
Medullary carcinoma	1.2	1.1	1.6
Mucinous carcinoma	2.5	2.2	3.2
Inflammatory	1.0	–	0.8
Adenoid cystic carcinoma	0.3	0.1	1.6
Papillary carcinoma	0.6	0.7	0
Mixed types	6.2	4.0	8.0
Other/NOS	8.8	0.5	9.6

To allow comparison with the published results, the column includes only invasive cancers (in situ cancers are excluded). NOS = Not otherwise specified.

Table 2

Results of multivariate logistic regression for all breast cancer cases in women with SLE

Outcome	Multivariate prevalence, OR	95% CI
Lobular versus ductal carcinoma		
Age at cancer diagnosis	1.07	1.01–1.14
SLE duration	0.99	0.90–1.08
Calendar period	0.56	0.11–2.88
Special subtypes versus ductal carcinoma		
Age at cancer diagnosis	1.06	1.01–1.10
SLE duration	1.05	1.00–1.11
Calendar period	0.60	0.18–2.05

Two outcomes were modeled: lobular versus ductal breast cancer and special histological subtypes versus ductal cancer (n = 120). Each model included the three variables listed. Age was a continuous variable. SLE duration was assessed at cancer diagnosis, categorical (≤5 years', 5–10 years', and >10 years' duration). Calendar year period in which cancer occurred was dichotomized (≤1990 and >1990).