Hormonal Dependence and Cancer in Systemic Lupus Erythematosus

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Objective. To estimate the incidence and analyze any cancer-associated factors in patients with systemic lupus erythematosus (SLE), differentiating between hormone-sensitive (HS) and non-HS cancers.

Methods. This was a retrospective multicenter study of a patient cohort from the Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology. Included were the first cancer post-SLE diagnosis, clinical and sociodemographic information, cumulative damage, severity, comorbidities, treatments, and refractoriness. Cancers were classified as HS (prostate, breast, endometrium, and ovarian) and non-HS (the remainder). The standardized incidence ratio (SIR) was calculated and logistic regression models were built.

Results. A total of 3,539 patients (90.4% women) were included, 154 of whom had cancer (91% female), and 44 had HS cancer (100% female). The cancer SIR was 1.37 (95% confidence interval [95% CI] 1.15–1.59), with higher values in women age <65 years (SIR 2.38 [95% CI 1.84–2.91]). The SIR in women with HS versus non-HS cancer was 1.02 (95% CI 0.13–1.91) and 1.93 (95% CI 0.98–2.89). In HS versus non-HS cancers, SLE diagnostic age (odds ratio [OR] 1.04 [P = 0.002] versus 1.04 [P = 0.019]), and period of disease evolution (OR 1.01 [P < 0.001] versus 1.00 [P = 0.029]) were associated with cancer. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (OR 1.27 [P = 0.022]) and angiotensin-converting enzyme (ACE) inhibitor prescriptions (OR 2.87 [P = 0.048]) were associated with non-HS cancers.

Conclusion. Cancer incidence in patients with SLE was higher than in the Spanish population, particularly among young women. This increase might be due to non-HS cancers, which would be associated with SLE involving greater cumulative damage where more ACE inhibitors are prescribed.

INTRODUCTION

Cancer is one of the most serious illnesses a person can have, because it affects both the physical and emotional state and can sometimes lead to death. Furthermore, when cancer is diagnosed in a patient with a chronic autoimmune disease such as systemic lupus erythematosus (SLE), with its associated cumulative damage and comorbidities, it presents challenges not only for that patient, but also for the doctors assessing and treating both illnesses. At present, there is insufficient knowl-

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edge regarding the immune system alterations that occur in SLE, changes that may influence cancer onset and/or development (1). Several studies carried out in different countries, races, and ethnic groups show that the global cancer incidence in patients with SLE is higher than in the general population (2–7). In particular, the cancer standardized incidence ratio (SIR) is higher across virtually all anatomic locations (hematologic, lung, thyroid, hepatobiliary, vulva-vagina, cervix, and pancreas) (2,3,5,6,8,9). However, different studies have also highlighted a risk reduction in hormone-sensitive (HS) cancers such as breast, endometrial, and ovarian (2–4,10,11). The suggestion has been made that if the metabolism of estrogen or other predominantly female hormones was altered in SLE, that alteration could slow the progression of HS cancers. On the other hand, a nucleolytic lupus autoantibody, anti-5GC6, might help prevent DNA repair mechanisms in breast, ovarian, and prostate cancers associated with BRCA2 mutations (12). Therefore, SLE autoantibodies may contribute to a decreased risk of certain HS cancers. Thus, in patients with SLE, there might exist some differences in the cancers in regard to hormonal dependence, although the exact mechanisms linking the immune and endocrine systems to cancer risk are unknown. For this reason, determining whether factors associated with HS cancer differ from those with non-HS cancer would be interesting. Most studies have focused on searching for factors associated with cancer onset in SLE and have grouped all cancer types, whereas other studies have explored factors related to the onset of hematologic, lung, and breast cancer. Yet, to date, no study has explored stratified cancers in relation to hormone-sensitivity. Thus, an analysis comparing HS and non-HS cancers within a multicenter cohort with a large number of patients might expand our understanding in this sense. The purpose of this study was to estimate the cancer incidence in patients with SLE and to analyze factors associated with its onset, differentiating between HS and non-HS cancers.

PATIENTS AND METHODS

Design, scope, and patients. We performed a retrospective observational, longitudinal study of a cohort of the Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology (RELESSER). RELESSER includes patients ages >16 years with SLE (according to the revised American College of Rheumatology [ACR] criteria of 1997) (13) from 45 hospitals registered with the Spanish Society of Rheumatology hospital database. At least 80% of patients from each center were included, all of whom had had ≥1 appointment with a rheumatology department at some time since their initial disease diagnosis. Patients whose clinical history did not contain at least 50% of the information deemed essential were excluded. The design, variables, and general characteristics of the RELESSER registry have been published previously (14).

Data collection. Rheumatologists with experience in diagnosing and treating patients with SLE collected the data from each center and then uploaded it via an online software application designed ad hoc for the project. Data quality control was performed via professional online monitoring.
Variables and operational definitions. The main study variable was the first cancer after SLE diagnosis. Endometrial, breast, ovarian, and prostate cancers were classified as HS and the remainder as non-HS. Patient follow-up was defined as the period between the date of SLE diagnosis and the date of the first cancer for those who had cancer, and the RELESSER data collection date (2010–2011) for patients who did not develop cancer. Patients for whom information was unavailable until the data collection date were censored to the date of their last appointment at the rheumatology clinic. Secondary variables included: sociodemographic; general symptoms; cancer location; accumulated SLE symptoms, defined according to ACR diagnostic criteria (13,15) and British Isles Lupus Assessment Group definitions (16); systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (17,18); damage defined by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (19), excluding cancer; the degree of severity (Katz index) (20); comorbidities, hospitalizations, and causes of death; the Charlson comorbidity index, Deyo modified version (21); treatments for comorbidities and SLE control; and refractoriness, as defined for the registry (22).

Statistical analysis. A descriptive analysis was performed using absolute and relative frequencies of qualitative variables, and mean or median and dispersion measures (SD, interquartile range [IQR]) for quantitative variables. The accumulated incidence of cancers in patients included in RELESSER for 2011 was calculated. To estimate the cancer accumulated incidence in the general population, cancer cases in Spain for 2012 were compiled and measured against the overall population according to the 2011 Housing and Population Censuses (23,24). Both accumulated incidence measures were compared by calculating the SIR. The SIR calculation was made at the same time, differentiating between HS and non-HS cancers, and taking into account the number of cases per cancer type in Spain during 2014 (25). In addition, the prevalence of cancer globally and per anatomic location was estimated. The years between the diagnosis of SLE and the development of the first cancer were also calculated, as well as the mortality rate for each cancer type according to anatomic location. With a view to analyzing the association between cancer onset and the clinical characteristics of patients with SLE, a logistics regression model was built to analyze female patients, differ-

Table 1. Characteristics of patients with SLE, stratified by cancer incidence*

| Variables                              | All (n = 3,539) | Cancer: yes (n = 154) | Cancer: no (n = 3,385) | P        |
|----------------------------------------|-----------------|-----------------------|------------------------|----------|
| Female sex                             | 3,194 (90.4)    | 140 (90.9)            | 3,054 (90.4)           | 0.821    |
| Age at first SLE criterion met, mean ± SD years | 32.84 ± 14.4    | 38.35 ± 16.0          | 32.72 ± 14.3           | <0.001   |
| Age at SLE diagnosis, mean ± SD years  | 34.85 ± 14.5    | 40.37 ± 15.7          | 34.75 ± 14.5           | <0.001   |
| Age at last assessment, mean ± SD years| 46.52 ± 14.8    | 57.74 ± 14.4          | 46.17 ± 14.6           | <0.001   |
| Race                                   |                 |                       |                        |          |
| Caucasian                              | 3,196 (93.0)    | 145 (96.7)            | 3,051 (92.8)           | 0.071    |
| Others                                 | 241 (7.0)       | 5 (2.7)               | 236 (7.2)              |          |
| Period of disease evolution, mean ± SD months | 142.86 ± 100.6  | 208.71 ± 103.0        | 140.1 ± 99.7           | 0.001    |
| Follow-up in rheumatology, mean ± SD months | 120 ± 87.6      | 170.1 ± 90.8          | 118.1 ± 86.9           | <0.001   |
| Sjögren’s syndrome                     | 503 (14.4)      | 31 (20.5)             | 472 (14.1)             | 0.029    |
| SLEDAI, median (IQR)                   | 2 (0–4)         | 1 (0–3)               | 2 (0–4)                | 0.026    |
| Katz index, median (IQR)               | 2 (1–3)         | 3 (2–4)               | 2 (1–3)                | 0.001    |
| Modified SDI, median (IQR)†           | 1 (0–2)         | 1 (0–3)               | 0 (0–1)                | <0.001   |
| Modified Charlson comorbidity index, median (IQR)† | 2 (1–3)         | 3 (2–4)               | 1 (1–3)                | <0.001   |
| Antimalaria treatment, median (IQR) months | 60 (24–120)     | 78 (27–136)           | 60 (24–110)            | 0.099    |
| Smoking (past and current smokers)     | 1,656 (46.8)    | 76 (49.4)             | 1,580 (46.7)           | 0.515    |
| Alcohol use                            | 111 (3.4)       | 6 (4.4)               | 105 (3.4)              | 0.517    |
| Statins                                | 165 (5.1)       | 15 (10.7)             | 150 (4.9)              | 0.002    |
| ACE inhibitors                         | 313 (9.7)       | 20 (14.6)             | 293 (9.5)              | 0.05     |
| Acetylsalicylic acid                   | 1,061 (37.18)   | 55 (40.4)             | 1,006 (36.9)           | 0.408    |
| Immunosuppressants                     | 1,939 (57.2)    | 80 (53.3)             | 1,859 (57.4)           | 0.326    |
| Immunosuppressant type                 |                 |                       |                        |          |
| Nonimmunosuppressants                  | 2,133 (60.3)    | 98 (63.7)             | 2,035 (60.1)           | 0.668    |
| Cyclophosphamide/mycophenolate/mycophenolic | 973 (27.59)     | 38 (24.7)             | 935 (27.6)             | 0.668    |
| Methotrexate/leflunomide               | 433 (12.3)      | 18 (11.7)             | 415 (12.3)             | 0.668    |
| Oral contraception                     | 655 (26.9)      | 25 (23.6)             | 630 (27.0)             | 0.437    |
| Corticoids at maximum doses, occasionally | 776 (27.4)      | 36 (27.1)             | 740 (27.4)             | 0.93     |
| Hospitalization per activity           | 1,902 (54.6)    | 88 (57.9)             | 1,814 (54.5)           | 0.41     |
| No. of hospitalizations per activity, median (IQR) | 2 (1–3)         | 2 (1–3)               | 2 (1–4)                | 0.01     |
| Refractoriness                         | 873 (24.6)      | 39 (25.3)             | 834 (24.6)             | 0.847    |

* Values are the number (%) unless indicated otherwise. SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; IQR = interquartile range; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ACE = angiotensin-converting enzyme.
† The score corresponding to cancer was excluded when calculating the index.
Differentiating between HS and non-HS cancer. The odds ratio (OR) was calculated for all independent variables together with their 95% confidence intervals (95% CIs). Inclusion of independent variables in a multivariant model was based on clinical judgment and on a $P$ value less than 0.25 obtained in the bivariant analysis. The absence of multicolinearity among independent variables included was checked with the kappa correlation coefficients in the case of qualitative variables, and with Pearson’s correlation for quantitative variables. In the final logistic regression model, the independent variables were adjusted by all the other model variables.

**Ethical aspects.** This project complied with principles of the Helsinki Declaration (26). The project also received the approval of the general Clinical Research Ethics Committee (Doctor Negrín University Hospital of Gran Canaria), as well as the approval of the Clinical Research Ethics Committee at each center where required.

### Table 2. Characteristics of women with SLE and cancer, stratified by hormone sensitivity*

| Variables                                      | Hormone-sensitive cancer: yes (n = 44) | Hormone-sensitive cancer: no (n = 96) | $P$  |
|------------------------------------------------|--------------------------------------|--------------------------------------|------|
| Age at first SLE criterion met, mean ± SD years| 39.1 ± 15.6                          | 37.65 ± 16.18                        | 0.582|
| Age at SLE diagnosis, mean ± SD years         | 41.9 ± 14.4                          | 39.58 ± 16.07                        | 0.497|
| Age at last evaluation, mean ± SD years       | 57.9 ± 13.1                          | 57.31 ± 15.29                        | 0.901|
| Race                                           |                                      |                                      |      |
| Caucasian                                      | 44 (100)                             | 87 (94.57)                           | 0.107|
| Others                                         | 0 (0)                                | 5 (5.43)                             | 0.107|
| Period of disease evolution, mean ± SD months | 198.8 ± 85.9                         | 212.76 ± 112.33                      | 0.352|
| Follow-up in rheumatology, mean ± SD months   | 175.66 ± 81.58                       | 163.80 ± 94.78                       | 0.493|
| Sjogren’s syndrome                             | 11 (26.2)                            | 19 (20)                              | 0.294|
| SLEDAI, median (IQR)                           | 0 (0–2)                              | 2 (0–4)                              | 0.268|
| Katz index, median (IQR)                       | 2 (2–3)                              | 3 (2–4)                              | 0.059|
| Modified Sj, median (IQR)†                    | 1 (0–2)                              | 1.5 (1–3.5)                          | 0.011|
| Modified Charlson comorbidity index, median (IQR)†| 2 (2–3)                              | 3 (2–4.5)                            | 0.034|
| Antimalaria treatment, median (IQR) months    | 84 (19–144)                          | 74.5 (32–133.5)                      | 0.715|
| Smoking (past and current smokers)            | 22 (60.0)                            | 44 (45.83)                           | 0.78 |
| Alcohol                                        | 1 (2.9)                              | 2 (2.27)                             | 0.779|
| Statins                                        | 2 (5.4)                              | 8 (8.89)                             | 0.425|
| ACE inhibitors                                 | 4 (10.8)                             | 11 (12.64)                           | 0.735|
| Acetylsalicylic acid                           | 15 (38.5)                            | 33 (39.29)                           | 0.836|
| Immunosuppressants                             | 19 (46.3)                            | 53 (55.79)                           | 0.188|
| Type of immunosuppressant                     |                                      |                                      |      |
| Nonimmunosuppressants                          | 31 (70.5)                            | 59 (61.46)                           | 0.314|
| Cyclophosphamide/mycophenolate/mycophenolic   | 8 (18.2)                             | 25 (26.04)                           | 0.314|
| Methotrexeate/lefunomide                       | 5 (11.4)                             | 12 (12.5)                            | 0.314|
| Oral contraception                             | 9 (32.1)                             | 16 (23.19)                           | 0.307|
| Corticoids at maximum doses, occasionally      | 6 (16.7)                             | 24 (28.92)                           | 0.163|
| Hospitalization per activity                   | 21 (50.0)                            | 57 (59.38)                           | 0.382|
| No. of hospitalizations per activity, median (IQR)†| 2 (1–3)                              | 2 (1–3)                              | 0.257|
| Refractoriness                                 | 8 (18.2)                             | 25 (26.04)                           | 0.194|

* Values are the number (%) unless indicated otherwise. See Table 1 for definitions.

† The score corresponding to cancer was excluded when calculating the index.

### Table 3. Accumulated incidence of cancer in RELESSER patients and general population according to the 2012 Cancer Registry of the National Institute of Statistics, stratified by age and sex*

| Age       | RELESSER† | General population‡ |
|-----------|-----------|---------------------|
|           | Men       | Women               | Total    | Men               | Women             | Total        |
| <65 years | 3.54 (0.01–19.59) | 4.9 (2.68–8.21) | 4.78 (2.68–3.07) | 2.25 (2.23–2.37) | 2.06 (2.04–2.08) | 2.21 (2.20–2.22) |
| ≥65 years | 14.10 (0.03–75.99) | 15.98 (6.45–32.65) | 15.71 (6.81–30.73) | 23.72 (23.65–23.89) | 10.27 (10.19–10.37) | 16.03 (15.94–16.12) |
| Total     | 5.66 (0.68–20.3) | 6.37 (3.95–9.73)  | 6.31 (4.00–9.45)  | 5.56 (5.53–5.59) | 3.67 (3.64–3.69) | 4.60 (4.58–4.62) |

* Values are the accumulated incidence (95% confidence interval). RELESSER = Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology.

† Accumulated incidence per 1,000 patients.

‡ Accumulated incidence per 1,000 inhabitants.
Table 4. Standardized incidence ratio of cancer (no. of cancer cases observed/no. of expected cancer cases), stratified by age and sex.

| Age   | Men         | Women        | Total         |
|-------|-------------|--------------|---------------|
| <65 years | 1.51 (0.62–2.40) | 2.38 (1.84–2.91) | 2.16 (1.71–2.61) |
| ≥65 years | 0.59 (0.0–1.26)    | 1.55 (1.15–1.95)    | 0.98 (0.73–1.23)    |
| Total | 1.02 (0.49–1.56)    | 1.74 (1.45–1.55)    | 1.37 (1.15–1.59)    |

* Values are the standardized incidence ratio (95% confidence interval).

RESULTS

Patients. The total number of patients included in the analysis was 3,539 (90.4% women), with a mean age at diagnosis of 35 years and a mean period of disease evolution of 143 months (Table 1). The main characteristics of the registry patients have been published previously (14).

Patient characteristics according to cancer presence. The main characteristics of patients with a first cancer onset since SLE diagnosis compared to those without cancer are detailed in Table 1. The total number of patients with cancer was 154 (4.35%), 91% women, with a mean ± SD age at diagnosis of 40.37 ± 15.7 years. Age at diagnosis, the period of disease evolution, Sjögren’s syndrome (SS) association, Katz index score, SDI and Charlson comorbidity index scores, and the prescription of statins were higher in patients with cancer. However, the SLEDAI score and number of hospitalizations due to SLE activity were higher in patients without cancer.

Patient characteristics per HS and non-HS cancers. Of the 154 patients with cancer, only 14 were men, and none of those cases were hormone dependent. Table 2 shows the HS and non-HS cancer characteristics in women. Both the SDI and Charlson indexes had higher values in patients with non-HS cancers.

Cancer incidence. The cancer accumulated incidence in patients with SLE was 6.31 cases per 1,000 patients (95% CI 4.00–9.45). After stratifying by age and sex, the group with the highest number of first cancers (16 cases per 1,000 patients [95% CI 6.45–32.65]) was women ages >64 years (Table 3). The cancer SIR was 1.37 (95% CI 1.15–1.59) and the group with the highest values was women ages <65 years, with 2.38 (95% CI 1.84–2.91) (Table 4). In women, the HS cancer SIR was 1.02 (95% CI 0.13–1.91), and for non-HS patients it was 1.93 (95% CI 0.98–2.89).

Cancer prevalence and distribution. As to the distribution of cancer according to anatomic location, breast and gynecologic cancer were the most frequently recorded (23.4% and 20.1%, respectively), followed by hematologic (75% non-Hodgkin’s lymphoma and 25% Hodgkin’s lymphoma) and skin (nonmelanoma), both 11.7%. These were followed by colorectal and thyroid cancer (both 5.2%), lung cancer (3.25%), and other locations (19.5%). After analyzing the subgroup of patients with SLE with associated SS, we found that the most frequent location was breast cancer at 29%, followed by gynecologic and hematologic cancers, both at 16.1%. Non-Hodgkin’s lymphoma was the most common hematologic cancer (60%) in patients with SLE with associated SS.

Time frame for cancer onset. The median time frame until the onset of the first cancer was 10 years (IQR 5.75–17.00), which was significantly shorter in women (9.5 years [IQR 5.00–17.00]) than in men (12.5 years [IQR 8.75–17.50]), and in patients ages <45 years (8.0 years [IQR 5.00–16.00]) versus patients ages >45 years (10.9 years [IQR 7.00–18.60]).

Death due to cancer. Global mortality was 5.5% of patients, with cancer being the fourth leading cause of death, after SLE itself, cardiovascular disease, and infections. Death due to cancer in patients included in the study was 10.66%, with the most prevalent types being hematologic (19%) and breast (19%) cancers, followed by lung (14.3%) and colorectal (9.5%).

Factors associated with cancer onset in women. Tables 5 and 6 show the results obtained in the bivariant analysis of HS and non-HS cancers. Regarding the multivariable model, the variables with significant associations with HS cancer onset were SLE diagnostic age (OR 1.04 [95% CI 1.01–1.07], P = 0.002) and period of disease evolution (OR 1.01 [95% CI 1.00–1.01], P < 0.001). The multivariate model of non-HS cancers showed a significant association with SLE diagnostic age (OR 1.04 [95% CI 1.01–1.07], P = 0.019), evolution period (OR 1.00 [95% CI 1.00–1.01], P = 0.029), SDI (OR 1.27 [95% CI 1.04–1.57], P = 0.022), and prescription of angiotensin-converting enzyme (ACE) inhibitors (OR 2.87 [95% CI 1.01–8.14], P = 0.048) (Tables 5 and 6).

DISCUSSION

The results obtained in this national retrospective multicenter study showed that the cancer incidence in patients with SLE is higher than in the general population, with differences being more striking in women ages <65 years and in those with non-HS cancers. Furthermore, breast, gynecologic, and hematologic cancers were the most frequently recorded in patients with SLE and in those patients with associated SS. Onset of the first cancer post-SLE diagnosis occurred approximately 10 years later, with breast and hematologic cancers causing more deaths. Both SLE diagnostic age and the period of disease evolution were factors associated with HS and non-HS cancers. However, SDI score and ACE inhibitor prescriptions were solely associated with non-HS cancers.

The differences found among patients with and without cancer on the Katz and Charlson indexes, as well as among patients with a statin prescription, suggest that cancer patients have a
more serious clinical state and greater risk of comorbidities. These variables had not been analyzed in previous studies, although the SDI had been, showing higher values in patients with cancer (27), results consistent with our own study. As to the number of hospitalizations per SLE activity, we noted a paradox, i.e., patients without cancer were hospitalized more frequently. This finding might be due to the effect of oncologic drugs on the activity and evolution of SLE.

On analyzing the differences between women with HS or non-HS cancers, our study revealed that the damage associated with SLE and comorbidity was higher only in patients with non-HS cancers. Notwithstanding such evidence, these results have yet to be replicated by other groups. Nonetheless, we consider this a relevant finding, since patients with non-HS cancers might require a more complex clinical and therapeutic approach.

Several studies in different countries, races, and ethnic groups have noted a global cancer increase, with an SIR between 1.14 and 3.6 (1). Likewise, those studies that stratified the SIR by sex and age found this increase particularly prevalent in women between ages 21 and 64 years (2,28). In our Spanish cohort, the results support previously published findings. Regarding HS breast, endometrial, and ovarian cancers, a very slight and not significant increase has been suggested (29,30); likewise, a significant drop in the SIR has been observed (2,3,6,10,11). This finding has led to the belief that a direct association cannot be established between SLE and the risk of HS cancers. Our study detected a very slight, albeit not significant, increase in the SIR in women with HS cancers. In non-HS cancers, the increase was higher, although it remained at the limit of statistical significance.

Regarding distribution by location, breast, gynecologic, and hematologic cancers (especially non-Hodgkin’s lymphoma) were the most prevalent. These 3 cancers were also among the most frequent in other cohorts, which was true of studies carried out on different races or ethnic groups (2–4,28,30). In fact, this distribution was maintained in SLE and SS patients, with the hematologic tumor non-Hodgkin’s lymphoma being the most frequently recorded, as is the case in patients with primary SS (28).

Focusing on the time frame relationship between SLE and cancer, our patients developed cancer following the SLE diagnosis within a median of 10 years (9 years in women ages <45 years). Other authors have tackled this time frame relationship via cancer risk stratification (SIR) pursuant to follow-up time. They

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**Table 5.** Factors associated with hormone-sensitive cancers in women with systemic lupus erythematosus*

| Variable                                      | Bivariant OR (95% CI) | P     | Multivariant OR (95% CI) | P     |
|-----------------------------------------------|-----------------------|-------|--------------------------|-------|
| Age at first SLE criterion met, years         | 1.03 (1.01–1.05)      | 0.001 | –                        | –     |
| Age at SLE diagnosis, years                   | 1.03 (1.01–1.05)      | 0.001 | 1.04 (1.01–1.07)         | 0.002 |
| Age at last evaluation, years                 | 1.05 (1.03–1.07)      | <0.001| –                        | –     |
| Race                                          |                       |       |                          |       |
| Caucasian (reference)                         | –                     | –     | –                        | –     |
| Others                                        | –                     | –     | –                        | –     |
| Period of disease evolution, months           | 1.00 (1.00–1.01)      | 0.001 | 1.01 (1.00–1.01)         | <0.001|
| Follow-up in rheumatology, months             | 1.01 (1.00–1.01)      | <0.001| –                        | –     |
| Sjögren’s syndrome                            | 1.94 (0.98–3.94)      | 0.057 | 1.60 (0.72–3.53)         | 0.246 |
| SLEDAI                                        | 0.89 (0.78–1.01)      | 0.063 | 0.94 (0.82–1.08)         | 0.394 |
| Katz index                                    | 0.96 (0.80–1.16)      | 0.707 | –                        | –     |
| Modified SDI†                                 | 1.11 (0.95–1.29)      | 0.188 | –                        | –     |
| Modified Charlson comorbidity index†          | 1.27 (1.10–1.46)      | 0.001 | –                        | –     |
| Antimalaria treatment, months                 | 1.00 (1.00–1.00)      | 0.818 | –                        | –     |
| Smoking (past and current smokers)            | 1.25 (0.69–2.26)      | 0.464 | –                        | –     |
| Alcohol                                       | 1.40 (0.19–10.36)     | 0.745 | –                        | –     |
| Statins                                       | 1.07 (0.26–4.50)      | 0.925 | –                        | –     |
| ACE inhibitors                                | 1.22 (0.43–3.48)      | 0.706 | –                        | –     |
| Acetylsalicylic acid                          | 1.10 (0.57–2.11)      | 0.772 | –                        | –     |
| Immunosuppressants                            | 0.66 (0.36–1.23)      | 0.188 | –                        | –     |
| Type of immunosuppressant                     |                       |       |                          |       |
| Nonimmunosuppressants (reference)             | –                     | –     | –                        | –     |
| Cyclophosphamide/mycophenolate/mycophenolic   | 0.60 (0.27–1.30)      | 0.194 | –                        | –     |
| Methotrexate/leflunomide                      | 0.78 (0.30–2.03)      | 0.618 | –                        | –     |
| Oral contraception                            | 1.10 (0.50–2.45)      | 0.813 | –                        | –     |
| Corticoids at maximum dose, occasionally      | 0.55 (0.23–1.33)      | 0.186 | 0.74 (0.29–1.85)         | 0.516 |
| Hospitalization per activity                  | 0.89 (0.48–1.63)      | 0.699 | –                        | –     |
| No. of hospitalizations per activity          | 1.01 (0.86–1.19)      | 0.887 | –                        | –     |
| Refractoriness                                | 0.72 (0.33–1.55)      | 0.394 | –                        | –     |
| Anti-DNA                                      | 0.69 (0.37–1.30)      | 0.249 | 0.88 (0.40–1.92)         | 0.75  |
| No. of pregnancies                            | 1.19 (1.01–1.39)      | 0.038 | 1.00 (0.80–1.25)         | 0.987 |
| Menopause                                     | 1.21 (1.50–28.75)     | <0.001| –                        | –     |

* OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The score corresponding to cancer was excluded when calculating the index.
have found an increased global cancer risk between <1 year and >8 years from the time of SLE diagnosis, with a greater risk during the first year of follow-up (2,4,28).

Among the Spanish population, the cancers most frequently causing death in men are lung, colorectal, and prostate, while in women they are breast, colorectal, and lung (24,25). In our essentially female cohort, the same distribution held true, though hematologic cancers also met first-line inclusion. This finding is not surprising, given that chronic immune dysregulation due to SLE is associated with greater lymphoid proliferation, thus increasing the risk of hematologic tumors, specifically non-Hodgkin’s lymphoma (31).

We are aware that the global standardized mortality rate for cancer in SLE has not increased (32). Patients with chronic diseases are subject to greater vigilance, which may favor early cancer diagnosis and improved prognosis. A suggestion has also been made that patients with SLE have a competitive premature mortality due to other causes, such as cardiovascular disease, infections, and lupus nephritis (32). Our results support this suggestion, since cancer was the fourth leading cause of death after SLE itself, cardiovascular disease, and infections.

SLE diagnostic age and period of disease evolution were associated with both HS and non-HS cancers. In other studies, age was associated with cancer in general, in particular with breast cancer and lymphomas (27,33,34). Bernatsky et al (27) have suggested that lupus duration confers a protective effect against cancer onset. This suggestion potentially contradicts our results, although their study had a different design, and SLE duration was established from the time the patient was included in the cohort, as opposed to the time of SLE diagnosis, as in our study. Accumulated SLE damage and ACE inhibitor prescriptions were solely associated with non-HS cancers. The SDI was found to be a possible factor associated with cancer (27); however, until now this association has not been known as an underlying factor in non-HS cancers. We have no information regarding ACE inhibitor prescriptions as a cancer-associated factor in SLE, since such information had not been included in previous analyses. In our cohort, those patients with cancer who had been prescribed ACE inhibitors suffered hypertension and lupus nephritis with greater frequency than those without ACE inhibitors. The role that ACE inhibitors might play in cancer risk is highly controversial, not only in SLE but in the general population as well. While some studies suggest they

| Table 6. Factors associated with non–hormone-sensitive cancer in women with systemic lupus erythematosus* |
|---|---|---|---|---|
| Variables | Bivariant OR (95% CI) |  | Multivariant OR (95% CI) |  |
| Age at first SLE criterion met, years | 1.03 (1.01–1.04) | <0.001 | – | – |
| Age at SLE diagnosis, years | 1.02 (1.01–1.04) | <0.001 | 1.04 (1.01–1.07) | 0.019 |
| Age at last evaluation, years | 1.05 (1.03–1.07) | <0.001 | – | – |
| Race |  |  |  |  |
| Caucasian (reference) | 0.72 (0.29–1.79) | 0.478 | – | – |
| Others |  |  |  |  |
| Period of disease evolution, months | 1.01 (1.00–1.01) | <0.001 | 1.01 (1.00–1.01) | 0.029 |
| Follow-up in rheumatology, months | 1.01 (1.00–1.01) | <0.001 | – | – |
| Sjögren’s syndrome | 1.39 (0.83–2.31) | 0.213 | 0.95 (0.35–2.57) | 0.246 |
| SLEDAI | 0.96 (0.90–1.02) | 0.209 | 0.97 (0.86–1.09) | 0.394 |
| Katz index | 1.16 (1.05–1.29) | 0.005 | – | – |
| Modified SDI† | 1.32 (1.21–1.43) | <0.001 | 1.27 (1.04–1.57) | 0.022 |
| Modified Charlson comorbidity index† | 1.43 (1.31–1.56) | <0.001 | – | – |
| Antimalaria treatment time, months | 1.00 (1.00–1.00) | 0.264 | 1.00 (1.00–1.00) | 0.947 |
| Smoking (past and current smokers) | 1.06 (0.70–1.59) | 0.791 | – | – |
| Alcohol | 1.10 (0.27–4.59) | 0.893 | – | – |
| Statins | 1.83 (0.87–3.86) | 0.112 | 0.33 (0.04–3.04) | 0.329 |
| ACE inhibitors‡ | 1.46 (0.77–2.78) | 0.25 | 2.87 (1.01–8.14) | 0.048 |
| Acetylsalicylic acid | 1.14 (0.73–1.78) | 0.565 | – | – |
| Immunosuppressants | 0.96 (0.64–1.46) | 0.864 | – | – |
| Type of immunosuppressant |  |  |  |  |
| Nonimmunosuppressants (reference) | – | – | – | – |
| Cyclophosphamide/mycophenolate/mycophenolic acid | 0.98 (0.61–1.57) | 0.929 | – | – |
| Methotrexate/eflunomide | 0.99 (0.53–1.86) | 0.975 | – | – |
| Oral contraception | 0.70 (0.40–1.24) | 0.221 | 1.20 (0.47–3.06) | 0.704 |
| Corticoids at maximum dose, occasionally | 1.12 (0.69–1.82) | 0.638 | – | – |
| Hospitalization per activity | 1.30 (0.86–1.96) | 0.219 | 0.52 (0.22–1.26) | 0.148 |
| No. of hospitalizations per activity | 1.10 (1.04–1.17) | 0.001 | – | – |
| Refractoriness | 1.13 (0.71–1.80) | 0.597 | – | – |

* OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The score corresponding to cancer was excluded when calculating the index.
‡ Cancer patients prescribed ACE inhibitors were more commonly hypertensive than those not prescribed these drugs (75% versus 41%; \( P = 0.005 \)); furthermore, they were more frequently diagnosed with lupus nephritis (85% versus 18.8%; \( P < 0.001 \)).
may increase the risk of certain cancers, such as in the lung (35), others show a reduction or absence of such an association (36). We found no association between HS cancers and oral contraception, the number of pregnancies, or menopause, nor has this association been previously demonstrated with breast cancer (33).

Our results provide evidence that there are several factors exclusively associated with non-HS cancers. This interpretation would support the hypothesis that there are differences in cancer according to hormonal dependence. If these differences are confirmed by subsequent studies, the manner in which patients are assessed will also likely change. Preventative measures and/or cancer screening in patients with SLE based on the risk associated with hormonal dependence may be adopted.

Our study has several limitations. Its retrospective design might render the results somewhat less reliable. Nevertheless, the study remains an acceptable design for tackling infrequent events like cancer. The increased risk of non-HS cancers was on the threshold of significance, for although the total number of cancers was not depreciable when the SIRs of HS and non-HS cancers were separated, statistical power was nonetheless lost. The variables included in our model better explain the non-HS cancers, which leads us to believe that there are still other variables requiring identification and which are associated with HS cancers.

One of the strengths of this study is that it is the largest SLE multicenter cohort from Europe. In addition, we included variables not previously analyzed in other studies. Moreover, because the data were drawn from a clinical registry, as opposed to an administrative national health insurance database, we had more detailed information on the disease, allowing us to better adjust the models. Finally, the comparison between HS and non-HS cancers had not been explored before; thus, the study has greatly expanded upon information previously only hypothesized regarding the differences among these cancer types.

In conclusion, the cancer incidence in patients with SLE is higher than in the general Spanish population, particularly in young women. Above all, the incidence rate may be dependent on non-HS cancers. SLE age at diagnosis and period of disease evolution were common factors associated with both HS and non-HS cancers. However, non-HS cancers were also associated with ACE inhibitor prescriptions and greater accumulated damage. Further studies confirming our findings on the differences between HS and non-HS cancer are greatly warranted, as is a renewed search for factors that most clearly determine the risk of such cancers.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Cobo-Ibáñez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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