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ABSTRACT

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: Retrospective multicentric study of a patient cohort from the SLE Registry of the Spanish Society of Rheumatology (RELESSER – Spanish acronym). Included are the following: 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 rest). Standardized Incidence Ratio (SIR) was calculated and logistic regression models were built.

Results: 3,539 patients (90.4% women) were included, 154 of whom presented cancer (91% women), 44 HS (100% women). Cancer SIR was 1.37 (CI 95%: 1.15-1.59), with higher values in women under 65s [2.38 (CI 95%: 1.84-2.91)]. SIR in women with HS vs. non-HS cancer was 1.02 (CI 95%: 0.13-1.91) and 1.93 (CI 95%: 0.98-2.89)], respectively. In HS vs. non-HS cancers, SLE diagnostic age [odds ratio (OR) 1.04 (p= 0.002) vs. 1.04 (p= 0.019), respectively] and period of disease evolution [OR 1.01 (p< 0.001) vs. 1.00 (p= 0.029), respectively] were associated with cancer. SLICC/ACR damage index [OR 1.27 (p= 0.022)] and ACE inhibitor prescriptions [OR 2.87 (p= 0.048)] were associated with non-HS cancers.

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

Keywords: systemic lupus erythematosus, cancer, incidence, hormone-sensitive

SIGNIFICANCE AND INNOVATIONS

- Cancer incidence rate in SLE patients is estimated to be higher with regard to the Spanish population.

- Cancer risk was higher in women under 65 and those with non-HS cancers.

- SLE diagnostic age and period of disease evolution were common factors associated with both HS and non-HS cancers.

- ACE inhibitor prescriptions and the greater cumulative damage were also associated with non-HS cancers.

Cancer is one of the most serious illnesses a person can have, as 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 knowledge regarding the immune system alterations that occur in SLE, changes which 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 SLE patients is higher than in

the general population (2-7). In particular, the cancer standardized incidence ratio (SIR) is higher across virtually all anatomic locations (hematological, 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). It has been suggested that if the metabolism of estrogen or other predominantly female hormones was altered in SLE, it could slow the progression of hormone-sensitive cancers. On the other hand, a nucleolytic lupus autoantibody, anti-5C6, might help prevent DNA repair mechanisms in breast, ovarian, and prostate cancers associated with BRCA2 mutations (12). Therefore it is possible that SLE autoantibodies may contribute to a decreased risk of certain hormone-sensitive cancers. Thus, it appears that in patients with SLE there might exist some differences in the cancers vis-à-vis hormonal dependence, although the exact mechanisms linking the immune and endocrine systems to cancer risk are unknown. For this reason, it would be interesting to determine whether factors associated with HS cancer differ from those with non-HS. Most studies have focused on searching for factors associated with cancer onset in SLE and have grouped all cancer types, whereas others have explored factors related to the onset of hematological, lung and breast cancer. Yet to date no study has explored stratified cancers vis-à-vis hormone-sensitivity. Thus, an analysis comparing HS and non-HS cancers within a multicentric 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 SLE patients and to analyze factors associated with its onset, differentiating between HS and non-HS cancers.

PATIENTS AND METHODS

1. Design, scope and participants
A retrospective observational longitudinal study of a cohort of RELESSER registry patients.
Participants. RELESSER includes patients over 16 years of age with SLE (per the revised American College Rheumatology (ACR) criteria of 1997) (13) from 45 hospitals registered with the Spanish Society of Rheumatology (SER) hospital database. At least 80% of patients from each centre were included, all of whom having had at least one 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).

2. Data collection

Rheumatologists with experience in diagnosing and treating SLE patients collected the data from each centre, and then uploaded it via an online software application designed *ad hoc* for the project. Data quality control was performed via professional online monitoring.

3. Variables and operational definitions

The main study variable was the first cancer after SLE diagnosis. Endometrial, breast, ovarian and prostate cancers were classified HS and the rest 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 presenting the study event, 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 surgery. Secondary variables included: 1) sociodemographic; 2) general symptoms; 3) cancer location; 4) accumulated SLE symptoms, defined per ACR diagnostic criteria (13, 15) and BILAG definitions (16); 5) SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) activity (17, 18); 6) damage per the SLICC/ACR DI (Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index) (19), excluding cancer; 7) degree of severity (Katz index) (20); 8) comorbidities, hospitalizations and causes of death; 9) Charlson comorbidity index, Deyo modified version (21); 10) treatments for comorbidities and SLE control; and 11) refractoriness, as defined for the registry (22).

4. Statistical analysis

A descriptive analysis was performed using absolute and relative frequencies of qualitative variables, mean or median and dispersion measures (SD: standard deviation, IR: interquartile range) for quantitative variables. The accumulated incidence (AI) of cancers in patients included in RELESSER for 2011 was calculated. To estimate cancer AI in the general population, cancer cases in Spain for 2012 were compiled and measured against the overall population per the 2011 Housing & Population Census (23, 24). Both AI measures were compared by calculating the standardized incidence ration (SIR). The latter was determined 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 anatomical location. With a view to analyzing the association between cancer onset and the clinical characteristics of SLE patients, a logistics regression model was built to analyze female patients, differentiating between HS and non-HS cancer. The Odds Ratio (OR) was calculated for all independent variables together with their confidence value (CI) at 95%. Inclusion of independent variables in a multivariant model was based on clinical judgment and a *p-value* < 0.25 obtained in the bivariant analysis. The absence of multi-co-linearity among independent variables included was checked with the Kappa correlation coefficients in the case of qualitative variables, and with the Pearson 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 (CREC) (Doctor Negrín University Hospital of Gran Canaria), as well as the approval of the CREC at each centre where required.

RESULTS

1. Participants

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

2. Patient characteristics according to cancer presence

The main characteristics of patients with a first cancer onset since SLE diagnosis compared to those without are detailed in Table 1. The total number of patients with cancer was 154 (4.35%), 91% of whom were women, with a mean diagnostic age of 40.37 (SD 15.7) years. Age at diagnosis, the period of disease evolution, Sjögren Syndrome (SS) association, KATZ, SLICC/ACR and Charlson indexes, and the prescription of statins was higher in patients with cancer.

However, the SLEDAI and number of hospitalizations due to SLE activity were higher in patients without cancer.

3. Patient characteristics per HS and non-HS cancers

Out of the 154 patients with cancer, only 14 presented in men and none were hormone dependent. Table 2 shows the HS and non-HS cancer characteristics in women. Both the SLICC/ACR and Charlson indexes had higher values in patients with non-HS cancers.

4. Cancer incidence

Cancer AI in SLE patients was 6.31 cases per 1000 patients (CI 95%: 4.00-9.45). After stratifying by age and gender, the group with the highest number of first cancers (16 cases per 1000 patients (CI 95%: 6.45-32.65)) was that of women over 64 (Table 3). Cancer SIR was 1.37 (CI 95%: 1.15-1.59) and the group with the highest values was that of women under 65, with 2.38 (CI 95%: 1.84-2.91) (Table 4). In women, HS cancer SIR was 1.02 (CI 95%: 0.13-1.91) and for non-HS patients it was 1.93 (CI 95%: 0.98-2.89).

5. Cancer prevalence and distribution

As to the distribution of cancer according to anatomic location, breast and gynecological cancer were the most frequently recorded (23.4% and 20.1%, respectively), followed by hematological (75% non-Hodgkin lymphoma (NHL) and 25% Hodgkin lymphoma) and skin (non-melanoma), 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 SLE patients with associated SS, the most frequent location was breast cancer at 29%, followed by gynecological and hematological, both at 16.1%. NHL was the most common hematological cancer (60%) in SLE patients with associated SS.

6. Time frame for cancer onset

The median time frame until the onset of the first cancer was 10 years (IR: 5.75-17.00), which was significantly shorter in women [9.5 (IR: 5.00-17.0) years] than in men [12.5 (IR: 8.75-17.5)

years], and in patients under 45 [8.0 (IR: 5.00-16.00) years] versus over 45 [10.9 (IR: 7.0-18.6 years)].

7. 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 being hematological (19%) and breast (19%) cancers, followed by lung (14.3%) and colorectal (9.5%).

8. 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 multivariant model, the variables presenting significant associations with HS cancer onset were SLE diagnostic age (OR 1.4; CI 95%: 1.01-1.07; p= 0.002) and period of disease evolution (OR 1.01; CI 95%: 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; CI 95%: 1.01-1.07; p= 0.019), evolution period (OR 1.00; CI 95%: 1.00-1.01; p= 0.029), SLICC/ACR DI (OR 1.27; CI 95%: 1.04-1.57; p= 0.022) and prescription of angiotensin-converting enzyme (ACE) inhibitors (OR 2.87; CI 95%: 1.01-8.14; p= 0.048) (Tables 5 and 6).

DISCUSSION

The results obtained in this national retrospective multicentric study showed that the cancer incidence in SLE patients is higher than in the general population, with said differences being more striking in women under 65, and those with non-HS cancers. Furthermore, breast, gynecological and hematological cancers were the most frequently recorded in SLE patients and those with associated SS. Onset of the first cancer post-SLE diagnosis occurred around 10 years later, with breast and hematological cancers causing more deaths. Both SLE diagnostic age and the period of disease evolution were factors associated with HS and non-HS cancers. However, SLICC/ACR DI 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 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 SLICC/ACR DI had, the latter 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 might be due to the effect of oncological 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 SIR by gender and age found this increase particularly prevalent in women between 21 and 64 years of age (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 SIR has been observed (2, 3, 6, 10, 11). This 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 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, gynecological and hematological (especially NHL) cancers were the most prevalent. These three 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 hematological tumor NHL being the most frequently recorded, as is the case with primary SS (28).

Focusing on the time frame relationship between SLE and cancer, our patients developed cancer post-SLE diagnosis within a median of 10 years (9 years in women under 45). Other authors have tackled this time frame relationship via cancer risk stratification (SIR) pursuant to follow-up time. They found an increased global cancer risk between under one year and over 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 hematological cancers also met first-line inclusion. This is not surprising given that chronic immune deregulation due to SLE is associated with greater lymphoid proliferation, thus increasing the risk of hematological tumors, specifically NHL(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. It has also been suggested that SLE patients present a competitive premature mortality due to other causes like 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 breast cancer and lymphomas (27, 33, 34). Bernasky et al. have suggested that lupus duration confers a protective effect against cancer onset (27). This 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 SLICC/ACR DI was found to be a possible factor associated with cancer (27); however, until now it was not known that this association is an underlying factor in non-HS cancers. We have no information regarding ACE inhibitor prescriptions as a cancer-associated factor in SLE, since it 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 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 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 would support the hypothesis that there are differences in cancer according to hormonal dependence. If these differences are confirmed by subsequent studies, the way 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, it 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 multicentric cohort published in Europe. In addition, we included variables not previously analyzed in other studies. Moreover, as 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; as such, it has greatly expanded upon information previously only hypothesized regarding the differences among these cancer types.

In conclusion, the cancer incidence in SLE patients 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 CONTRIBUTION:

All authors who made substantial contributions to data collection were not only involved in drafting the article and/or revising it critically for intellectual content, but also approved the final version for submission. Dr. Martín-Martínez 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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Data collection: all authors.

Analysis and interpretation of data: Cobo-Ibáñez, Martín-Martínez, Rúa-Figueroa.

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Table 1. Characteristics of patients with Systemic Lupus Erythematosus stratified by cancer

Variables	All	Cancer		p-
	(n=3,539)	YES (n=154)	NO (n= 3,385)	*value*
Female, n (%)	3,194 (90.4)	140 (90.9)	3,054 (90.4)	0.821
Age at first SLE criterion (years), mean (SD)	32.84 (14.4)	38.35 (16.0)	32.72 (14.3)	< 0.001
Age at SLE diagnosis (years), mean (SD)	34.85 (14.5)	40.37 (15.7)	34.75 (14.5)	< 0.001
Age at last assessment (years), mean (SD)	46.52 (14.8)	57.74 (14.4)	46.17 (14.6)	< 0.001
Race, n (%)				
Caucasian	3196 (93.0)	145 (96.7)	3051(92.8)	0.071
Others	241 (7.0)	5 (2.7)	236 (7.2)	
Period of disease evolution (months), mean (SD)	142.86 (100.6)	208.71 (103.0)	140.1 (99.7)	< 0.001
Follow-up time in rheumatology dept. (months), mean (SD)	120 (87.6)	170. 1 (90.8)	118.12 (86.9)	< 0.001
Sjögren Syndrome, n (%)	503 (14.4)	31 (20.5)	472 (14.1)	0.029
SLEDAI, median [p25-p75]	2 [0-4]	1 [0-3]	2 [0-4]	0.026
KATZ Index, median [p25-p75]	2 [1-3]	3 [2-4]	2 [1-3]	0.001
Modified SLICC/ACR DI*, median [p25-p75]	1 [0-2]	1 [0-3]	0 [0-1]	< 0.001
Modified Charlson Index*, median [p25-p75]	2 [1-3]	3 [2-4]	1 [1-3]	< 0.001
Anti-malaria treatment time (months), median [p25-p75]	60 [24-120]	78 [27-136]	60 [24-110]	0.099
Smoking (past and current smokers), n (%)	1656 (46.8)	76 (49.4)	1580 (46.7)	0.515
Alcohol, n (%)	111 (3.482)	6 (4.4)	105 (3.4)	0.517
Statins, n (%)	165 (5.1)	15 (10.7)	150 (4.9)	0.002
ACE Inhibitors, n (%)	313 (9.7)	20 (14.6)	293 (9.5)	0.05
Acetylsalicylic acid, n (%)	1061 (37.180)	55 (40.4)	1006 (36.9)	0.408
Immunosuppressants, n (%)	1939 (57.2)	80 (53.3)	1859 (57.4)	0.326
Immunosuppressants type				
Non immunosuppressants, n (%)	2133 (60.3)	98 (63.7)	2035 (60.1)	
Cyclophosphamide/Mycophenolate/Mycophenolic, n (%)	973 (27.59	38 (24.7)	935 (27.6)	0.668
Methotrexate/Leflunomide, n (%)	433 (12.3)	18 (11.7)	415 (12.3)	
Oral contraception, n (%)	655 (26.89	25 (23.6)	630 (27.0)	0.437

Corticoids at maximum doses, occasionally, n (%)	776 (27.4)	36 (27.1)	740 (27.4)	0.93
Hospitalization per activity, n (%)	1902 (54.6)	88 (57.9)	1814 (54.5)	0.41
Nº of hospitalizations per activity, median [p25-p75]	2 [1-3]	2 [1-3]	2 [1-4]	0.01
Refractoriness, n (%)	873 (24.6)	39 (25.3)	834 (24.6)	0.847

SD: Standard Deviation; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; ACE Inhibitors: angiotensin-converting enzyme inhibitors; *The score corresponding to cancer was excluded when calculating the index.

Table 2. Characteristics of women with Systemic Lupus Erythematosus and cancer stratified per hormone-sensitivity

Variables	Hormone-sensitive Cancer		p-value
	YES (n=44)	**NO (n=96)**	
Age at first SLE criterion (years), mean (SD)	39.1 (15.6)	37.65 (16.18)	0.582
Age at SLE diagnosis (years), mean (SD)	41.9 (14.4)	39.58 (16.07)	0.497
Age at last evaluation (years), mean (SD)	57.9 (13.1)	57.31 (15.29)	0.901
Race, n (%)			
Caucasian	44 (100)	87 (94.57)	
Others	0 (0)	5 (5.43)	0.107
Period of disease evolution (months), mean (SD)	198.8 (85.9)	212.76 (112.33)	0.352
Follow-up time in rheumatology dept. (months), mean (SD)	175.66 (81.58)	163.80 (94.78)	0.493
Sjögren Syndrome, n (%)	11 (26.2)	19 (20)	0.294
SLEDAI, median [p25-p75]	0 [0-2]	2 [0-4]	0.268
KATZ Index, median [p25-p75]	2 [2-3]	3 [2-4]	0.059
Modified SLICC/ACR DI*, median [p25-p75]	1 [0-2]	1.5 [1-3.5]	0.011
Modified Charlson Index*, median [p25-p75]	2 [2-3]	3 [2-4.5]	0.034
Anti-malaria treatment time (months), median [p25-p75]	84 [19-144]	74.5 [32-133.5]	0.715
Smoking (past and current smokers), n (%)	22 (60.0)	44 (45.83)	0.78
Alcohol, n (%)	1 (2.9)	2 (2.27)	0.779
Statins, n (%)	2 (5.4)	8 (8.89)	0.425
ACE Inhibitors, n (%)	4 (10.8)	11 (12.64)	0.735

Acetylsalicylic acid, n (%)	15 (38.5)	33 (39.29)	0.836
Immunosuppressants, n (%)	19 (46.3)	53 (55.79)	0.188
Type of Immunosuppressants			
Non immunosuppressants, n (%)	31 (70.5)	59 (61.46)	
Cyclophosphamide/Mycophenolate/Mycophenolic, n (%)	8 (18.2)	25 (26.04)	0.314
Methotrexate/Leflunomide, n (%)	5 (11.4)	12 (12.5)	
Oral contraceptives, n (%)	9 (32.1)	16 (23.19)	0.307
Corticoids at maximum doses, occasionally, n (%)	6 (16.7)	24 (28.92)	0.163
Hospitalization per activity, n (%)	21 (50.0)	57 (59.38)	0.382
Nº of hospitalizations per activity, median [p25-p75]	2 [1-3]	2 [1-3]	0.257
Refractoriness, n (%)	8 (18.2)	25 (26.04)	0.194

SD: Standard Deviation; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; ACE Inhibitors: angiotensin-converting-enzyme inhibitors; *The score corresponding to cancer was excluded when calculating the index.

Table 3. Accumulated incidence of cancer in RELESSER patients and general population per the 2012 Cancer Registry of the National Institute of Statistics, stratified by age and gender

Age	RELESSER[*]			GENERAL POPULATION[£]		
	Men	Women	Total	Men	Women	Total
< 65 years, AI (CI 95%)	3.54 (0.01-19.59)	4.9 (2.68-8.21)	4.78 (2.68-3.07)	2.35(2.33-2.37)	2.06 (2.04-2.08)	2.21 (2.20-2.22)
≥ 65 years, AI (CI 95%)	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, AI (CI 95%)	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)

*Accumulated Incidence (AI) per 1000 patients; [£]AI per 1000 inhabitants.

Table 4. Standardized Incidence Ratio of cancer (nº cancer cases observed /nº of expected cancer cases) stratified by age and gender

Age	Men	Women	Total
< 65 years, SIR (CI 95%)	1.51 (0.62-2.40)	2.38 (1.84-2.91)	2.16 (1.71-2.61)
≥ 65 years, SIR (CI 95%)	0.59 (0.0-1.26)	1.55 (1.15-1.95)	0.98 (0.73-1.23)
Total, SIR (CI 95%)	1.02 (0.49-1.56)	1.74 (1.45-1.55)	1.37 (1.15-1.59)

SIR: Standardized Incidence Ratio.

Table 5. Factors associated with hormone-sensitive cancers in women with Systemic Lupus Erythematosus

Variable	Bivariant		Multivariant	
	OR (CI95%)	p-value	OR (CI95%)	p-value
Age at first SLE criterion (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 time in rheumatology dept. (months)	1.01 (1.00-1.01)	< 0.001		
Sjögren 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 SLICC/ACR DI*	1.11 (0.95-1.29)	0.188		
Modified Charlson Index*	1.27 (1.10-1.46)	0.001		
Anti-malaria treatment time (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 Immunosuppressants				
Non immunosuppressants (reference)				
Cyclophosphamide /Mycophenolate/Mycophenolic,	0.60 (0.27-1.30)	0.194		
Methotrexate/Leflunomide	0.78 (0.30-2.03)	0.618		
Oral contraceptives	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	12.1 (5.10-28.75)	<0.001		

SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; ACE Inhibitors: angiotensin converting-enzyme inhibitors; *The score corresponding to cancer was excluded when calculating the index.

Table 6. Factors associated with non-Hormone-sensitive cancer in women with Systemic Lupus Erythematosus.

Variables	Bivariant		Multivariant	
	OR (IC 95%)	**p-value**	OR (IC 95%)	**p-value**
Age first criterion (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)		0.478		
Others	0.72 (0.29-1.79)			
Period of disease evolution (months)	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	0.029
Follow-up time in rheumatology dept. (months)	1.01 (1.00-1.01)	< 0.001		
Sjögren 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 SLICC/ACR DI *	1.32 (1.21-1.43)	< 0.001	1.27 (1.04-1.57)	0.022
Modified Charlson Index*	1.43 (1.31-1.56)	< 0.001		
Anti-malaria 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 Immunosuppressants				
Non immunosuppressants (reference)				
Cyclophosphamide	0.98 (0.61-1.57)	0.929		
/Mycophenolate/Mycophenolic,				
Methotrexate/Leflunomide	0.99 (0.53-1.86)	0.975		
Oral contraceptives	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		

SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; ACE Inhibitors: angiotensin converting-enzyme inhibitors; *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 (75% vs. 41%, p=0.005); furthermore, they were more frequently diagnosed with lupus nephritis (85% vs. 18.8%, p<0.001).