Original Article

Incidence of Cancer in a Cohort of Spanish Patients With Systemic Lupus Erythematosus

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Malignancy
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Abstract

Objective: To determine the incidence and prevalence of cancer in a cohort of patients with systemic lupus erythematosus (SLE) and identify associated risk factors.

Patients and methods: The study comprised a dynamic cohort of SLE patients (November 1989 to December 2006) at a tertiary referral centre. An adjusted external control from the hospital tumour registry was used.

Results: The study included 175 SLE patients (90% women), with a mean time at risk of 1370.5 patient-years. Fourteen women (8%) died, mainly from cardiovascular events. No patient died due to malignancy. We found 35 tumours in 28 patients, 25 of them after the diagnosis of SLE, of which 5 were malignant. The rate of benign tumours was 14.6/1000 patient-years (95% CI, 8.9–22.5) and of malignant tumours 3.6/1000 patient-years (95% CI, 1.5–8.8), with a crude incidence odds ratio for malignant tumours of 3.5 (95% CI, 1.5–7.9). However, this significance was lost after standardizing the rates. Concerning associated risk factors, differences were found in the mean erythrocyte sedimentation rate [HR 1.4 (1.1–1.7)], and the presence of thrombosis [HR 6.9 (1.49–41.2)], especially arterial thrombosis.

Conclusions: We found a crude incidence rate of cancer that was almost four times greater in our SLE patients as compared with the expected rate in the hospital area of western Malaga.

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Incidencia de cáncer en una cohorte de pacientes con lupus eritematoso sistémico

Resumen

Objetivo: Determinar la incidencia y prevalencia del cáncer en una cohorte de pacientes con lupus eritematoso sistémico (LES) e identificar los factores de riesgo asociados.

Pacientes y métodos: El estudio incluyó una cohorte dinámica de los pacientes con LES (de noviembre de 1989 a diciembre del 2006) en un centro hospitalario de tercer nivel. Se utilizó un control externo ajustado por edad y sexo a través de un registro hospitalario de tumores de la misma área sanitaria.

Resultados: El estudio incluyó a 175 pacientes con LES (90% mujeres), con un tiempo en riesgo de 1370,5 pacientes-año. Catorce mujeres (8%) murieron, principalmente por eventos cardiovasculares. Ningún paciente falleció por tumor maligno. Se encontraron 35 tumores en 28 pacientes, 25 de ellos después del diagnóstico de LES, de los cuales 5 fueron malignos. La tasa de tumores benignos fue de 14,6/1000 pacientes-año (IC del 95%, 8,9–22,5) y de los tumores malignos 3,6/1000 pacientes-año (IC del 95%, 1,5 a 8,8), con una razón de momios de incidencia cruda para los tumores malignos de 3,5 (IC del 95%, 0,01 a 0,07). Sin embargo, esta significación se perdió cuando se estandarizaron las tasas. En cuanto a los factores de riesgo asociados, se encontraron diferencias en la velocidad de sedimentación globular media [HR 1,4 (1,1–1,7)], y la presencia de trombosis [HR 6,9 (1,49 a 41,2)], en especial la trombosis arterial.

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Conclusiones: Encontramos una tasa cruda de incidencia de cáncer casi 4 veces mayor en los pacientes con LES en comparación con la tasa esperada en nuestra área de influencia del hospital (zona oeste de Málaga).

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Introducción

Sistémico lupus eritematoso (SLE) es una enfermedad inflamatoria sistémica mediada por mecanismos inmunológicos con una compleja base genética. La interacción entre genes y factores ambientales favorece que esta enfermedad resulte en una respuesta inmune autolimitada con un mayor riesgo de daño al cuerpo y sistemas. Este complejo mecanismo del ambiente e inmunitario es responsable de las consecuencias del envejecimiento y calidad de vida en pacientes SLE. A pesar de la aterosclerosis acelerada, la neoplasia de pacientes lupus y otros trastornos inflamatorios es uno de los dos efectos graves que ha recibido mucha atención, sin embargo, las prácticas de tratamiento utilizadas en los diferentes estudios, como se describe más adelante, son esenciales de la realización de los estudios involucrados en el desarrollo de SLE y SLE. Por lo tanto, conocen las neoplasias involucradas en el desarrollo de SLE y SLE, y también los factores que contribuyen al desarrollo de estas neoplasias.

Métodos

Este estudio, un estudio de cohorte dinámico prospectivo, se realizó entre febrero de 1990 y diciembre de 2006 en una población de 14 años de edad o más en el Hospital Universitario Virgen de la Victoria en Málaga, España. Este hospital es el hospital de referencia para el cáncer y enfermedades autoinmunitarias del distrito de Málaga. El estudio de la cohorte fue hospitalizado y comenzó en 1990. Se recogieron datos de un grupo de pacientes tratados en nuestro centro hasta que se recopilaron datos retrospectivamente. Sin embargo, el seguimiento completo fue prospectivo desde 1990 y se estableció un protocolo para la recopilación de datos de base y datos biológicos hasta que se recibieron datos de los pacientes en el hospital en el que se consideraron. Los pacientes han sido seguidos en el hospital y en el centro de tratamiento fuera de los servicios hospitalarios. Se creó un documento de tratamiento en el centro de tratamiento fuera del hospital y en el centro de tratamiento fuera del hospital.

Casos

El estudio incluyó 175 pacientes con SLE clasificados de acuerdo con los criterios revisados del American College of Rheumatology (ACR) para SLE.7 Para ser incluido como caso de SLE, los pacientes tuvieron que cumplir con los criterios de la Organización Mundial de la Salud (OMS)8 incorporados en el ICD-10 (Clasificación Internacional de Enfermedades para la Oncología). Los casos de cáncer fueron confirmados mediante un examen histológico y obtenidos desde el registro del cáncer del hospital.

Controles

El grupo control se obtuvo del registro del hospital de cáncer del Hospital Universitario Virgen de la Victoria. Este registro activo, propuesto por el Servicio de Medicina de Malaga University, al School of Medicine, tiene un registro continuo, sistemático de datos de la Patología Departamento, la Clínica de Medicina, la Oncología y los Servicios de Hematología, informando de todos los pacientes de cáncer (tumores) diagnosticados y trata dos desde 1 de enero de 1993 en el hospital. Para que los pacientes fuesen incluidos, se propusieron incidentes que tuvieron que cumplir con los criterios de la OMS9, indicados en el ICD-O. Este registro es el sistema de coordinación del Hospital Tumor Registros, el cual es más descriptivo y no contiene ningún dato sobre el estado de evolución.

Protocolo y Variables

Los datos se recogieron prospectivamente y se incluyeron en una base de datos electrónica cuando los pacientes de SLE cohort. Los datos se recogieron en cada visita hospital, que variaron en frecuencia según las necesidades del paciente, aunque el tiempo medio entre las visitas fue de 6 meses.

El registro de los SLE se incluyó en el registro de los pacientes incluyendo la información personal, factores de riesgo, como el hábito de fumar (fumadores, exfumadores y fumadores activos) y el consumo de alcohol, índice de masa corporal (BMI) (norma: BMI < 25.9 kg/m², exceso: BMI > 30), hipertensión,10 diabetes mellitus,11 dislipidemia,12 y la historia geográfica.

Los datos relacionados con SLE se incluyeron desde el momento del diagnóstico en SLE, definido por la presencia de signos o síntomas sugestivos de lupus; la fecha de diagnóstico de SLE, definida como la primera vez que el paciente objetivamente cumplía 4 o más de los criterios de la OMS; los síntomas presentes en la inclusión en la cohorte y en cada visita (recopilados prospectivamente); el tiempo de la enfermedad a la hora del protocolo, utilizando SLEDAI2K9 y SLICC/ACR DII10; la severidad de la enfermedad11; tratamiento durante la enfermedad, incluyendo fármacos inmunosupresores. En el registro se recopilaron datos de pacientes de la misma referencia en el caso de las tasas. Los datos de los tumores registrados fueron cruzados con los datos de nuestro SLE database para confirmar que no se incluyó un caso de SLE.

En el caso de la enfermedad del tumor, se incluyeron en el registro de los tumores, los datos del caso de la enfermedad de SLE, definido por el diagnóstico de la enfermedad del tumor, el tipo de tumor, número de tumores, el estado de la enfermedad en el momento del diagnóstico, tratamiento y resultado, y la correspondencia con la historia geográfica. Las tasas de eventos de SLE fueron calculadas antes o después del diagnóstico de SLE. Se consideraron aquellos aquéllos incluidos en el registro como el momento en el cual el paciente comenzó el seguimiento en el hospital.

Análisis estadístico

Para estimar el riesgo de cáncer y compararlo con las poblaciones, las respectivas calculaciones se realizaron mediante el cálculo de los intervalos de confianza. Los 95% y los intervalos de incidencia estándar (SIR) fueron calculados utilizando la Poisson's method.12 La incidencia de cáncer en el SLE cohort fue calculada dividiendo el número de cánceres detectados por el "tiempo a tiempo" del caso. El "tiempo a tiempo" fue calculado en años, a la vez que los SLE y el paciente permanecieron bajo observación en el centro de tratamiento, desde la fecha de diagnóstico de SLE hasta la fecha de la primera consulta (caso incidente), menos el seguimiento, el tiempo de la enfermedad o la fecha de la observación (31 de diciembre de 2006 – censura caso).
calculate the incidence rates we excluded cases of cancer diagnosed prior to the diagnosis of SLE. The SIR was adjusted for age and sex by the indirect method or internal standardization. The number of expected cases was obtained from the incidence rate of the registry, adjusted for age, sex and calendar year of the cases. The incidence rate of cancer in the registry was calculated by dividing the number of cancers detected by the “time at risk” of the inhabitants covered by the tertiary referral hospital between February 1990 and December 2006. The “time at risk” was calculated in person-years taking into account the annual variations for men and women in our population census registries during the same period.

Normality was assessed by the Kolmogorov–Smirnov test. Contrast of the quantitative variables was done with the Student t test for independent variables or the Wilcoxon–Mann–Whitney U test, and for the qualitative variables using the Pearson χ²-test, with the Fisher exact test if necessary. The significance shown beside the SIR in each table was obtained with the Mantel–Haenszel homogeneity test (M–H). The multivariate analysis of the factors associated with the incidence of cancer in the SLE cohort was done using Cox regression, considering those patients without cancer at the end of the follow-up or death as censored cases. The results are expressed as the hazards ratio (HR) with their 95% CI. The multivariate analysis only included those variables that reached P<.1 in the univariate analysis. The erythrocyte sedimentation rate (ESR) values introduced into the model correspond to the mean values observed during the follow-up. The multivariate model was adjusted for age using the Wald forward stepwise method with an input likelihood of 0.05 and an output likelihood of 0.1. The results computed were both crude and age-adjusted. All the calculations and the statistical analyses were done with SPSS 14.0 and the epidemiological analysis with STATA 10.0

Results

The cohort comprised 175 SLE patients included between November 1989 and December 2006. Table 1 summarizes the descriptive data of the cohort. Most patients were younger than 40 years of age at the end of the follow-up and there was no male patient aged over 65 years. Proportionally more men than women abandoned the follow-up [7 (40%) vs. 22 (14%); P=.018].

Concerning immunosuppressive therapy, 96 patients (55%) had at some time at least one immunosuppressive drug, mostly bolus cyclophosphamide, followed by methotrexate and azathioprine.

Frequency and Types of Cancer

In the whole SLE cohort, nine patients had cancer, four of whom had cancer before diagnosis of SLE and five after diagnosis of SLE. Table 2 shows the characteristics of the cancers. The mean age at diagnosis of the cancer in those who already had SLE was 45 years, with a mean of five years between diagnosis of SLE and diagnosis of the cancer. The most usual type of cancer before SLE was cancer of the cervix, followed by breast cancer. However, in those whose cancer was diagnosed after their diagnosis of SLE, the most common type was breast cancer. Most cancers were diagnosed in situ or at stage I (6 of 9) and all were treated surgically; only one patient, with breast cancer, also required chemotherapy and radiotherapy. All recovered satisfactorily. One of the cervical cancers was stage IIb, and the patient was treated successfully with surgery and radiotherapy. Only two cancers recurred, one stage IV breast cancer and one bladder cancer (PT1-A1G). No malignant haematological neoplasm was detected.

Table 3 shows that the crude incidence rate of cancer after diagnosis of SLE was 3.6 per 1000 patient-years (95% CI, 1.5–8.8). Our hospital tumour registry, used to calculate the expected cases, recorded 2654 cancers in 2,527,047 patient-years, giving a crude incidence rate of expected cases of 1.05 per 1000 person-years (95% CI, 1.01–1.09). The same table also shows that the stratum-specific odds ratios of the incidence rates differed, and the effect of the

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)/mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women)</td>
<td>158 (90%)</td>
</tr>
<tr>
<td>Age at onset lupus (yrs)</td>
<td>31 ± 11</td>
</tr>
<tr>
<td>Age at diagnosis lupus (yrs)</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>Age at protocol (yrs) a</td>
<td>39 ± 21</td>
</tr>
<tr>
<td>Time at risk (pt-yrs) b</td>
<td>1370.5</td>
</tr>
<tr>
<td>Sicca syndrome (yes) c</td>
<td>56 (32%)</td>
</tr>
<tr>
<td>Antiphospholipid syndrome (yes) d</td>
<td>22 (13%)</td>
</tr>
<tr>
<td>Lymphopenia (yes) e</td>
<td>134 (77%)</td>
</tr>
<tr>
<td>ANA (yes) f</td>
<td>175 (100%)</td>
</tr>
<tr>
<td>Anti-DNA (yes) g Δ</td>
<td>113 (65%)</td>
</tr>
<tr>
<td>Anti-Sm (yes) h</td>
<td>45 (26%)</td>
</tr>
<tr>
<td>Anti-RNP (yes) i</td>
<td>40 (23%)</td>
</tr>
<tr>
<td>Anti-Ro(SSA) (yes) j</td>
<td>77 (44%)</td>
</tr>
<tr>
<td>Anti-La(SSB) (yes) k</td>
<td>39 (22%)</td>
</tr>
<tr>
<td>Antiphospholip antibodies (yes) l</td>
<td>76 (43%)</td>
</tr>
<tr>
<td>Lupus anticoagulant (yes) m</td>
<td>25 (15%)</td>
</tr>
<tr>
<td>Mean CRP (mg/dl) n</td>
<td>0.3 ± 0.5</td>
</tr>
<tr>
<td>Mean ESR (mm/1st hour) o</td>
<td>16 ± 24</td>
</tr>
<tr>
<td>SLEDAI (0–49) p</td>
<td>1.3 ± 1.8</td>
</tr>
<tr>
<td>SLEDM (0–105) q</td>
<td>2 ± 4</td>
</tr>
</tbody>
</table>

Comorbidities

Hypertension 65 (37%)
Obesity 59 (34%)
Diabetes mellitus 5 (3%)
Hypercholesterolemia 41 (23%)
Hypertriglyceridemia 28 (16%)
Low HDL 20 (11%)
Smoking 56 (32%)
Alcohol 10 (6%)

Severity

Slight 62 (35%)
Moderate 65 (37%)
Severe 50 (28%)

Glucocorticoids

Hydroxychloroquine 148 (85%)

Immunosuppressive

Cyclophosphamide
Oral 4 (2.3%)
Boluses 29 (17%)
Azathioprine 24 (14%)
Methotrexate 27 (15%)
Cyclosporin A 9 (5%)
Mycophenolate 3 (1.7%)

a Age at protocol, defined as the patient’s age at the latest revision.
b The “time at risk” was calculated adding the times that each SLE patient had remained under observation in the cohort, from the date of diagnosis of SLE to the date of the first cancer (incident case), lost to follow-up, death or end date of the observation period (31 December 2006 – censored case).
c Xerostomia and xerophthalmia.
d APS was classified according to the Sydney revision of the Sapporo criteria (Miyakis et al., J Thromb Haemost 2006; 4:295–306).
e Reference values according to the ACR criteria.
f ANA, antinuclear antibodies.
g Anti-DNA, anti-DNA antibodies.
h CRP, C-reactive protein.
i ESR, erythrocyte sedimentation rate.
j SLEDAI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology.
k SLEDM, Systemic Lupus Erythematosus Disease Activity Index.


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Table 2
Descriptive Characteristics of SLE Patients With Cancer.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cancer before the diagnosis of SLE</th>
<th>Cancer after the diagnosis of SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>45.6 ± 9.1 (34.6–55.2)</td>
<td>44.9 ± 10.7 (32.6–59.3)</td>
</tr>
<tr>
<td>Duration of lupus, months</td>
<td>–</td>
<td>62.3 ± 45.1 (6.2–116.5)</td>
</tr>
<tr>
<td>Time before lupus, months</td>
<td>24.5 ± 12.4 (9.8–37.2)</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Localization</th>
<th>N=4</th>
<th>N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1 (25%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Cervix</td>
<td>3 (75%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>

a Number of cases (%) or mean ± SD (range).

b Calculated from lupus diagnosis to date of cancer.

c Calculated from the diagnosis of cancer to diagnosis of lupus.

Factors Associated With the Development of Cancer in SLE

As it can be seen in Table 4, of the variables included in the regression analyses, only history of thrombosis [HR 6.9 (95% CI, 1.49–41.2; P=0.035), especially of the arterial territory [HR 8.6 (95% CI, 1.4–51.7); P=0.018] and mean ESR [HR for each 10 mm/h 1.4 (95% CI, 1.1–1.7); P=0.002] showed a significant association with the incidence of cancer. Nonetheless, both obesity and a SLICC score above 2 also showed a certain association. In multivariate analysis, only ESR [HR for each 10 mm/h 1.4 (95% CI, 1.1–1.7); P=0.012] and arterial thrombosis [HR 7.0 (95% CI, 1.1–43.4); P=0.035] remained associated. We found no association between the incidence of cancer and other manifestations of SLE, nor with alcohol consumption, smoking, age at diagnosis, oral contraceptives, drugs used for the SLE, autoantibodies, complement consumption or disease severity.

In the SLE cohort, 14 (8%) patients died, giving a mortality rate of 101 per 1000 patient-years (95% CI, 56–171). All the deaths were in women. The three main causes of death were cardiovascular events (36%), infection (29%) and disease activity (21%). No patient died due to a malignant tumour.

Discussion

This study suggests that the incidence rate of cancer in our SLE patients is almost four times greater than expected for our hospital area of western Malaga. This finding was seen after observation of our cohort of SLE patients for 1370.5 patient-years, which is no different clinically or analytically from the large SLE series. Although the crude rate of cancer in the SLE patients was higher than that of the controls, the significance was lost after standardizing the rates. This is very likely due to the small sample size as compared with large multicentre studies. Another methodological factor that could influence in higher cancer rate of the SLE patients was a greater chance of detecting cancer in a prospective hospital cohort compared with controls that came freely. The same reason could be behind the observation that none of our lupus patient died from cancer.

The relation between cancer and immunologically mediated inflammatory diseases, including SLE, has been the subject of great debate for some time, and it has, consequently, been examined by many authors in several different countries. In 2005, Bernatsky et al. published the largest multicentre study, comprising 9547 patients from 23 centres in six different areas (Canada, United States, United Kingdom, Sweden, Korea and Iceland) and representing 76,948 patient-years, with a mean follow-up of 8 years. Like us, these authors also found an increased risk of cancer among SLE patients, though the risk was lower than in our study as they estimated a SIR of 1.15 (95% CI, 1.05–1.27). Prior to this study, many

Table 3
Incidence Rates Cancer in 175 Patients After Diagnosis of Lupus.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patient-year</th>
<th>Observed cases</th>
<th>Expected cases</th>
<th>SIR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>1370.49</td>
<td>5</td>
<td>1.439289</td>
<td>3.5</td>
<td>1.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Standardized</td>
<td>3.6</td>
<td>1.5</td>
<td>8.6</td>
<td>.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–39 years</td>
<td>517.25</td>
<td>2</td>
<td>0.191848</td>
<td>10.4</td>
<td>3.4</td>
<td>31.9</td>
</tr>
<tr>
<td>40–64 years</td>
<td>619.58</td>
<td>3</td>
<td>1.154649</td>
<td>2.6</td>
<td>0.9</td>
<td>7.7</td>
</tr>
<tr>
<td>≥65 years</td>
<td>128.00</td>
<td>0</td>
<td>0.404684</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Standardized</td>
<td>1.751182</td>
<td>2.8</td>
<td>1.2</td>
<td>6.9</td>
<td>.187</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–39 years</td>
<td>55.58</td>
<td>0</td>
<td>0.001178</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40–64 years</td>
<td>39.50</td>
<td>0</td>
<td>0.027488</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥65 years</td>
<td>10.58</td>
<td>0</td>
<td>0.032776</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Standardized</td>
<td>0.061443</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>.927</td>
<td></td>
</tr>
</tbody>
</table>

SIR, standardized incidence ratios; CI, confidence intervals.

* Adjusted by sex, age, and calendar year.

Table 4
Univariate and Multivariate Cox Regression Analysis of Risk Factors for Cancer in SLE Patients.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR* Univariate (IC 95%)</th>
<th>P-value</th>
<th>HR Multivariate (IC 95%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>7.9 (0.9–70.3)</td>
<td>.065</td>
<td>1</td>
<td>.220</td>
</tr>
<tr>
<td>ESR × 10, mm/h</td>
<td>1.4 (1.1–1.7)</td>
<td>.002</td>
<td>1.4 (1.1–1.7)</td>
<td>.012</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6.9 (1.49–41.2)</td>
<td>.035</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>8.6 (1.4–51.7)</td>
<td>.018</td>
<td>7.0 (1.1–43.4)</td>
<td>.035</td>
</tr>
<tr>
<td>SLICC ≥ 2</td>
<td>4.6 (0.8–27.9)</td>
<td>.097</td>
<td>–</td>
<td>.873</td>
</tr>
</tbody>
</table>

Were also included in the univariate analysis, but were not significant: age at diagnosis of SLE, age at diagnosis of cancer, smoking, alcohol, oral contraceptives, history of benign tumor, hypocomplementemia, Anti-DNA, Antiphospholipid antibodies, severe lupus and immunosuppressive drugs (ever).

* HR, hazard ratio.

b The mean values of ESR during the follow-up.
other studies had been done, with conflicting results. Some studies found a higher risk of cancer in patients with SLE,1,2,18 whereas several others failed to find this association,20,21 showing that this topic remains unresolved. This great variation in the results may have several explanations, including, importantly, the different distribution of the risk of cancer among the various countries (and even within the same country). Accordingly, it is even more important for each country to undertake its own studies on cancer incidence.

Another factor possibly influencing the variation in the results in cancer incidence concerns the study method employed. Some studies have involved a clinical group with no external control group, whereas others did use an external control group, either from a statistics center,20,21 or a national/provincial cancer registry,17,18 and even a hospital registry, like that used by us.

The mean time between diagnosis of SLE and diagnosis of cancer in our cohort was 5 years. Bernatsky et al.,1 in a cohort of 9547 SLE patients, found that most of the cancers occurred after the first year of diagnosis of SLE. Nevertheless, considering that tumours have a very variable, prolonged subclinical period of development, the presence of SLE can hardly be held responsible solely for this greater incidence. This is so even though there is always a delay between the onset of lupus symptoms and its diagnosis, particularly in patients whose cancer is diagnosed during the initial years of SLE, which has led several authors to suggest that SLE may be considered a paraneoplastic syndrome in these patients.22

The genetic and immunological changes giving rise to SLE may also play a fundamental role in the development of malignant tumours many years before the disease is clinically expressed. To this extent, changes in immune vigilance and loss of tolerance may share certain mechanisms. In fact, cancer incidence was associated with chronic inflammation as determined by ESR in our patients. This association has been also observed in patients with rheumatoid arthritis.23 By contrast, the temporal association between cancer and thrombosis observed in our study could be explained by a dual mechanism, i.e., by the relationship between thrombosis and antiphospholipid antibodies in SLE and by thrombophilic state induced by the cancer as “second hit” that triggers thrombosis.24

Although we have not found an association between cancer and immunosuppressants, such as azathioprine or cyclophosphamide, it is worth mentioning that this association has been observed by others.25

The spectrum of malignant tumours in SLE patients is very variable. Almost all types of tumours have been reported,26 though the disease has most commonly been associated with haematological malignancies, mainly non-Hodgkin’s lymphoma.1,14,19 The types of neoplasia that we observed were those expected for age and sex in general population. In our cohort we only found one pretumour haematological disorder, a myelodysplastic syndrome, which we did not include among the malignant tumours as it did not progress to acute leukaemia. Thus, we found no relation between SLE and haematological tumours, not even non-Hodgkin’s lymphoma, as in other studies.18,21 Three main reasons may explain this lack of association. As Zintzaras et al. point out in their meta-analysis,27 the SIR has become lower over the years (in 1992 it was 44.40, in 1995 it was 27.10, and in 2001 it was 7.42), which would explain why our series, despite being an open observational study from 1992, found no lymphomas. Secondly, non-Hodgkin’s lymphoma is usually more common in men26 and only 10% of our cohort was male. The third reason for the lack of association between SLE and haematological tumours relates to the association between lymphoma and inflammation. The improved control in SLE activity attained over recent years has contributed to lymphoma becoming an increasingly rarer complication, and sustained activity is related with the appearance of neoplasms and greater associated mortality.23

We want to emphasize that an important limitation of our study concerns the restricted number of patients, though not the observation period, which covered 17 years and resulted in a total observation of 1370.5 patient-years. Nevertheless, to reduce instability in the calculation of the stratum-specific rates associated with the observation of such a low number of events, we standardized the SIR by an indirect method, which assigned weights according to the stratum size of the SLE cohort, making them less susceptible to random variation. This aspect is important, because we saw that the SLE patients belonging to the younger age strata were those who had higher incidence rates of cancer, a finding not seen in other studies.21,29,30

In conclusion, the crude incidence rate of cancer in our cohort of SLE patients was almost four times greater than that seen in the equivalent population without SLE. Our results support the hypothesis that patients with SLE have a greater risk of cancer. A chronic increase in the ESR and the presence of thrombosis were associated with a greater risk of cancer in our SLE patients.

Ethical Responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of Interest

The authors declare no conflict of interest.

References


