The relationship between cancer and medication exposure in patients with systemic lupus erythematosus: a nested case-control study

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Jinyan Guo
Zhengzhou University First Affiliated Hospital

Zhigang Ren
Zhengzhou University First Affiliated Hospital

Jianhao Li
Zhengzhou University First Affiliated Hospital

Tianfang Li
Zhengzhou University First Affiliated Hospital

Shengyun Liu  757612099@qq.com
Zhengzhou University First Affiliated Hospital
Corresponding Author

Zujiang Yu
Zhengzhou University First Affiliated Hospital

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Abstract

Background Systemic lupus erythematosus (SLE) is associated with increased risk of cancer and the mechanism remains unclear. Here, we examined the level of auto-antibodies and disease activity index scores in SLE patients with cancers, and analyzed whether medications for SLE management might contribute higher cancer risk in SLE patients.

Methods In this retrospective study, we carried out a nested case-control study in a large cohort of SLE patients. We screened 5858 SLE patients to identify the newly diagnosed and yet to be treated cancers. The following clinical features were evaluated: auto-antibodies levels, SLE disease activity index scores and previous medication used for SLE management. Systemic glucocorticoid, cyclophosphamide, hydroxychloroquine (HCQ), methotrexate and azathioprine were considered the main medication indices.

Results Our analyses identified 51 SLE patients who also had cancer, and 204 matched control patients who had SLE but not cancer. Of the 51 SLE patients, thyroid cancer (14/51, 27.45%), cervical cancer (10/51, 19.61%) and lung cancer (7/51, 13.73%) were the most common types. Our analyses did not reveal any significant differences in the levels of auto-antibodies in SLE patients with cancers relative to the control group. Further, we observed that disease activity was significantly lower in SLE patients with cancers relative to the matched control SLE group. There was no statistically significant association between the cancer risk and the use of systemic glucocorticoid, cyclophosphamide, methotrexate or azathioprine. Importantly, the administration of HCQ was significantly lower in SLE patients suffering cancers relative to the cancer free matched control group.

Conclusions Our analyses indicate that SLE patients with cancers might have a lower disease activity at the time of cancer diagnosis. HCQ was negatively correlated with cancer risk in SLE patients. These findings highlight a potential and novel prevention
strategy for SLE.

**Background**

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disorder characterized by an aberrant production of auto-antibodies and a wide range of clinical manifestations and complications. Antinuclear antibodies (ANAs) refer to a broad class of antibodies targeting a wide range of cellular and nuclear components. These class of antibodies are generated as a result of loss of immune tolerance. anti-double stranded DNA antibody (anti-dsDNA) and anti-Sm antibody (anti-Sm) are the important hallmarks of SLE [1]. For patients presenting with SLE, treatment with hydroxychloroquine (HCQ) is recommended unless contraindicated. In cases where the disease affects major organs or present refractory symptoms, treatment with systemic glucocorticoid (GC), cyclophosphamide (CTX), methotrexate (MTX) or azathioprine (AZA) is recommended. As early diagnosis and advanced treatments have significantly improved the survival, malignancies are becoming an important cause of mortality in SLE patients [2–10]. However, the mechanism underlying such an increase in cancer risk is not completely understood.

Although they are important serological markers of autoimmune disease, ANAs are not unique to autoimmune disorders and multiple studies have reported the involvement of ANAs in a variety of neoplastic diseases [11, 12]. Interestingly, several lines of evidence suggests that ANAs have anti-neoplastic effects in cancer patients without concomitant autoimmune diseases [13, 14] and are associated with a better prognosis [15–17]. A previous report showed that the damage index, defined by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR), is correlated with overall cancer risk [18]. Contradictory findings were observed in another study in which no association was found between the adjusted mean SLE Disease Activity
Index scores (SLEDAI-2K) and the risk of lymphoma [19]. Similarly, the relationship between the use of immunosuppressant and cancer risk in SLE is inconsistent. A previous report showed that the application of CTX and AZA did not increase cancer risk in SLE patients [20]. Another study demonstrated that although immunosuppressant including CTX, AZA and MTX were not associated with overall cancer risk, they may increase the risk of hematological malignancies in patients with SLE [18]. It has been reported that CTX administration has been associated with increased cancer risk while administration of HCQ is thought to lower cancer risk [21].

To improve our understanding of the relationship between cancer risk and SLE pharmacologic interventions, we carried out a nested case-control study. To this end we analyzed clinical features including auto-antibodies and disease activity in 5858 SLE patients as well as the pharmacologic interventions used in the management of SLE. Our results showed that SLE patients with cancers had lower disease activity and that HCQ was negatively correlated with cancer risk in these patients.

Methods

Study design

All patients recruited into this retrospective cohort study met updated American College of Rheumatology criteria for the classification of SLE [22]. All patients included in the study were hospitalized at the First Affiliated Hospital of Zhengzhou University between October 1, 2010 and October 1, 2019. Any SLE patients younger than 18 years old or less than 18 years at SLE diagnosis age were excluded from the study. Cancer diagnosis was confirmed by histological analyses and any patients diagnosed with premalignant lesions were excluded. Patients diagnosed with rheumatoid arthritis, Sjögren syndrome, inflammatory myopathy, autoimmune hepatitis or primary biliary cholangitis were defined as having overlapping syndrome. Participants were assigned into a cancer group and control group.
This study was approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University, ethical approval number No.2019-KY-199 (Additional file 1).

**Clinical and laboratory examinations**

The following patient information was collected: age, gender, age at SLE diagnosis, course of SLE progression as well as chronic comorbidities including hypertension, diabetes mellitus and dyslipidemia. In addition, the positivity and titers of autoantibodies were assessed including antinuclear antibody (ANA) and other autoantibodies such as anti-dsDNA, anti-Sm, anti-Ro52 antibody (anti-Ro52), anti-Ro60 antibody (anti-Ro60), anti-SSB antibody (anti-SSB), anti-nucleosome antibody (anti-Nuc), anti-histone antibody (anti-His), anti-ribosome antibody (anti-Rib), and anti-nRNP antibody (anti-nRNP). The SLE Disease Activity Index (SLEDAI) scores were calculated at the day of cancer diagnosis as previously described [23]. The information on the use of GC, HCQ, CTX, MTX and AZA was also collected from the date of SLE diagnosis to the date of cancer diagnosis for participants in the cancer group or the date of admission for those in the control group.

**Propensity score matching**

Propensity score matching was performed to minimize selection bias when evaluating the effect of immunosuppressant on cancer risk. Based on the propensity scores, each participant with cancer was matched with four cancer free participants. The propensity score was calculated by taking into account the following variables: age, gender, age at SLE diagnosis, disease course of SLE and comorbidities such as hypertension, diabetes mellitus and dyslipidemia.

**Statistical analysis**
Patient clinical features and SLEDAI scores were compared between the cancer group and the control group using independent-sample t tests for continuous variables or the chi-square test for categorical variables. Conditional logistic regression analysis was used for the evaluation of the association between cancer risk and medical intervention with pharmacologic agents. Associations were firstly evaluated without consideration for confounding factors followed by an analysis taking into account such factors (Table 1). SPSS statistical software version 20.0 was used to conduct data analysis and propensity score matching [SPSS Inc., Chicago, IL].

Results

**Patient characteristics**

A total of 5858 patients diagnosed with SLE between October 1, 2010 and October 1, 2019 were recruited into this study. Eighteen patients that had been diagnosed with cancer prior to SLE diagnosis, 18 patients that had metastasis or received chemotherapy prior to hospital admission and 274 patients with overlap syndrome were excluded from subsequent analyses. Of the 5548 patients that were eligible for further analyses, 51 were cancer patients while the remaining 5497 were cancer free patients. Each cancer case was matched with four cancer free patients. Our study therefore consisted of 51 cancer patients and 204 matched cancer-free patients (Figure 1).

Patients’ characteristics of the cancer group and the control group are showed in table 1. Before matching, the cancer group patients were older, diagnosed with SLE at a more advanced age, had longer disease course of SLE and a higher prevalence of comorbidities. However, such difference was not clear after matching (Table 1).

**Table 1 Characteristics of patients in the cancer and control groups**
**Characteristics**

|                         | Before matching | Control group | \( P \)-value | After matching | Control group | \( P \)-value |
|-------------------------|-----------------|---------------|--------------|--------------|---------------|--------------|
| Cancer group (n=51)     |                 |               |              | Cancer group (n=51) |               |              |
| Age, median             | 47              | 35            | <0.0001      | 47           | 46            | 0.69         |
| Female gender, n (%)    | 49, 96.08       | 4930, 89.68   | 0.2055       | 49, 96.08    | 192,94.12    | 0.74         |
| Age at SLE diagnosis, median | 41              | 33            | 0.0024       | 41           | 39            | 0.96         |
| Disease course of SLE, median | 60              | 6             | <0.0001      | 60           | 60            | 0.92         |
| Hypertension            | 5, 9.80%        | 199, 3.620%   | 0.0195       | 5, 9.80%     | 15, 7.35%     | 0.56         |
| Diabetes mellitus       | 5, 9.80%        | 189, 3.438%   | 0.0375       | 5, 9.80%     | 14, 6.86%     | 0.55         |
| Dyslipidemia            | 8, 15.38%       | 494, 8.18%    | 0.0969       | 8, 15.38%    | 28, 13.72%    | 0.72         |

**Distribution of all cancers and specific cancer types**

The specific types of cancer are showed in Table 2. Four patients had hematological cancer (2 leukemia and 2 non-Hodgkin’s lymphoma). No patient had Hodgkin’s lymphoma in this cohort. A total of 47 SLE patients had non-hematological cancer, with thyroid cancer being the most frequently observed type of cancer (27.45%), followed by cervical cancer (19.61%) and lung cancer (13.73%).

**Table 2 Specific types of cancers in the cancer cohort**

| Sites and types           | N (%)       |
|---------------------------|-------------|
| Hematological cancer      |             |
| Leukemia                  | 2 (3.92%)   |
| Non-Hodgkin’s lymphoma    | 2 (3.92%)   |
| Non-hematological cancer  |             |
| Reproductive system       |             |
| Cervical cancer           | 10 (19.61%) |
| Vulvar cancer             | 2 (3.92%)   |
| Uterus cancer             | 1 (1.96%)   |
| Non-reproductive system   |             |
| Thyroid cancer            | 14 (27.45%) |
| Lung cancer               | 7 (13.73%)  |
| Gastric carcinoma         | 3 (5.89%)   |
| Rectal carcinoma          | 2 (3.92%)   |
| Hepatic carcinoma         | 1 (1.96%)   |
| Appendix cancer           | 1 (1.96%)   |
| Bile duct cancer          | 1 (1.96%)   |
| Pancreatic cancer         | 1 (1.96%)   |
| Renal cell cancer         | 2 (3.92%)   |
| Breast cancer             | 2 (3.92%)   |

**Level of auto-antibodies in the cancer and control groups**

The levels of auto-antibodies in both groups are summarized in Table 3. No significant differences were observed between the two groups in the positivity of ANA, anti-dsDNA,
anti-Sm, anti-RO52, anti-RO60, anti-SSB, anti-Nuc, anti-His, anti-Rib and anti-nRNP.

Table 3 Comparison of levels of auto-antibodies between the two groups

| Auto-antibodies | Cancer group (n=51) | Control group (n=204) | P-value |
|----------------|---------------------|----------------------|---------|
|                | (positive/total)   | (positive/total)     |         |
| (percentage)   |                     |                      |         |
| ANA            | 37/37, 100%         | 198/200, 99.00%      | 1.00    |
| anti-dsDNA     | 15/35, 42.86%       | 95/180, 52.78%       | 0.36    |
| anti-Sm        | 5/36, 13.89%        | 33/172, 19.19%       | 0.63    |
| anti-RO52      | 26/37, 70.27%       | 110/172, 63.95%      | 0.57    |
| anti-RO60      | 20/37, 54.05%       | 110/172, 63.95%      | 0.57    |
| anti-SSB       | 4/36, 11.11%        | 16/172, 9.30%        | 0.76    |
| anti-Nuc       | 11/36, 30.56%       | 70/172, 40.70%       | 0.35    |
| anti-His       | 7/36, 19.44%        | 50/172, 29.07%       | 0.31    |
| anti-Rib       | 10/36, 27.78%       | 58/172, 33.72%       | 0.56    |
| anti-nRNP      | 11/36, 30.56%       | 64/172, 37.21%       | 0.57    |

ANA: antinuclear antibody; anti-dsDNA: anti-double stranded DNA antibody; anti-Sm: anti-Sm antibody; anti-RO52: anti-RO52 antibody; anti-RO60: anti-RO60 antibody; anti-SSB: anti-SSB antibody; anti-Nuc: anti-nucleosome antibody; anti-His: anti-histone antibody; anti-Rib: anti-ribosome antibody; anti-nRNP: anti-nRNP antibody.

SLEDAI and disease activity indexes in cancer and control groups

The SLEDAI and disease activity indexes in cancer and control groups are showed in Table 4. The rate of patients with decreased C3 and proteinuria was higher in the control group than in the cancer group (82.22% vs 44.44%, p <0.01; 36.00% vs 12.24%, p <0.01; respectively). The SLEDAI was higher in the control group than that in the cancer group (8 vs 2, p <0.01). No significant differences in low C4, white blood cell and thrombocytopenia were observed between the two groups.

Table 4 Comparison of SLEDAI between the two groups

| Indicator | Cancer group [n=51] | Control group [n=204] | P-value |
|-----------|---------------------|----------------------|---------|
|           | (positive/total)   | (positive/total)     |         |
|           | (percentage)        | (percentage)         |         |
| Low C3    | 16/36, 44.44%       | 74/90, 82.22%        | <0.01   |
| Low C4    | 14/36, 38.89%       | 48/90, 53.33%        | 0.17    |
| Low WBC   | 6/48, 12.50%        | 26/102, 25.49%       | 0.09    |
| Low PLT   | 10/48, 20.83%       | 34/102, 33.33%       | 0.13    |
| Proteinuria | 6/49, 12.24%      | 36/100, 36.00%       | <0.01   |
| SLEDAI, median | 2                  | 8                    | <0.01   |

WBC: white blood cell; PLT: platelet; SLEDAI: SLE Disease Activity Index
**Medication exposure and cancer risk**

The results of correlation analysis between medication exposure and cancer risk are provided in Additional file 2 and Figure 2.

Univariate analysis revealed that HCQ was associated with a lower risk of cancer (OR = 0.417, CI: 0.220, 0.791), while GC (OR = 0.783, CI: 0.273, 2.248), CTX (OR = 1.378, CI: 0.517, 3.670), MTX (OR = 0.788, CI: 0.219, 2.831) and AZA (OR = 0.653, CI: 0.141, 3.014) was not significantly correlated with cancer risk. The results were not changed after adjustment for confounding variables.

**Discussion**

To the best of our knowledge, only a handful of studies have been done to explore the association between cancer and the drugs used in SLE, and the results were inconsistent [18–21]. In this large nested case-control study, we found that the SLE patients with cancer had lower disease activity, and that HCQ was negatively correlated with cancer risk in SLE patients.

Both SLE and cancer have been associated with immune dysfunction [24]. In SLE patients, the impaired immune system is not able to discriminate between self and non-self antigens, leading to aberrant production of autoantibodies causing host tissue damage. On the contrary, cancer formation is caused by compromised host’s immune system that cannot recognize cancer antigens. It has been previously reported that cancer immunogenicity induced the production of a wide range of auto-antibodies including ANA, anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, anti-Rib and anti-nRNP [25]. The level of ANA has been reported to be elevated in 31.5% lymphoma patients relative to the control group [12]. While it is well established that anti-dsDNA is highly specific for SLE, it has been found in patients with different malignancies and may serve as a prognostic indicator for
cancer. The association between anti-dsDNA and cancer was first demonstrated in bronchogenic carcinoma [26]. A study suggests that this antibody may play a role in the pathogenesis of lymphoma and thymoma [27]. It has been hypothesized that the presence of anti-dsDNA autoantibodies in patients with colorectal cancer might indicate better disease outcome [15]. Our current study evaluated the significance of disparities in the levels of ANA, anti-dsDNA, anti-Sm, anti-RO52, anti-RO60, anti-SSB, anti-Nuc, anti-His, anti-Rib and anti-nRNP antibodies between the cancer group and the cancer free control group at the time of cancer diagnosis. Our results demonstrate there were no significant difference in the levels of these factors between the cancer group and the control group at the time of cancer diagnosis.

The organ damage and disease activity in SLE patients with or without cancers were investigated, and the results were inconsistent, likely due to the differences in inclusion criteria, race, ethnicity, and scoring systems. For instance, a mean SLICC/ACR damage score of 1.9 and 1.7 has been reported for the cancer group and the control group respectively, suggesting that organ injury was more severe in the cancer group [18]. A different study did not find statistically significant differences in the adjusted mean SLEDAI-2K between a lymphoma group and a control group [19]. It should be noted that while SLICC/ACR mainly evaluates organ damage [28], the adjusted mean SLEDAI-2K reflects the mean disease activity after onset [29]. Our results indicate that SLE with different malignancies had lower SLEDAI scores, lower rates of renal involvement and low level of complement compared with the control group. The SLEDAI mainly reflects the disease activity within ten days [23]. Taken together, these data indicate that SLE patients with cancers have lower disease activity at the time of cancer diagnosis.

The role of immunosuppressant in cancer development in SLE patients remains controversial. One study showed that immunosuppressant therapy was not associated with
overall cancer risk in patients with SLE but might contribute to an increased risk of hematological malignancy [18]. A different research reported that exposure to CTX might contribute to a higher lymphoma risk in SLE patients [19], although this was contradicted by a different report showing that the use of CTX and AZA did not contribute to lymphoma risk [20]. It has been demonstrated that CTX increases cancer risk in SLE patients in a dose-dependent manner [21]. Therefore, more investigations looking at a larger number of participants is needed.

HCQ is extensively used in SLE treatment. Besides its well-established effects on the skin and joint symptoms, several studies have indicate that HCQ has important long-term effects on lupus, including reduced long-term accrual damage and decreased long-term mortality [30, 31]. A protective function of antimalarial against cancer in SLE patients has been proposed [32]. Hsu et al. found that HCQ decreased cancer risk in a dose-dependent manner [21]. Our current large-scale study has also elucidated a negative correlation between HCQ and cancer.

It has been proposed that HCQ might modulate autophagy by impacting lysosomal acidification and blocking the fusion of auto phagosomes with lysosomes [33]. Chloroquine may trigger the expression of Tp53 which may protect the cells from genotoxic stimuli [34]. In addition, the antimalarial may inhibit unlimited replication of cancer cells via their strong DNA intercalating properties [35]. Chloroquine may promote DNA repair following DNA damage as a result of alkylating therapy [36]. Multiple preclinical and clinical trials have demonstrated a synergistic anticancer effect of HCQ with chemotherapies and targeted therapies [37]. For instance, cytotoxicity of tamoxifen against breast cancer cells has been shown to be enhanced by combination therapy with HCQ [38]. In addition, HCQ is effective against hepatocellular carcinoma and pancreatic ductal adenocarcinoma [39, 40], as well as hematologic cancer like chronic myeloid leukemia, myeloma and lymphoma
Taken together, these reports suggest that HCQ may decrease the cancer risk in SLE patients.

In the SLE cohort included in this study, thyroid cancer, cervical cancer and lung cancer were the top three cancer types. Studies suggest an increased risk of cervical cancer among SLE patients compared with the general population [44, 45]. It has been reported that immunosuppressant increases the risk of cervical neoplasia in SLE patients and this is attributable to decreased HPV clearance [44, 46]. This suggests that SLE patients under immunosuppressive agents should undergo regular screening for cervical dysplasia. This retrospective study of a large cohort of SLE patients analyzed the distribution of cancers in SLE patients. Our results suggest that SLE patients with cancers have lower disease activity at the time of cancer diagnosis. In addition, a negative correlation between HCQ administration and cancer risk in SLE patients was unveiled, highlighting a novel potential cancer prevention strategy for SLE patients.

**Conclusions**

Our analyses indicate that SLE patients with cancers might have a lower disease activity at the time of cancer diagnosis. HCQ was negatively correlated with cancer risk in SLE patients. These findings highlight a potential and novel prevention strategy for SLE.

**Abbreviations**

Systemic lupus erythematosus: SLE; hydroxychloroquine: HCQ; antinuclear antibodies: ANAs; anti-double stranded DNA antibody: anti-dsDNA; anti-Sm antibody: anti-Sm; systemic glucocorticoid: GC; cyclophosphamide: CTX; methotrexate: MTX; azathioprine: AZA; Systemic Lupus International Collaborating Clinics/American College of Rheumatology: SLICC/ACR; SLE Disease Activity Index scores: SLEDAI-2K; antinuclear antibody: ANA; anti-Ro52 antibody: anti-Ro52; anti-Ro60 antibody: anti-Ro60; anti-SSB
antibody: anti-SSB; anti-nucleosome antibody: anti-Nuc; anti-histone antibody: anti-His; anti-ribosome antibody: anti-Rib; anti-nRNP antibody: anti-nRNP; SLE Disease Activity Index: SLEDAI; white blood cell: WBC; platelet: PLT; odds ratio: OR.

Declarations

**Ethics approval and consent to participate**

This study was approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University, ethical approval number No.2019-KY-199.

**Consent for publication**

All the results presented in this article are in aggregate form, and no personally identifiable information was used for this study.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

JG, ZR, SL and ZY designed the study. JG and JL collected clinical data; JG, ZR and JL analyzed the data; JG, ZR and TL wrote the manuscript. All authors reviewed and approved the manuscript.
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Figures

![Flow chart of the study design](image-url)
The effect of medication exposure on cancer risk in patients with SLE. (a):
Univariate analysis between medication exposure and cancer risk. (b):
Multivariate analysis between medication exposure and cancer risk. Notes: GC:
glucocorticoid; HCQ: hydroxychloroquine; CTX: cyclophosphamide; MTX:
methotrexate; AZA: azathioprine. aadjusted for age, gender, age at SLE
diagnosis, disease course of SLE, hypertension, diabetes mellitus and
dyslipidemia. OR: odds ratio.

Supplementary Files
This is a list of supplementary files associated with the primary manuscript. Click to download.

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