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Risk of malignancy in patients with systemic lupus erythematosus: Systematic review and meta-analysis

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ABSTRACT

Background: Malignancy is a potential comorbidity in patients with systemic lupus erythematosus (SLE). However, risk by malignancy type remains to be fully elucidated. We evaluated the risk of malignancy type in SLE patients in a systematic review and meta-analysis.

Methods: MEDLINE and EMBASE were searched from inception to July 2018 to identify observational studies that evaluated malignancy risk in adult SLE patients compared with the general population. Random-effects models were used to calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs). Heterogeneity was quantified using the I^2 test.

Findings: Forty-one studies reporting on 40 malignancies (one overall, 39 site-specific) were included in the meta-analysis. The pooled RR for all malignancies from 3694 events across 80 833 patients was 1.18 (95% CI: 1.00–1.38). The risk of 24 site-specific malignancies (62%) was increased in SLE patients. For malignancies with ≥6 studies, non-Hodgkin lymphoma and Hodgkin lymphoma risk was increased >3-fold; myeloma and liver >2-fold; cervical, lung, bladder, and thyroid ≥1.5-fold; stomach and brain >1.3-fold. The risk of four malignancies (breast, uterine, melanoma, prostate) was decreased, whereas risk of 11 other malignancies did not differ between SLE patients and the general population. Heterogeneity ranged between 0% and 96%, and 63% were non-significant.

Interpretation: The risk of overall and some site-specific malignancies is increased in SLE compared with the general population. However, the risk for some site-specific malignancies is decreased or did not differ. Further examination of risk profiles and SLE patient phenotypes may support guidelines aimed at reducing malignancy risk.

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex and chronic autoimmune disorder, affecting multiple organ systems with variable severity. SLE is characterised by intermittent, unpredictable flares and is associated with irreversible organ damage, resulting in a high rate of disability [1]. SLE is associated with multiple comorbidities, including specific cancer types [2-10], which adds to the challenge in managing SLE [11].

Previous meta-analyses, evaluating various malignancies, identified an increased risk of some malignancy types in SLE [9,10]. However, these meta-analyses did not account for overlapping study

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populations, and because many individual studies were also part of the international cohort study of cancer in SLE [12], some patient populations may have been included more than once, limiting the interpretation of the findings. Previous meta-analyses have reported few sensitivity analyses. To the best of our knowledge, there are currently no meta-analyses that include all cancer types for which there are available data and exclude potential overlapping SLE populations to elucidate the appropriate risk.

The objective of this study was to evaluate the risk of all malignancies in patients with SLE compared with the general population. This study supports and extends the growing evidence on risk of various cancers in patients with SLE.

2. Methods

2.1. Search strategy

This study was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting systematic reviews [13,14]. The study protocol was prepared and published via the international prospective register of systematic reviews, PROSPERO (#CRD42018110433). Searches for full-text reports containing original data were run in Ovid MEDLINE and EMBASE from inception until July 2018 (Supplementary Table S1). We also searched article reference lists and contacted experts.

2.2. Eligibility criteria

Full publications of observational studies (cohort, cross-sectional studies) published in English, reporting the risk of malignancy in adult patients with SLE compared with a general population and/or healthy controls, were included. SLE diagnosis was confirmed using International Classification of Diseases (ICD) codes, American College of Rheumatology (ACR) criteria, or clinician review/diagnosis [15,16]. The outcomes evaluated included fatal or non-fatal malignancies. Studies were included if they reported one of the following relative risk measures: hazard ratio, rate ratio, risk ratio, odds ratio, incidence rate ratio, proportionate morbidity ratio, standardised mortality rate, or standardised incidence rate with 95% confidence intervals (CIs). Abstracts of unpublished studies were excluded.

2.3. Screening and abstraction process

Two-stage screening (title/abstract and full-text), data extraction, and risk of bias assessment were performed independently by two reviewers (NP and LN); disagreement was resolved by consensus involving a third reviewer (JL). Studies that met the eligibility criteria and reported original data were included in the review. Data on study characteristics and the effect measure for outcomes of interest (fatal and non-fatal events) were extracted.

2.4. Risk of bias assessment

Studies were classified as having low, moderate, or high risk of bias based on results from the Newcastle-Ottawa Scale [17] and an SLE-specific 12-point scale [18] (Supplementary Tables S2 and S3). Studies were classified as having low risk of bias if they scored $\geq$3/4 for selection, $\geq$1/2 for comparability, 3/3 for outcome domains of the Newcastle-Ottawa Scale, and $\geq$8 on the 12-point scale.

2.5. Statistical analysis

We grouped malignancy outcomes and conducted a meta-analysis in which $\geq$2 studies reported usable data that could be synthesised quantitatively. For malignancy outcomes with $\geq$2 studies reporting findings from overlapping populations, one study was selected for inclusion based on quality, population size, and length.

Hazard ratios, rate ratios, risk ratios, odds ratios, incidence rate ratio, proportionate morbidity ratios, standardised mortality rates, or standardised incidence rates were considered as equal estimates assuming rare occurrence [19] and are referred to as risk ratio (RR) throughout this report. The most adjusted RR was used in the meta-analysis. A DerSimonian and Laird [20] random-effects model was fitted to calculate the pooled RR and 95% CIs for all outcomes.

Heterogeneity was measured using the Cochran's Q statistic (statistical significance set at $p<0.10$) and using the I^2 test. Publication bias was assessed using funnel plots and the Egger's test [21].

Robustness of pooled estimates was assessed using the leave1out function [22], which examined the effect of removing individual studies. Sensitivity analyses were performed when >2 studies and relevant data were available, including for least-adjusted analysis, studies published during or after 2014, studies published before 2014, studies reporting non-fatal/fatal events, studies reporting non-fatal events, studies with low risk of bias, and studies stratified by geographical location (Europe, North America, or Asia). All analyses were conducted in R version 3.5.1 using the packages metafor and forestplot.

2.6. Data sharing

Data are available upon reasonable request (data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

3. Results

The literature search of MEDLINE and EMBASE identified 3042 records, with 2544 articles remaining after removal of duplicates. Of these, 2437 were excluded after screening titles and abstracts. Of 107 articles retained, 56 publications were excluded after full-text review. Thus, 51 publications were identified as eligible for inclusion in this analysis (Figure 1) (Supplementary Table S4 lists excluded studies with reasons.)

Of 51 publications, 50 were cohort studies and one was a cross-sectional study (Table 1) [23]. Studies were conducted in Europe (n=25), Asia (n=11), North America (n=7), the Middle East (n=1), or multiple countries (n=7). The average follow-up per study, where reported, ranged from 2.1 to 25.7 years with the proportion of female participants ranging from 74% to 100%. Average age, where reported, ranged from 29 to 51 years. Risk of bias was low in 39 studies, moderate in eight studies, and high in four studies (Table 1; Supplementary Table S5).

The 51 studies included in the meta-analysis report relative risks for 82 different malignancy outcomes. Meta-analyses were performed for 40 malignancy outcomes, but not for 42 outcomes, as 39 outcomes were reported in only one study and heterogeneous findings for three outcomes could not be pooled (Supplementary Table S6).

There were 37 studies with overlapping populations. Sixteen studies reported data included in the International lupus cohort [12,24-38], and there were data overlaps from two studies in Denmark [39,40], two from Finland [41,42], 12 from Sweden [43-54], and five from Taiwan [55-59].

When considering meta-analyses for the 40 malignancies, five of 51 studies [28,29,33,60,61] were excluded from analyses because they could not be pooled or had overlapping populations. Overlapping populations were considered on a malignancy outcome level. Thirty-eight of the 51 studies (75%) reported more than one malignancy outcome; therefore, a study was excluded from the meta-

Figure 1. Flow diagram of the systematic literature review process to evaluate the risk of malignancy in patients with SLE compared with the general populationSLE=systemic lupus erythematosus.

analysis for those malignancy outcomes in which populations overlapped but was included for malignancy outcomes in which overlapping populations were not present (Supplementary Table S7). A further five studies, excluded from the main analysis based on an overlapping population, were only used in sensitivity analyses if they presented relevant data not provided by the study it overlapped with in the main analysis [31,34,35,37,41]. The remaining 41 studies were included in meta-analyses for 40 malignancy outcomes, and 46 studies were included in various sensitivity analyses (Table 1). Supplementary Tables S8 and S9 list all 40 malignancy outcomes by study, and Supplementary Table S7 lists studies included in the main analysis by malignancy outcome with reasons for exclusion.

This meta-analysis and associated sensitivity analyses report findings from a minimum of 145 135 unique SLE patients on 40 malignancies. In the 46 studies included in the main and/or sensitivity analyses, malignancies were identified using ICD codes (n=23), unspecified clinical codes/a combination of clinical records and histopathology (n=18), or methods that were not reported (n=5).

Thirteen studies were eligible for inclusion in the meta-analysis for the composite outcome 'all malignancies' [28,39,42,43,59,62-69]. The category 'all malignancies' varied widely across studies (Supplementary Tables S8 and S9). SLE was associated with a marginally increased risk of all malignancies (RR 1.18; 95% CI 1.00–1.38) (Figure 2). There was high heterogeneity across studies (I^2=94%; p<0.001). Of nine sensitivity analyses, six supported an increased malignancy risk (Table 2). Restriction to ten studies with low risk of bias suggested a higher risk of all malignancies (RR 1.33; 95% CI 1.20–1.47).

Of reproductive-related cancers, cervical cancer was the most frequently evaluated. Fourteen studies [23,27,39,42,47,54,59,62,64-66,68-70] demonstrated a significantly increased risk of cervical cancer in SLE patients compared with the general population (RR 1.66; 95% CI 1.16–2.36) (Figure 2). There was substantial statistical heterogeneity (I^2=77%; p<0.001). The RR in the included studies ranged from 0.55 (95% CI 0.39–0.75) [69] to 6.90 (95% CI 2.75–14.44) (Supplementary Figure S1) [62]. Of seven sensitivity analyses performed, only two did not support increased risk (Table 2).

Meta-analysis identified an increased risk of vagina/vulva or vulva-only cancer (RR 3.63; 95% CI 2.54–5.20; I^2=64%; p=0.03) based on five studies [27,42,56,68,69] and an increased risk of other female genital cancer (RR 3.41; 95% CI 1.86–6.23; I^2=0%; p=0.39) based on two studies [39,47] (Figure 2). Of five sensitivity analyses for vagina and/or vulva cancer, all but one supported the observed increased risk (Table 2).

Of haematologic cancers, non-Hodgkin lymphoma (NHL) was the second most frequently studied, with 11 eligible studies [23,27,39,42,45,59,64-66,68,69]. SLE was significantly associated with an increased risk compared with the general population (RR 4.32; 95% CI 3.42–5.47; I^2=81%; p<0.001) (Figure 2). The RR ranged from 2.44 (95% CI 2.22–3.34) to 15.37 (95% CI 2.90–37.68). All seven sensitivity analyses supported an increased risk of NHL.

Several other haematologic cancers (Hodgkin lymphoma [23,27,39,46,68,69], myeloma [23,27,39,42,48,69], all haematologic cancers [27,42,43,56,63,64], all leukaemia [27,39,43,59,69], lymphoma [30,58], and myeloid malignancies [58,69]) also showed a significantly increased risk in patients with SLE compared with the general population; RR ranged from 1.94 (95% CI 1.56–2.41; I^2=0%;

Table 1
Characteristics of the studies included in the systematic review to assess the risk of malignancy in people with SLE compared with the general population

Author and year	Country	Time period	Source of SLE data	Source of control data	Number of patients (SLE; control)	Fatal/non-fatal	% female SLE population	Mean/median age, years (SLE; control)	Risk of bias	RR measure	Included in the meta-analysis
Studies included in the international cohort											
Abu-Shakra 1996 [32]	Canada	24 years (date range NR)	The University of Toronto Lupus Clinic Database	National Cancer Incidence Reporting System (1985–1986)	724; NR	Fatal or non-fatal	86.6	33.3/NR	Low	SIR	Yes
Bernatsky 2004 [33]	Canada, USA, and UK	1984–1998, Montreal; 1985–1995, Chicago; 1990–2000, Birmingham	SLE clinic cohorts at 3 centres	Geographically appropriate matched mortality rates	871; NR	Fatal or non-fatal	100.0	41.0/NR	Low	SIR	No
Bernatsky 2005 [12] (international)	Canada, USA, UK, Iceland, Sweden, Korea	1958–2000	23 lupus centres	Geographically appropriate matched mortality rates	9547; NR	Fatal or non-fatal	90.0	NR	Low	SIR	Yes
Bernatsky 2005 [30] (race)	Canada, USA, UK, Iceland, Sweden, Korea	1958–2000	23 lupus centres	US SEER Program	7312; NR	Fatal or non-fatal	91.0	44.3/NR	Low	SIR	Yes
Bernatsky 2006 [31]	Canada, USA, UK, Iceland, Sweden, South Korea	1958–2001, majority of observations 1970–2001	23 lupus centres	Geographically appropriate matched mortality rates	9547; NR	Fatal	90.0	NR	Low	SMR	SA
Bernatsky 2007 [28]	Canada, USA, Europe, Korea	1958–2000, majority from 1970s onward	23 clinical centres	Geographically appropriate matched mortality rates	9547; NR	Fatal or non-fatal	NR	NR	Low	SIR	No
Bernatsky 2013 [27]	Canada, USA, Europe, Korea	1958–2009, majority from 1970s onward	30 international clinical centres	Geographically appropriate matched mortality rates	16 409; NR	Fatal or non-fatal	90.0	NR	Low	SIR	Yes
Chun 2005 [34]	South Korea	1992–2001	Hanyang Lupus Cohort, Seoul	Seoul Cancer Registry	434; NR	Fatal	93.1	36.1/NR	High	SIR	SA
Cibere 2001 [24]	Canada	1975–1994	University-based rheumatic disease unit	Provincial cancer statistics	297; NR	Fatal or non-fatal	84.0	NR	Moderate	SIR	Yes
Dreyer 2011 [25]	Denmark	1943–2006	8 Danish hospital departments	Danish Cancer Registry	576; NR	Fatal or non-fatal	88.0	NR	Low	SIR	Yes
Lu 2013 [29]	Canada, USA, Korea, Denmark, Sweden	NR	30 international clinical centres	Regional general population cancer rates	NR; NR	Fatal or non-fatal	90.0	NR	Low	SIR	No
Nived 2001 [35]	Sweden	1981–1996	SLE cohort registry with National Cancer Registry of southern Sweden and National Population Registry	National Cancer Registry of southern Sweden, the National Population Registry	NR; NR	Fatal or non-fatal	85.0	NR	Low	Standardised morbidity rate	SA
Ragnarsson 2003 [26]	Iceland	1957–2001	Icelandic SLE database, Icelandic cancer registry	Icelandic cancer registry	238; NR	Fatal or non-fatal	89.5	NR	Low	SIR	Yes
Ramsey-Goldman 1998 [37]	USA	1985–1995	Chicago Lupus Cohort	Illinois State Cancer Registry	616; NR	Fatal or non-fatal	100.0	35.3/NR	Moderate	SIR	SA
Sultan 2000 [36]	UK	1978–1999	University College London Lupus Clinic Database	Thames Cancer Registry	276; NR	Fatal or non-fatal	93.5	NR	Low	SIR	Yes
Sweeney 1995 [38]	USA	1981–1991	University of Pittsburgh	Pennsylvania Cancer Incidence Registry	219; NR	Fatal or non-fatal	100.0	NR	High	SIR	Yes

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Table 1 (*Continued*)

Author and year	Country	Time period	Source of SLE data	Source of control data	Number of patients (SLE; control)	Fatal/non-fatal	% female SLE population	Mean/median age, years (SLE; control)	Risk of bias	RR measure	Included in the meta-analysis
Denmark population overlap											
Mellemkjer 1997 [39]	Denmark	1977–1989	Hospital Discharge Register, Central Population Register, Cancer Registry in Denmark	Cancer Registry in Denmark	1585; NR	Fatal or non-fatal	83.0	NR	Low	RR	Yes
Sunesen 2010 [40]	Denmark	1978–2005	Danish National Patient Registry, Danish Cancer Registry	Danish Cancer Registry	3612; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Finland population overlap											
Pettersson 1992 [41]	Finland	1967–1987	Helsinki University Central Hospital, Finnish Cancer Registry, Central Statistical Office of Finland	Finnish Cancer Registry	205; NR	Fatal or non-fatal	89.0	NR	Low	RR	SA
Tallbacka 2018 [42]	Finland	1967–1987	Helsinki University Central Hospital, Statistics Finland	Finnish Cancer Registry	205; NR	Fatal or non-fatal	89.0	NR	Low	SIR	Yes
Sweden population overlap											
Björnådal 2002 [43]	Sweden	1964–1994	Hospital Discharge Register, National Swedish Cancer Register	National Swedish Cancer Register	5715; NR	Fatal or non-fatal	74.0	NR	Low	SIR	Yes
Castro 2014 [44]	Sweden	1964–2008	Swedish Hospital Discharge Register, Swedish Cancer Registry	Swedish population not hospitalised for autoimmune disease	NR; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Fallah 2014 [46] (HL)	Sweden	1964–2010	Hospital Discharge Registry, Outpatient Registry, Primary Health Care Registry, Swedish Cancer Registry	Swedish Cancer Registry	12 207; NR	Fatal or non-fatal	81.7	NR	Low	SIR	Yes
Fallah 2014 [45] (NHL)	Sweden	1964–2010	Outpatient Registry, Primary Health Care Registry (Stockholm, Region Skåne), Swedish Cancer Registry	Swedish Cancer Registry	12 207; NR	Fatal or non-fatal	81.7	NR	Low	SIR	Yes
Hemminki 2012 [50] (digestive)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	NR; NR	Fatal or non-fatal	NR	NR	Low	HR/SMR	Yes
Hemminki 2012 [51] (digestive histology)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	5318; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Hemminki 2012 [47] (female)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	5353; NR	Fatal or non-fatal	100.0	NR	Low	SIR	Yes
Hemminki 2012 [49] (lung)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	7624; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Hemminki 2012 [48] (MM)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	7624; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Hemminki 2013 [52] (brain)	Sweden	1964–2008	Swedish Hospital Discharge Register	Swedish Cancer Registry	7624; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes
Liu 2013 [53]	Sweden	1964–2008	Swedish Hospital Discharge Registry	MigMed2 Database, Swedish Hospital Discharge Registry, National Swedish Cancer Registry	7624; NR	Fatal or non-fatal	NR	NR	Low	SIR	Yes

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Table 1 (*Continued*)

Author and year	Country	Time period	Source of SLE data	Source of control data	Number of patients (SLE; control)	Fatal/non-fatal	% female SLE population	Mean/median age, years (SLE; control)	Risk of bias	RR measure	Included in the meta-analysis
Wadström 2017 [54]	Sweden	2006–2012	National Patient Register, Prescribed Drug Register, Swedish Cancer Register, Cause of Death Register, Total Population Register, Multigeneration Register	Same source as SLE data	4976; 29 703	Fatal or non-fatal	100.0	51.0/51.0	Moderate	SIR	Yes
Taiwan population overlap											
Chang 2013 [55]	Taiwan	2001–2008	National Health Insurance Research Database, Catastrophic Illness Patient Database	National Health Insurance Research Database	8751; 87 510	Fatal or non-fatal	88.3	35.1/35.1	Low	IRR	Yes
Chen 2010 [56]	Taiwan	Enrolment: 1996–2005; observation: 1996–2007	Taiwan National Health Insurance Research Database	Taiwan National Cancer Registry	11 763; NR	Fatal or non-fatal	88.4	NR	Low	SIR	Yes
Liang 2012 [57]	Taiwan	1999–2002	National Health Insurance system of Taiwan, National Health Research Institute	Same source as SLE data	2150; 17 207	Fatal or non-fatal	77.4	NR	Low	HR	Yes
Lin 2012 [58]	Taiwan	1997–2008	National Health Insurance database, Registry of Catastrophic Illness database	Same source as SLE data	9349; 46 745	Fatal or non-fatal	100.0	37.3/37.1	Low	SIR	Yes
Yu 2016 [59]	Taiwan	1997–2012	National Health Insurance Research Database in Taiwan	Same source as SLE data	15 623; NR	Fatal or non-fatal	87.6	NR	Low	SIR	Yes
Studies without population overlap											
Azrielant 2017 [23]	Israel	NR	Clalit Health Services database	Same source as SLE data	5018; 25 090	Fatal or non-fatal	82.0	50.2/50.2	Moderate	OR	Yes
Chang 2014 [65]	South Korea	2000–2012	Seoul National University Hospital	Korean National Cancer Registry (2008)	1052; NR	Fatal or non-fatal	88.9	35.0/NR	Low	SIR	Yes
Hidalgo-Conde 2013 [67]	Spain	1989–2006	Hospital Universitario Virgen de la Victoria, Malaga	Same source as SLE data	175; NA	Fatal or non-fatal	90.0	39.0/NR	Low	SIR	Yes
Kang 2010 [66]	South Korea	1997–2007	Kangnam St. Mary's Hospital	Korea National Cancer Registry	914; NR	Fatal or non-fatal	100.0	29.1/NR	Low	SIR	Yes
Khaliq 2015 [72]	USA	2007–2011	Medicare data	Same source as SLE data	18 432; 3 651 715	Fatal or non-fatal	100.0	NR	Low	Incidence ratio	Yes
Kim 2015 [70]	USA	2001–2012	Wellpoint and the United Healthcare	Same source as SLE data	14 513; 533 332	Fatal or non-fatal	100.0	47.7/50.3	Low	HR	Yes
Lerang 2014 [60]	Norway	1999–2009	Hospital discharge diagnosis registers, local cohort (1995), NOSVAR, private rheumatologists, Norway's Cause of Death Registry	Norway's Cause of Death Registry	325; NR	Fatal	90.0	NR	Moderate	OR	No
Parikh-Patel 2008 [69]	USA	1991–2002	Patient Discharge Dataset, California Cancer Registry	California Cancer Registry	30 478; NR	Fatal or non-fatal	89.0	NR	Moderate	SIR	Yes
Rees 2016 [68]	UK	1999–2012	Clinical Practice Research Datalink	Clinical Practice Research Datalink	6636 eligible; 25 111	Fatal or non-fatal	85.8	48.1/48.1	Low	IRR	Yes
Tarr 2007 [64]	Hungary	1970–2004	University of Debrecen, Debrecen	Health for All database	860; NR	Fatal or non-fatal	90.0	NR	Moderate	SIR	Yes

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Table 1 (*Continued*)

Author and year	Country	Time period	Source of SLE data	Source of control data	Number of patients (SLE; control)	Fatal/non-fatal	% female SLE population	Mean/median age, years (SLE; control)	Risk of bias	RR measure	Included in the meta-analysis
Thomas 2014 [63]	France	2000–2009	French Epidemiological Center for the Medical Causes of Death	French National Institute for Statistics and Economic Studies	956; NR	Fatal	79.0	NR	Moderate	SIR	Yes
Wang 2018 [62]	China	2005–2015	Division of Rheumatology, Guang An Men Hospital, China Academy of Chinese Medical Science	Chinese National Cancer Registry (2009)	225; NR	Fatal or non-fatal	NR	NR	High	SIR	Yes
Yap 2012 [61]	Hong Kong	1968–2008	Queen Mary Hospital	Local department of health	NR; NR	Fatal or non-fatal	88.7	45.9/NR	High	SIR	No
Yun 2017 [71]	South Korea	2009–2013	Korean National Health Insurance Claims Database of the Health Insurance Review Agency	Same source as SLE data	17 495; 52 485	Fatal or non-fatal	90.5	40.0/40.0	Low	SIR	Yes

HL=Hodgkin lymphoma. HR=hazard ratio. IRR=incidence rate ratio. NHL=non-Hodgkin lymphoma. NOSVAR=Norwegian Systemic Connective Tissue Disease and Vasculitis Registry. NR=not reported. OR=odds ratio. RR=risk ratio. SA=sensitivity analysis. SEER=Surveillance, Epidemiology, and End Results. SIR=standardised incidence ratio. SLE=systemic lupus erythematosus. SMR=standardised mortality ratio.

p=0.83) for all leukaemia to 3.52 (95% CI 2.01–6.17; I^2=79%; p<0.001) for Hodgkin lymphoma. Twenty of 23 sensitivity analyses supported an increased risk of haematologic cancer (Table 2).

SLE was associated with a significant increased risk of liver cancer (RR 2.81; 95% CI 1.72–4.59; I^2=64%; p=0.02) (Figure 2) in six studies [27,39,42,44,57,69]. The RR ranged between 1.28 (95% CI 0.66–2.47) and 8.00 (95% CI 2.60–18.60). All four sensitivity analyses supported an increased risk of liver cancer (Table 2).

Meta-analysis of all hepatobiliary cancers and liver/gallbladder cancer, reported in four [12,44,59,64] and three [24,56,68] studies, respectively, demonstrated an increased risk in patients with SLE compared with the general population (RR 2.07; 95% CI 1.37–3.12; I^2=56%; p=0.08 and RR 1.83; 95% CI 1.76–1.90; I^2=0%; p=0.76, respectively) (Figure 2). All sensitivity analyses supported an increased risk of hepatobiliary and liver/gallbladder cancers (Table 2).

Risk of lung cancer and all respiratory cancers (composite outcome) was increased in SLE patients compared with the general population (RR 1.75; 95% CI 1.37–2.24; I^2=74%; p<0.001 from nine studies [27,39,49,59,62,64,66,68,69] and RR 1.53; 95% CI 1.11–2.11; I^2=78%; p=0.01 from three studies [39,43,56], respectively) (Figure 2). The RR for lung cancer ranged between 0.48 (95% CI 0.11–1.23) and 3.27 (95% CI 2.06–5.18). Of eight sensitivity analyses performed, all but one supported the increased risk of respiratory cancer (Table 2).

Risk of cancers of the larynx and oropharynx was increased in patients with SLE (RR 4.21; 95% CI 1.97–9.03; I^2=1%; p=0.36 from three studies [26,39,43] and RR 7.35; 95% CI 1.12–48.35; I^2=0%; p=0.80 from two studies [24,55]) (Figure 2).

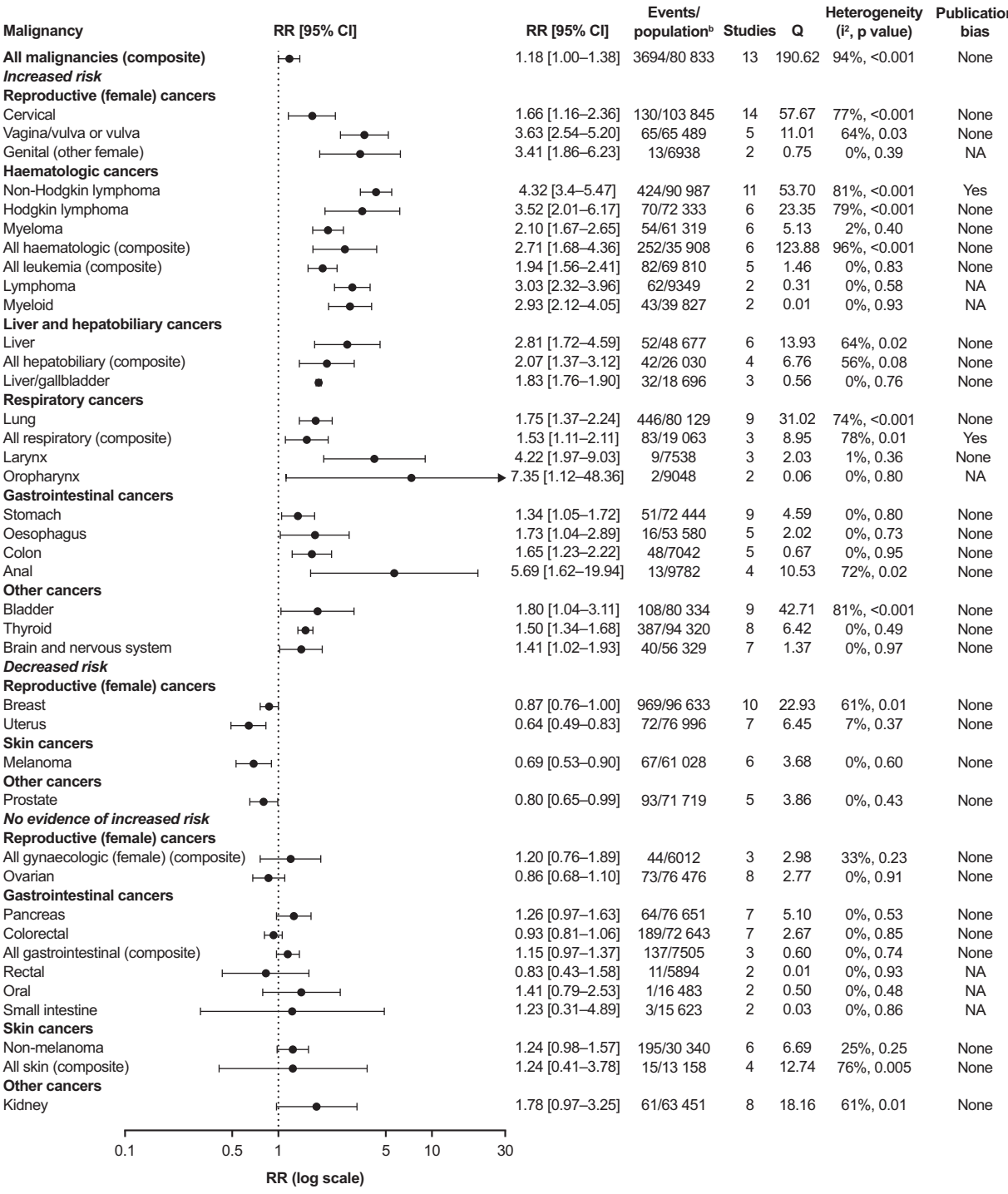
We observed an increased risk of stomach cancer (RR 1.34; 95% CI 1.05–1.72; I^2=0%; p=0.80) in patients with SLE in nine studies [27,39,42,51,59,64-66,69] (Figure 2). The RR ranged between 0.60 (95% CI 0.12–1.74) and 1.88 (95% CI 1.21–2.91). Two of five sensitivity analyses supported an increased risk of stomach cancer (Table 2).

The risk of oesophagus [25,39,51,59,69], colon [25,32,38,42,51], and anal [25,36,40,51] cancers was increased in patients with SLE (oesophagus RR 1.73; 95% CI 1.03–2.89; I^2=0%; p=0.73; colon RR 1.65; 95% CI 1.23–2.22; I^2=0%; p=0.95; and anal RR 5.69; 95% CI 1.62–19.94; I^2=72%; p=0.02) (Figure 2). One of three sensitivity analyses for oesophagus cancer and three of four sensitivity analyses for colon cancer supported an increased cancer risk (Table 2).

The risk of several other cancers was increased in patients with SLE, including bladder cancer [27,39,42,53,59,64,66,68,69] (RR 1.80; 95% CI 1.04–3.11; I^2=81%; p<0.001), thyroid cancer [27,43,59,65,66,68,69,71] (RR 1.50; 95% CI 1.34–1.68; I^2=0%; p=0.49), and brain and nervous system cancer [25,26,39,42,52,59,69] (RR 1.41; 95% CI 1.02–1.93; I^2=0%; p=0.97) (Figure 2). Two of six and five of six sensitivity analyses supported the increased risk of bladder and thyroid cancer, respectively (Table 2).

The risk of breast, uterine, melanoma, and prostate cancers was decreased in SLE patients compared with the general population (Figure 2). Breast cancer risk, reported in ten studies, was decreased by 13% (RR 0.87; 95% CI 0.76–1.00; I^2=61%; p=0.01) [27,39,42,47,59,64,65,68,69,72]. The risk of cancer of the uterus, reported in seven studies, was reduced by 36% (RR 0.64; 95% CI 0.49–0.83; I^2=7%; p=0.37) [27,39,47,59,66,68,69]. Melanoma risk, reported in six studies, was 31% lower (RR 0.69; 95% CI 0.53–0.90; I^2=0%; p=0.60) [27,39,42,43,68,69]. Prostate cancer risk, reported in five studies, was decreased by 20% (RR 0.80; 95% CI 0.65–0.99; I^2=0%; p=0.43) [27,39,53,59,69]. One of seven (breast), two of six (uterus), one of four (melanoma), and two of four (prostate) sensitivity analyses supported the decreased cancer risk (Table 2).

For 11 cancers, meta-analyses demonstrated no evidence of increased risk in SLE patients (Figure 2). This includes two female malignancies: the composite endpoints 'all gynaecologic (female) cancers' (RR 1.20; 95% CI 0.76–1.89) [24,43,57] and ovarian cancer (RR 0.86; 95% CI 0.68–1.10) [27,42,47,59,64,66,68,69]; six gastrointestinal malignancies: pancreas (RR 1.26; 95% CI 0.97–1.63)



Malignancy	RR [95% CI]	Events/ population[b]	Studies	Q	Heterogeneity (i^2, p value)	Publication bias
All malignancies (composite)	1.18 [1.00–1.38]	3694/80 833	13	190.62	94%, <0.001	None
Increased risk						
Reproductive (female) cancers						
Cervical	1.66 [1.16–2.36]	130/103 845	14	57.67	77%, <0.001	None
Vagina/vulva or vulva	3.63 [2.54–5.20]	65/65 489	5	11.01	64%, 0.03	None
Genital (other female)	3.41 [1.86–6.23]	13/6938	2	0.75	0%, 0.39	NA
Haematologic cancers						
Non-Hodgkin lymphoma	4.32 [3.4–5.47]	424/90 987	11	53.70	81%, <0.001	Yes
Hodgkin lymphoma	3.52 [2.01–6.17]	70/72 333	6	23.35	79%, <0.001	None
Myeloma	2.10 [1.67–2.65]	54/61 319	6	5.13	2%, 0.40	None
All haematologic (composite)	2.71 [1.68–4.36]	252/35 908	6	123.88	96%, <0.001	None
All leukemia (composite)	1.94 [1.56–2.41]	82/69 810	5	1.46	0%, 0.83	None
Lymphoma	3.03 [2.32–3.96]	62/9349	2	0.31	0%, 0.58	NA
Myeloid	2.93 [2.12–4.05]	43/39 827	2	0.01	0%, 0.93	NA
Liver and hepatobiliary cancers						
Liver	2.81 [1.72–4.59]	52/48 677	6	13.93	64%, 0.02	None
All hepatobiliary (composite)	2.07 [1.37–3.12]	42/26 030	4	6.76	56%, 0.08	None
Liver/gallbladder	1.83 [1.76–1.90]	32/18 696	3	0.56	0%, 0.76	None
Respiratory cancers						
Lung	1.75 [1.37–2.24]	446/80 129	9	31.02	74%, <0.001	None
All respiratory (composite)	1.53 [1.11–2.11]	83/19 063	3	8.95	78%, 0.01	Yes
Larynx	4.22 [1.97–9.03]	9/7538	3	2.03	1%, 0.36	None
Oropharynx	7.35 [1.12–48.36]	2/9048	2	0.06	0%, 0.80	NA
Gastrointestinal cancers						
Stomach	1.34 [1.05–1.72]	51/72 444	9	4.59	0%, 0.80	None
Oesophagus	1.73 [1.04–2.89]	16/53 580	5	2.02	0%, 0.73	None
Colon	1.65 [1.23–2.22]	48/7042	5	0.67	0%, 0.95	None
Anal	5.69 [1.62–19.94]	13/9782	4	10.53	72%, 0.02	None
Other cancers						
Bladder	1.80 [1.04–3.11]	108/80 334	9	42.71	81%, <0.001	None
Thyroid	1.50 [1.34–1.68]	387/94 320	8	6.42	0%, 0.49	None
Brain and nervous system	1.41 [1.02–1.93]	40/56 329	7	1.37	0%, 0.97	None
Decreased risk						
Reproductive (female) cancers						
Breast	0.87 [0.76–1.00]	969/96 633	10	22.93	61%, 0.01	None
Uterus	0.64 [0.49–0.83]	72/76 996	7	6.45	7%, 0.37	None
Skin cancers						
Melanoma	0.69 [0.53–0.90]	67/61 028	6	3.68	0%, 0.60	None
Other cancers						
Prostate	0.80 [0.65–0.99]	93/71 719	5	3.86	0%, 0.43	None
No evidence of increased risk						
Reproductive (female) cancers						
All gynaecologic (female) (composite)	1.20 [0.76–1.89]	44/6012	3	2.98	33%, 0.23	None
Ovarian	0.86 [0.68–1.10]	73/76 476	8	2.77	0%, 0.91	None
Gastrointestinal cancers						
Pancreas	1.26 [0.97–1.63]	64/76 651	7	5.10	0%, 0.53	None
Colorectal	0.93 [0.81–1.06]	189/72 643	7	2.67	0%, 0.85	None
All gastrointestinal (composite)	1.15 [0.97–1.37]	137/7505	3	0.60	0%, 0.74	None
Rectal	0.83 [0.43–1.58]	11/5894	2	0.01	0%, 0.93	NA
Oral	1.41 [0.79–2.53]	1/16 483	2	0.50	0%, 0.48	NA
Small intestine	1.23 [0.31–4.89]	3/15 623	2	0.03	0%, 0.86	NA
Skin cancers						
Non-melanoma	1.24 [0.98–1.57]	195/30 340	6	6.69	25%, 0.25	None
All skin (composite)	1.24 [0.41–3.78]	15/13 158	4	12.74	76%, 0.005	None
Other cancers						
Kidney	1.78 [0.97–3.25]	61/63 451	8	18.16	61%, 0.01	None

Figure 2. Forest plots of pooled RRs and strength of evidence for risk of malignancies in people with SLE compared with the general population[a]
[a]Each RR represents a separate meta-analysis. See Supplementary Figure S1 A–AH for individual site-specific malignancy outcomes;
[b]Partial event rate only, number of events, and number of patients were not reported for all studies. CI=confidence interval. NA=not applicable. NHL=non-Hodgkin lymphoma. RR=risk ratio. SLE=systemic lupus erythematosus.

[27,39,42,43,59,68,69], colorectal cancer (RR 0.93; 95% CI 0.81–1.06) [27,39,59,64,65,68,69], all gastrointestinal cancers (RR 1.15; 95% CI 0.97–1.37) [39,42,43], rectal cancer (RR 0.83; 95% CI 0.43–1.58) [25,51], oral cancer (RR 1.41; 95% CI 0.79–2.53) [59,64], and small intestine cancer (RR 1.23; 95% CI 0.31–4.89) [50,59]; two skin malignancies: non-melanoma (RR 1.24; 95% CI 0.98–1.57) [25,39,42,43,59,68] and all skin cancer (RR 1.24; 95% CI 0.41–3.78) [24,26,56,64]; and kidney cancer (RR 1.77; 95% CI 0.97–3.25) [25,32,39,42,53,59,68,69]. Twenty-six of 33 sensitivity analyses supported no evidence of increased risk for these malignancies (Table 2).

In addition to the sensitivity analyses performed, the leave1out analysis (Table 3) demonstrated no effect on the main result when removing individual studies for most cancers. Of the cancers with significantly increased or decreased risk (n=28), 11 lost significance with the removal of a single study. All but two cancers (NHL and all respiratory) had an Egger's test p-value ≥0.05, indicating no publication bias (Figure 2).

Table 2
Sensitivity analyses for risk of malignancy in people with SLE compared with the general population: RRs (95% CIs)

	Main analysis	Least-adjusted analysis	Date of publication		Reporting on fatal and/or non-fatal events		Risk of bias	Geographical location		
			During or after 2014	Before 2014	Reporting on non-fatal/fatal events	Reporting on fatal events	Only low risk of bias studies	Europe	North America	Asia
All malignancies (composite)	1.18 (1.00–1.38)	1.19 (1.01–1.40)	1.39 (1.12–1.72)	1.10 (0.71–1.70)	1.27 (1.16–1.38)	0.56 (0.29–1.11)	1.33 (1.20– 1.47)	1.25 (0.96–1.62)	1.15 (1.09–1.21)	1.42 (1.30– 1.56)
Increased risk										
Reproductive (female) cancers										
Cervical	1.66 (1.16–2.36)	1.72 (1.18–2.51)	1.11 (0.73–1.67)	2.12 (1.54–2.93)	..	..	1.62 (1.33–1.98)	1.49 (1.07–2.08)	1.56 (0.55–4.40)	3.48 (1.50–8.11)
Vagina/vulva or vulva	3.63 (2.54–5.20)	3.93 (3.00–5.15)	4.04 (2.99–5.46)	1.34 (0.43–4.14)	..	..	3.49 (1.93–6.33)	3.91 (1.07–14.28)	..	..
Genital (other, female)	3.41 (1.86–6.23)	..	..	..	..	..	..	..	..	..
Haematologic cancers										
NHL	4.32 (3.42–5.47)	4.56 (3.62–5.76)	5.61 (3.51–8.97)	4.56 (3.23–6.42)	..	..	5.12 (3.92–6.69)	4.97 (3.28–7.55)	3.77 (2.15–6.59)	6.51 (4.29–9.86)
Hodgkin lymphoma	3.52 (2.01–6.17)	3.88 (2.57–5.87)	3.05 (2.02–4.62)	4.20 (1.58–11.16)	..	..	4.36 (1.91–9.95)	7.63 (5.03–11.58)	3.17 (1.79–5.62)	..
Myeloma	2.10 (1.67–2.65)	1.82 (1.34–2.46)	1.59 (1.12–2.25)	2.58 (1.94–3.43)	..	..	1.82 (1.15–2.87)	1.77 (0.95–3.29)	..	..
All haematologic (composite)	2.71 (1.68–4.36)	..	2.93 (1.83–4.68)	2.59 (0.45–14.78)	3.34 (2.21–5.07)	1.47 (0.77–2.81)	3.72 (2.43–5.70)	2.67 (1.36–5.24)	4.45 (2.30–8.63)	..
All leukaemia (composite)	1.94 (1.56–2.41)	..	2.35 (1.99–2.78)	..	..	..	1.77 (1.31–2.40)	1.96 (1.25–3.06)	2.16 (1.59–2.92)	..
Lymphoma	3.03 (2.32–3.96)	3.01 (3.30–3.94)	..	..	..	..	..	..	..	..
Myeloid malignancies	2.93 (2.12–4.05)	..	..	..	..	..	..	..	..	..
Liver and hepatobiliary cancers										
Liver	2.81 (1.72–4.59)	..	2.22 (1.39–3.54)	4.18 (2.54–6.89)	..	..	2.90 (1.50–5.63)	5.11 (3.35–7.81)	..	..
All hepatobiliary (composite)	2.07 (1.37–3.12)	1.93 (1.13–3.30)	2.44 (1.27–4.69)	2.00 (1.12–3.55)	..	..	2.12 (1.37–3.27)	2.65 (1.83–3.82)	..	..
Liver/gallbladder	1.83 (1.76–1.90)	1.83 (1.76–1.90)	..	..	..	..	1.83 (1.76–1.90)	..	..	..
Respiratory cancers										
Lung	1.75 (1.37–2.24)	1.79 (1.37–2.33)	1.64 (1.26–2.13)	2.04 (0.99–4.22)	..	..	1.90 (1.34–2.69)	2.21 (1.64–2.98)	1.66 (1.45–1.90)	1.39 (1.01–1.92)
All respiratory (composite)	1.53 (1.11–2.11)	..	..	..	..	..	..	1.82 (1.41–2.33)	..	..
Larynx	4.22 (1.97–9.03)	..	..	..	..	..	..	..	..	..
Oropharynx	7.35 (1.12–48.36)	6.73 (1.03–44.06)	..	..	..	..	..	..	..	..
Gastrointestinal cancers										
Stomach	1.34 (1.05–1.72)	..	1.45 (1.02–2.04)	1.42 (0.70–2.88)	..	..	1.40 (1.05–1.88)	1.13 (0.63–2.02)	..	1.37 (0.62–3.00)
Oesophagus	1.73 (1.04–2.89)	..	1.65 (1.44–1.89)	..	..	..	1.467 (0.57–3.80)	2.46 (0.66–9.17)	..	..
Colon	1.65 (1.23–2.22)	..	1.65 (2.22–2.24)	..	..	..	1.63 (1.21–2.20)	1.61 (1.18–2.19)	2.36 (0.72–7.77)	..
Anal	5.69 (1.62–19.94)	..	..	..	..	..	..	..	..	..
Other cancers										
Bladder	1.80 (1.04–3.11)	1.83 (1.07–3.12)	1.76 (0.91–3.42)	1.12 (0.50–2.52)	..	..	2.16 (1.09–4.27)	1.77 (0.98–3.21)	..	6.65 (0.18–248.86)
Thyroid	1.50 (1.34–1.68)	1.51 (1.35–1.69)	2.09 (1.77–2.46)	1.45 (1.28–1.65)	..	..	1.47 (1.31–1.66)	1.35 (0.51–3.56)	..	1.45 (1.28–1.65)
Brain and nervous system	1.41 (1.02–1.93)	..	1.63 (0.65–4.13)	1.75 (0.97–3.16)	..	..	1.28 (0.84–1.93)	1.19 (0.76–1.88)	..	..
Decreased risk										
Reproductive (female) cancers										
Breast	0.87 (0.76–1.00)	0.85 (0.76–0.94)	0.97 (0.65–1.43)	1.02 (0.89–1.17)	..	..	0.92 (0.79–1.06)	0.90 (0.78–1.03)	0.92 (0.70–1.19)	1.17 (0.94–1.47)
Uterus	0.64 (0.49–0.83)	0.63 (0.49–0.80)	0.79 (0.49–1.28)	0.60 (0.19–1.97)	..	..	0.66 (0.45–0.97)	0.90 (0.62–1.32)	..	0.34 (0.11–1.02)
Skin cancers										
Melanoma	0.69 (0.53–0.90)	..	0.645 (0.484 –0.859)	1.142 (0.40 –3.25)	..	..	0.72 (0.48–1.08)	0.81 (0.50–1.33)	..	..
Other cancers										
Prostate	0.80 (0.65–0.99)	..	0.80 (0.71–0.90)	..	..	..	0.96 (0.67–1.37)	1.68 (0.78– 3.63)	0.70 (0.51–0.95)	..
No evidence of increased risk										
Reproductive (female) cancers										
All gynaecologic (female) (composite)	1.20 (0.76–1.89)	..	..	..	..	..	1.02 (0.76–1.37)	..	..	..
Ovarian	0.86 (0.68–1.10)	0.90 (0.71–1.14)	0.73 (0.66–0.81)	1.07 (0.64–1.78)	..	..	0.90 (0.67–1.21)	1.07 (0.74–1.57)	0.83 (0.56–1.23)	0.94 (0.47–1.89)
Gastrointestinal cancers										
Pancreas	1.26 (0.97–1.63)	1.44 (1.01–2.05)	1.34 (0.89–2.02)	1.93 (1.11–3.37)	..	..	1.35 (0.96–1.89)	1.55 (1.01–2.38)	2.11 (0.62–7.20)	..
Colorectal	0.93 (0.81–1.06)	..	0.83 (0.79–0.87)	1.03 (0.78–1.34)	..	..	0.97 (0.81–1.16)	0.89 (0.61–1.30)	0.91 (0.74–1.11)	1.07 (0.78–1.46)
All gastrointestinal (composite)	1.15 (0.97–1.37)	..	1.134 (0.95–1.36)	..	..	..	..	..	..	..
Rectal	0.83 (0.43–1.58)	..	..	..	..	..	..	..	..	..
Oral	1.41 (0.79–2.53)	..	..	..	..	..	..	..	..	..
Small intestine	1.23 (0.31–4.89)	..	..	..	..	..	..	..	..	..
Skin cancers										
Non-melanoma	1.24 (0.98–1.57)	1.25 (1.01–1.55)	1.50 (1.06–2.12)	1.07 (0.89–1.29)	..	..	..	1.29 (0.99–1.68)	..	..
All skin (composite)	1.24 (0.41–3.78)	..	..	..	..	..	2.77 (0.77–9.95)	0.59 (0.01–84.54)	..	..
Other cancers										
Kidney	1.78 (0.97–3.25)	1.78 (0.98–3.24)	2.21 (1.21–4.06)	1.69 (0.31–9.22)	..	..	1.67 (0.70–3.94)	1.83 (0.60–5.55)	2.16 (1.55–2.99)	..

Data are reported as RR (95% CIs).
CI=confidence interval. NHL=non-Hodgkin lymphoma. RR=risk ratio.

Table 3
Leave1out analysis

	Leave1out
All malignancies (composite)	No impact
Increased risk	
Cervical	No impact
Vagina/vulva or vulva	No impact
Genital (other, female)	NA
NHL	No impact
Hodgkin lymphoma	No impact
Myeloma	No impact
All haematologic (composite)	No impact
All leukaemia (composite)	No impact
Lymphoma	NA
Myeloid malignancies	NA
Liver	No impact
All hepatobiliary (composite)	No impact
Liver/gallbladder	Loss of significance
Lung	No impact
All respiratory (composite)	Loss of significance
Larynx	Loss of significance
Oropharynx	NA
Stomach	Loss of significance
Oesophagus	Loss of significance
Colon	Loss of significance
Anal	Loss of significance
Bladder	Loss of significance
Thyroid	No impact
Brain and nervous system	No impact
No evidence of increased risk	
All gynaecologic (female) (composite)	No impact
Ovarian	No impact
Pancreas	No impact
Colorectal	No impact
All gastrointestinal (composite)	No impact
Rectal	NA
Oral	NA
Small intestine	NA
Non-melanoma	Gain of significance
All skin (composite)	No impact
Kidney	No impact
Decreased risk	
Breast	Loss of significance
Uterus	No impact
Melanoma	Loss of significance
Prostate	Loss of significance

NA=not applicable. NHL=non-Hodgkin lymphoma.

4. Discussion

In this meta-analysis evaluating the risk of 40 malignancies, we identified an 18% increased risk of a composite outcome for all malignancies among patients with SLE compared with the general population. We identified 24 site-specific malignancies with increased risk, including reproductive cancers (cervical, vagina/vulva), all haematologic cancers, all liver and hepatobiliary cancers, all respiratory cancers, gastrointestinal cancers (stomach, oesophagus, colon, anal), and other cancers (bladder, thyroid, brain and nervous system). Of those with the largest body of evidence (≥6 studies), NHL and Hodgkin lymphoma had an increased risk of >3-fold; myeloma and liver >2-fold; cervical, lung, bladder, and thyroid ≥1.5-fold; and stomach and brain >1.3-fold.

Our findings suggest a decreased risk of breast, uterine, melanoma, and prostate malignancies in evidence obtained from ≥5 studies. There was no evidence of increased risk of 11 site-specific malignancies: reproductive cancers (all gynaecologic, ovarian), gastrointestinal cancers (pancreas, colorectal, all gastrointestinal, rectal, oral, small intestine), skin cancer (non-melanoma, all skin), and kidney cancer.

The current findings are consistent with previous systematic reviews that assessed the risk of specific cancer types in SLE patients compared with the general population [2-10]. Our study has several advantages over previous meta-analyses. First, it includes a wider range of cancer types. Second, it excludes overlapping populations to ensure patients were evaluated only once, creating improved precision in RR estimates. Third, it includes recently updated studies with data from longer follow-up durations. Additionally, our study presents full sensitivity analyses for each malignancy to support interpretation of the results.

The increased risk of malignancy observed in SLE patients may be attributable to various mechanisms including chronic immune stimulation as a result of SLE disease activity [73]; persistent viral infections, such as Epstein–Barr virus, viral hepatitis, or human papilloma virus; oxidative stress, which is increased in SLE, can lead to chronic inflammation and, in turn, contribute to development of fatal comorbidities[74], including malignancies [75]; or conventional risk factors, such as smoking [73]. Immunosuppressive treatment for SLE, such as cyclophosphamide, may also increase the risk of malignancy, either directly via immunosuppression and cytotoxicity or indirectly by promoting oncogenic virus emergence [73,76].

Some autoantibody profiles may alter malignancy risk. For example, antiphospholipid antibodies are associated with increased risk of haematologic cancers [77]. We observed an increased risk for all haematologic cancers, including NHL.

Our study identified a decreased risk of hormone-sensitive cancers: breast, uterine, and prostate cancers (13%, 36%, and 20% decreased risk, respectively). This observation could be the result of autoantibody profiles. Presence of cell-penetrating anti–double-stranded DNA is associated with a decreased risk of breast cancer [78]. Decreased risk of hormone-sensitive cancers may also be due to less exposure to endogenous and/or exogenous hormones, a result of earlier menopause, and/or avoidance of oral contraceptives or hormone-replacement therapy arising from concerns over adverse outcomes [79]. It is not known if the increased contact of lupus patients with the healthcare system leads to increased cancer surveillance, and potentially early detection of pre-malignant lesions, which may contribute to the decreased incidence of breast and prostate cancer. Guidelines recommend that cancer is screened for and managed as part of the regular monitoring and assessment of lupus patients and that screening should at least follow cancer screening recommended for the general population with some guidelines recommending enhanced screening [80,81]. However, evidence suggests that in some cases uptake of screening may be lower in patients with SLE than the general population [82,83].

Our findings suggest a 31% decreased risk of melanoma in patients with SLE. Because ultraviolent sunlight is known to exacerbate SLE disease activity [84], patients generally avoid sun over-exposure, which may provide the benefit of a lower risk of ultraviolet-related cancers like melanoma.

Our study has some limitations. We identified statistical heterogeneity among studies meta-analysed, potentially due to variations in population characteristics, differences in control group selection, and variability of risk measures reported. The stability and reliability of heterogeneity estimates from smaller studies with low event numbers should be interpreted carefully [85]. Low event numbers may decrease precision, with wide CIs for some outcomes. However, we applied several sensitivity analyses to support interpretation of our results.

5. Conclusions

This meta-analysis of 40 malignancies demonstrates that patients with SLE have a marginally increased risk of the composite endpoint of all malignancies and some site-specific cancer types, with decreased risk of other cancers, including breast, uterine, melanoma, and prostate. Malignancy risk may be driven by various mechanisms, including SLE disease activity; immunomodulatory and immunosuppressive therapy; autoantibody profiles; and viral, genetic, or

environmental factors, for which the evidence base is still evolving. Further research into the risk profiles and phenotypes of patients with SLE with increased malignancy risk is warranted to identify patients at highest risk and to guide development of guidelines and strategies to mitigate any potential cancer risk in patients with SLE.

Contributors

NP, JL, LN, SL, and ERH designed the research. NP, ZM, JL, LN, SL, and NE conducted the research. NP and NE performed the statistical analysis. NP drafted the manuscript. JL and SL supervised the writing. AC, NP, ZM, JL, LN, SL, NE, XW, BD, VB, and ERH contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. ERH had primary responsibility for the final content and is the guarantor. The corresponding author (AC) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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This study was funded by AstraZeneca. The funder of the study had a role in its design, interpretation of the data, and in the writing of the manuscript. The funder had no role in the conduct, collection, or analysis of the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

AC has received consulting fees from AstraZeneca, BMS, Exagen Diagnostics, and GSK. NP, ZM, JL, LN, SL, and NE have received personal fees from AstraZeneca during the conduct of the study and outside the submitted work. XW and VB are employees of AstraZeneca. BD is an employee and shareholder of AstraZeneca. ERH was an employee of AstraZeneca at the time of study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.09.009.

References

[1] Merrill JT, Manzi S, Aranow C, Askenase A, Bruce I, Chakravarty E, et al. Lupus community panel proposals for optimising clinical trials: 2018. Lupus Science & Medicine 2018;5:e000258.
[2] Wu Y, Hou Q. Systemic lupus erythematous increased lung cancer risk: Evidence from a meta-analysis. Journal of Cancer Research and Therapeutics 2016;12:721–4.
[3] Ni J, Qiu LJ, Hu LF, Cen H, Zhang M, Wen PF, et al. Lung, liver, prostate, bladder malignancies risk in systemic lupus erythematosus: evidence from a meta-analysis. Lupus 2014;23:284–92.
[4] Zhang M, Li XM, Wang GS, Qian L, Tao JH, Ma Y, et al. Thyroid cancer in systemic lupus erythematosus: A meta analysis. International Journal of Clinical and Experimental Pathology 2014;7:6270–3.
[5] Huang H-B, Jiang S-C, Han J, Cheng Q-S, Dong C-B, Pan C-M. A systematic review of the epidemiological literature on the risk of urological cancers in systemic lupus erythematosus. Journal of Cancer Research and Clinical Oncology 2014;140:1067–73.
[6] Apor E, O'Brien J, Stephen M, Castillo JJ. Systemic lupus erythematosus is associated with increased incidence of hematologic malignancies: A meta-analysis of prospective cohort studies. Leukemia Research 2014;38:1067–71.
[7] Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Archives of Internal Medicine 2005;165:2337–44.
[8] Bernatsky S, Ramsey-Goldman R, Foulkes WD, Gordon C, Clarke AE. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: A meta-analysis. British Journal of Cancer 2011;104:1478–81.
[9] Song L, Wang Y, Zhang J, Song N, Xu X, Lu Y. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Research & Therapy 2018;20:270.
[10] Cao L, Tong H, Xu G, Liu P, Meng H, Wang J, et al. Systemic lupus erythematous and malignancy risk: A meta-analysis. PLoS One 2015;10:e0122964.
[11] Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, Van Vollenhoven R, et al. Systemic lupus erythematosus. Nature Reviews Disease Primers 2016;2:16039.
[12] Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis & Rheumatism 2005;52:1481–90.
[13] Higgins JPT, Green S. The Cochrane Collaboration 2011 Available at www.handbook.cochrane.org.
[14] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[15] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism 1982;25:1271–7.
[16] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism 1997;40:1725.
[17] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2014 Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed 23 April 2020.
[18] Holmqvist M, Simard JF, Asplund K, Arkema EV. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. RMD Open 2015;1:e000168.
[19] Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiologic Reviews 1987;9:1–30.
[20] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177–88.
[21] Stuck AE, Rubenstein LZ, Wieland D. Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. The BMJ 1998;316(7129):469. author reply 470–1.
[22] Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36:1–48.
[23] Azrielant S, Tiosano S, Watad A, Mahroum N, Whitby A, Comaneshter D, et al. Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. Immunologic Research 2017;65:464–9.
[24] Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. Lupus 2001;10:394–400.
[25] Dreyer L, Faurschou M, Mogensen M, Jacobsen S. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: A long-term followup study in a Danish cohort. Arthritis & Rheumatism 2011;63:3032–7.
[26] Ragnarsson Ó, Gröndal G, Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. Lupus 2003;12:687–91.
[27] Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. Journal of Autoimmunity 2013;42:130–5.
[28] Bernatsky S, Ramsey-Goldman R, Isenberg D, Rahman A, Dooley MA, Sibley J, et al. Hodgkin's lymphoma in systemic lupus erythematosus. Rheumatology 2007;46:830–2.
[29] Lu M, Bernatsky S, Ramsey-Goldman R, Petri M, Manzi S, Urowitz MB, et al. Non-lymphoma hematological malignancies in systemic lupus erythematosus. Oncology 2013;85:235–40.
[30] Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Urowitz M, et al. Race/ethnicity and cancer occurrence in systemic lupus erythematosus. Arthritis Care & Research 2005;53:781–4.
[31] Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis & Rheumatism 2006;54:2550–7.
[32] Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. Arthritis & Rheumatism 1996;39:1050–4.
[33] Bernatsky S, Clarke A, Ramsey-Goldman R, Joseph L, Boivin JF, Rajan R, et al. Hormonal exposures and breast cancer in a sample of women with systemic lupus erythematosus. Rheumatology 2004;43:1178–81.
[34] Chun BC, Bae SC. Mortality and cancer incidence in Korean patients with systemic lupus erythematosus: results from the Hanyang lupus cohort in Seoul, Korea. Lupus 2005;14:635–8.
[35] Nived O, Bengtsson A, Jönsen A, Sturfelt G, Olsson H. Malignancies during follow-up in an epidemiologically defined systemic lupus erythematosus inception cohort in southern Sweden. Lupus 2001;10:500–4.
[36] Sultan SM, Ioannou Y, Isenberg DA. Is there an association of malignancy with systemic lupus erythematosus? An analysis of 276 patients under long-term review. Rheumatology 2000;39:1147–52.
[37] Ramsey-Goldman R, Mattai SA, Schilling E, Chiu YL, Alo CJ, Howe HL, et al. Increased risk of malignancy in patients with systemic lupus erythematosus. Journal of Investigative Medicine 1998;46:217–22.

[38] Sweeney DM, Manzi S, Janosky J, Selvaggi KJ, Ferri W, Medsger TA, et al. Risk of malignancy in women with systemic lupus erythematosus. Journal of Rheumatology 1995;22:1478–82.
[39] Mellemkjer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis & Rheumatism 1997;40:761–8.
[40] Sunesen KG, Nørgaard M, Thorlacius-Ussing O, Laurberg S. Immunosuppressive disorders and risk of anal squamous cell carcinoma: a nationwide cohort study in Denmark, 1978-2005. International Journal of Cancer 2010;127:675–84.
[41] Pettersson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. Annals of the Rheumatic Diseases 1992;51:437–9.
[42] Tallbacka KR, Pettersson T, Pukkala E. Increased incidence of cancer in systemic lupus erythematosus: a Finnish cohort study with more than 25 years of follow-up. Scandinavian Journal of Rheumatology 2018;47:461–4.
[43] Björnådal L, Löfström B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scandinavian Journal of Rheumatology 2002;31:66–71.
[44] Castro FA, Liu X, Försti A, Ji J, Sundquist J, Sundquist K, et al. Increased risk of hepatobiliary cancers after hospitalization for autoimmune disease. Clinical Gastroenterology and Hepatology 2014;12:1038–1045.e7 e1037.
[45] Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Annals of Oncology 2014;25:2025–30.
[46] Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Hodgkin lymphoma after autoimmune diseases by age at diagnosis and histological subtype. Annals of Oncology 2014;25:1397–404.
[47] Hemminki K, Liu X, Ji J, Försti A, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in female cancers. Gynecologic Oncology 2012;127:180–5.
[48] Hemminki K, Liu X, Försti A, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. Journal of Hematology and Oncology 2012;5:59.
[49] Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in histology-specific lung cancer. European Respiratory Journal 2012;40:1489–95.
[50] Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on mortality and survival in subsequent digestive tract cancers. Annals of Oncology 2012;23:2179–84.
[51] Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. Annals of Oncology 2012;23:927–33.
[52] Hemminki K, Liu X, Forsti A, Ji J, Sundquist J, Sundquist K. Subsequent brain tumors in patients with autoimmune disease. Neuro-Oncology 2013;15:1142–50.
[53] Liu X, Ji J, Forsti A, Sundquist K, Sundquist J, Hemminki K. Autoimmune disease and subsequent urological cancer. Journal of Urology 2013;189:2262–8.
[54] Wadström H, Arkema VE, Sjöwall C, Askling J, Simard JF. Cervical neoplasia in systemic lupus erythematosus: A nationwide study. Rheumatology 2017;56:613–9.
[55] Chang S-L, Hsu H-T, Weng S-F, Lin Y-S. Impact of head and neck malignancies on risk factors and survival in systemic lupus erythematosus. Acta Oto-Laryngologica 2013;133:1088–95.
[56] Chen YJ, Chang YT, Wang CB, Wu CY. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. American Journal of Medicine 2010;123 1150.e1151-1150.e1-6.
[57] Liang J-A, Sun L-M, Yeh J-J, Lin W-Y, Chang S-N, Sung H-C, et al. Malignancies associated with systemic lupus erythematosus in Taiwan: a nationwide population-based cohort study. Rheumatology International 2012;32:773–8.
[58] Lin YC, Yen JH, Chang SJ, Lin YC. The age-risk relationship of haematologic malignancies in female patients with systemic lupus erythematosus: a nationwide retrospective cohort study. Lupus 2012;21:1250–6.
[59] Yu KH, Kuo CF, Huang LH, Huang WK, See LC. Cancer risk in patients with inflammatory systemic autoimmune rheumatic diseases: a nationwide population-based dynamic cohort study in Taiwan. Medicine 2016;95:e3540.
[60] Lerang K, Gilboe IM, Steinar Thelle D, Gran JT. Mortality and years of potential life loss in systemic lupus erythematosus: a population-based cohort study. Lupus 2014;23:1546–52.
[61] Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrology Dialysis Transplantation 2012;27:3248–54.
[62] Wang HL, Zhou YM, Zhu GZ, Yang Z, Hua BJ. Malignancy as a comorbidity in rheumatic diseases: a retrospective hospital-based study. Clinical Rheumatology 2018;37:81–5.
[63] Thomas G, Mancini J, Jourde-Chiche N, Sarlon G, Amoura Z, Harle JR, et al. Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. Arthritis & Rheumatology 2014;66:2503–11.
[64] Tarr T, Gyorfy B, Szekanecz E, Bhattoa HP, Zeher M, Szegedi G, et al. Occurrence of malignancies in Hungarian patients with systemic lupus erythematosus: results from a single center. Annals of the New York Academy of Sciences 2007;1108:76–82.
[65] Chang SH, Park JK, Lee YJ, Yang JA, Lee EY, Song YW, et al. Comparison of cancer incidence among patients with rheumatic disease: a retrospective cohort study. Arthritis Research & Therapy 2014;16:428.
[66] Kang KY, Kim HO, Yoon HS, Lee J, Lee WC, Ko HJ, et al. Incidence of cancer among female patients with systemic lupus erythematosus in Korea. Clinical Rheumatology 2010;29:381–8.
[67] Hidalgo-Conde A, Liger MdH, Abarca-Costalago M, Álvarez Pérez M, Valdivielso-Felices P, González-Santos P, et al. Incidence of cancer in a cohort of Spanish patients with systemic lupus erythematosus. Reumatologia Clinica 2013;9:359–64.
[68] Rees F, Doherty M, Grainge M, Lanyon P, Davenport G, Zhang W. Burden of comorbidity in systemic lupus erythematosus in the UK, 1999-2012. Arthritis Care & Research 2016;68:819–27.
[69] Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes & Control 2008;19:887–94.
[70] Kim SC, Glynn RJ, Giovannucci E, Hernandez-Diaz S, Liu J, Feldman S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Annals of the Rheumatic Diseases 2015;74:1360–7.
[71] Yun J-S, Bae JM, Kim K-J, Jung YS, Kim GM, Kim H-R, et al. Increased risk of thyroid diseases in patients with systemic lupus erythematosus: a nationwide population-based Study in Korea. PLoS One 2017;12:e0179088.
[72] Khaliq W, Qayyum R, Clough J, Vaidya D, Wolff AC, Becker DM. Comparison of breast cancer risk in women with and without systemic lupus erythematosus in a Medicare population. Breast Cancer Research and Treatment 2015;151:465–74.
[73] Gonzalez LA, Alarcon GS. The evolving concept of SLE comorbidities. Expert Review of Clinical Immunology 2017;13:753–68.
[74] Perl A. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. Nature Reviews Rheumatology 2013;9:674–86.
[75] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radical Biology & Medicine 2010;49:1603–16.
[76] Goobie GC, Bernatsky S, Ramsey-Goldman R, Clarke AE. Malignancies in systemic lupus erythematosus: a 2015 update. Current Opinion in Rheumatology 2015;27:454–60.
[77] Dias C, Isenberg DA. Susceptibility of patients with rheumatic diseases to B-cell non-Hodgkin lymphoma. Nature Reviews Rheumatology 2011;7:360–8.
[78] Hansen JE, Chan G, Liu Y, Hegan DC, Dalal S, Dray E, et al. Targeting cancer with a lupus autoantibody. Science Translational Medicine 2012;4:157ra142.
[79] Choi MY, Flood K, Bernatsky S, Ramsey-Goldman R, Clarke AE. A review on SLE and malignancy. Best Practice & Research in Clinical Rheumatology 2017;31:373–96.
[80] Keeling SO, Alabdurubalnabi Z, Avina-Zubieta A, Barr S, Bergeron L, Bernatsky S, et al. Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus. The Journal of Rheumatology 2018;45:1426–39.
[81] Tessier-Cloutier B, Clarke AE, Pineau CA, Keeling S, Bissonauth A, Ramsey-Goldman R, et al. What investigations are needed to optimally monitor for malignancies in SLE? Lupus 2015;24:781–7.
[82] Bernatsky SR, Cooper GS, Mill C, Ramsey-Goldman R, Clarke AE, Pineau CA. Cancer screening in patients with systemic lupus erythematosus. The Journal of Rheumatology 2006;33:45–9.
[83] Cader RA, Mei Yee AK, Yassin A, Ahmad I, Haron SN. Malignancy in Systemic Lupus Erythematosus (SLE) Patients. Asian Pacific Journal of Cancer Prevention 2018;19:3551–5.
[84] Zandman-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y. Environment and lupus-related diseases. Lupus 2012;21:241–50.
[85] Thorlund K, Imberger G, Johnston BC, Walsh M, Awad T, Thabane L, et al. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. PLoS One 2012;7:e39471.