Received: 16 March 2022 | Revised: 1 February 2023 | Accepted: 3 June 2023

DOI: 10.1111/1756-185X.14784

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Cancer development in patients hospitalized with systemic lupus erythematosus: A population-level data linkage study

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Funding information
Arthritis and Osteoporosis Foundation of Western Australia; Arthritis Australia

Abstract

Aim: To explore the association between systemic lupus erythematosus (SLE) with the risk of cancer development and subsequent 5-year mortality in Western Australia (WA).

Methods: Population-level, data linkage study of SLE patients ($n = 2111$) and general population comparators ($n = 21\,110$) hospitalized between 1980 and 2014. SLE patients (identified by ICD-9-CM: 695.4, 710.0, and ICD-10-AM: L93.0, M32.0) were nearest matched (10:1) for age, sex, Aboriginality, and temporality. Follow up was from time zero (index SLE hospitalization) to cancer development, death or 31 December 2014. We assessed the risk of cancer development and subsequent 5-year mortality between SLE patients and comparators with univariate and multivariate-adjusted Cox proportional hazards regression models.

Results: SLE patients had similar multivariate-adjusted risk (adjusted hazard ratio [aHR] 1.03, 95% confidence interval [CI] 0.93–1.15; $p = .583$) of cancer development. Cancer development risk was higher in SLE patients <40 years old (aHR 1.58, 95% CI 1.29–1.94; $p < .001$), and from 1980 to 1999 (aHR 1.16, 95% CI 1.02–1.31; $p < .001$). SLE patients had higher risk of developing cancer of the oropharynx (aHR 2.13, 95% CI 1.30–3.50), vulvo-vagina (aHR 3.22, 95% CI 1.34–7.75), skin (aHR 1.20, 95% CI 1.01–1.43), musculoskeletal tissues (aHR 2.26, 95% CI 1.16–4.40), and hematological tissues (aHR 1.78 95% CI 1.25–2.53), all $p < .05$. After cancer development, SLE patients had increased risk of 5-year mortality (aHR 1.31, 95% CI 1.06–1.61); highest in patients <50 years old (aHR 2.03, 95% CI 1.03–4.00), and in those with reproductive system and skin cancers.

Conclusions: Hospitalized SLE patients had increased risk of multiple cancer subtypes. Following cancer development, SLE patients had increased risk of 5-year mortality. There is scope to improve cancer prevention and surveillance in SLE patients.

Trial registration: Not applicable. This low-risk risk study used de-identified administrative linked health data.

KEYWORDS
autoimmunity, cancer, epidemiology, lupus, survival

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease underwritten by the production of autoantibodies, immune complex deposition, and complement activation, which produces a variety of clinical manifestations, organ damage, and premature mortality.[1] Management of SLE patients often requires intensive and long-term use of immunosuppressive medications, the side effects of which, increase the patient's burden of disease. Consequently, SLE patients have poorer survival, especially after the onset of infection, cancer, renal failure, myocardial infarction, and central nervous system disorders.

Meta-analyses suggest that SLE is associated with increased risk of more than 16 types of cancer, and a decreased risk for prostate cancer and cutaneous melanoma[2,3]; however, those findings did not account for the impact of environmental triggers, ethnicity, alcohol use, and smoking status.[2] Other studies support an increased risk of cervical,[4] hematological, particularly non-Hodgkin's lymphoma, and kidney cancers[5]; with some showing a decreased risk of prostate cancer and bladder cancer,[6] or no association with breast, uterine, ovarian, colorectal, or brain cancers.[7] Australian data were not available for aggregation in the meta-analyses,[2,3] including data on cancer development in Aboriginal Australians with SLE; an ethnic group with higher demand for hospitalizations, including SLE-related hospitalizations.[1] Furthermore, Australia has unique environmental exposures, including very high levels of background ultraviolet radiation and high levels of silica dust particles, which makes data from this region important to include in future studies.[8] Therefore, this study explores the association between SLE with overall and type-specific cancer development in a cohort of SLE patients hospitalized in Western Australia (WA) between 1980 and 2014, and subsequent 5-year mortality.

2 | MATERIALS AND METHODS

This whole-of-population cohort study used data linked by the Western Australian Data Linkage System (WADLS), which uses probabilistic matching (99.7% accuracy) to identify individuals across administrative health data sets.[9] The Western Australian Rheumatic Disease Epidemiological Registry (WARDER) includes all private and public hospital separations (emergency department presentations, inpatient episodes, including same-day interventions and admissions, as well as, cancer notifications, and death notifications) statewide for over 200 000 patients with rheumatic disease conditions and another 200 000 non-exposed general population comparators.[1] The WARDER comprises of information linked from the Hospital Morbidity Data Collection (HMDC, from 1970), WA Cancer Registry (from 1982) and the Death Register (from 1969) and the Emergency Department Data Collection (from 2002). Since the 1970s, the HMDC has recorded the primary discharge diagnosis and (up to 20) co-diagnoses and the primary code and (up to 10) secondary procedure codes for each hospital-level inpatient separation using the International Statistical Classification of Diseases and Related Health Problems (ICD) ninth revision,[10,11] ICD 10th revision,[12] or the Australian Classification of Health Interventions codes.[13] The linkage of the WARDER data set was done on 1 February 2017. The WA Department of Health Human Research Ethics Committee approved this study (WADOH HREC#: 2016.24).

Within participants of the WARDER, hospitalizations for SLE were identified in the HMDC between 1 January 1980 and 31 December 2013 by ICD-9-CM: 695.4, and 710.0, and ICD-10-AM: M32.0, M32.1, M32.8, M32.9, L93.0, L93.1, and L93.2.[1] Administrative data have been validated for the identification of rare diseases, and suitable for producing epidemiological estimates[14]; and, having at least one ICD-9-CM code of SLE (ICD-9: 694.4 and 710) having a positive predictive value of 70%–96% in administrative or claims data,[15] which is even higher (≥97%) when patients are seen by a specialist.[16] Given that, 89%–93% of SLE patients meeting classification criteria are hospitalized during their disease course[17]; and that the HMDC also captures same-day drug infusions (although not the specific drug types) and procedures, our cohort will represent the majority of SLE patients in WA over the study period.

Systemic lupus erythematosus patients ($n = 2111$) were propensity score matched (1:10) to 22 110 control individuals free of rheumatic disease conditions. Time zero (study entry) was defined as the index hospitalization for SLE and a random hospitalization in the non-exposed comparators. SLE patients and controls were matched for the year of the index (first ever) hospital contact, year of time zero (study entry), age at time zero, sex, and Aboriginality.[1] Racial and ethnic demographic data are not comprehensively captured in the WADLS. However, self-reported Aboriginality is recorded during hospital admissions, with sensitivity over 90%.[18] Thus, to reduce the likelihood of under-identification, if an "Aboriginality" flag was present for >25% of all hospital admissions since 1980, then the patient was considered Aboriginal Australian.[19] Study entry (time zero) was the index hospitalization for SLE or a random hospitalization for the matched controls. The lookback period was the index hospitalization for any reason to time zero. The follow-up period was from time zero (index hospitalization for SLE) to prospective cancer development, date of death, or the study exit on 31 December 2014.

Comorbidities, including a modified Charlson Comorbidity Index (CCI) which removed SLE and cancer development, prevalent cancer development, viral infections, and smoking status, were identified

in the HMDC with the ICD codes defined in Table S1.[20,21] Cancer development was identified within the WARDER, which utilises data from the Cancer and Death Registers. The Cancer Register routinely collects statewide information on the cancer diagnoses from pathology reports and oncology treatment records. The Death Registry contains demographic information related to the individual and coded death certificate data using information in Parts 1 and 2 of the death certificate, or all diagnosis text fields from the death certificate. The Death Register data included the contributing causes of death data since 1980. Cancer development and sites were identified with the ICD codes defined in Table S1.[21]

2.1 | Statistical analysis

Results are summarized as a mean with standard deviation, median with interquartile range or frequency and proportion. Between-group differences were assessed with the *t*-test, Mann–Whitney *U* test, χ^2 test, and odds ratios (OR) with 95% confidence intervals (CI) as appropriate. We determined the association between a hospitalization for SLE and cancer development with univariate and multivariate Cox proportional hazards regression models. Sub-group and period specific (overall, 1980–1999, and 2000–2014) analysis looked at the association between a hospitalization for SLE and cancer development across the sexes, Aboriginality, age groups (<40, 40–49, 50–59, 60–69, and ≥70 years of age), and cancer site. The multivariate model (Model 1) for the association between SLE and cancer development risk was adjusted for prevalent cancer at time zero, smoking history (ever smoked), and the number of modified Charlson Comorbidity Items (0 = no CCI items, 1 = 1–2 CCI items, and 2 = 3 or more CCI items).[20] As SLE patients are susceptible to hematological diseases and infections throughout the disease course and viruses can increase the risk of cancer development. We performed further sub-group analyses (sex, age groups, Aboriginality, and year of index SLE hospitalization) to determine the association between risk of hospitalization for SLE with hematological, non-hematological and virus-induced cancers, e.g. human papillomavirus (HPV) -related cancers.[22] We performed an analysis of cancer development from 1990 to 2014 by Aboriginality, and then of cancer development of SLE patients within Aboriginal Australians.

The association between SLE with post-cancer mortality was assessed with univariate and multivariate Cox proportional hazards regression models from the date of prospective cancer development (after time zero) to the date of death or study exit (31 December 2014); and, at 1, 3, and 5 years of follow up. The association between SLE and 5-year post-cancer mortality was assessed across sex, age groups (<40, 40–59, 50–69, and ≥70), Aboriginality, and period of cancer development. The Cox proportional hazards regression models were adjusted for age, sex, and year of cancer development (Model 1); and, then further adjusted for Model 1 plus smoking status, prevalent cancer, and number of Charlson Comorbidity Items (0 = no CCI items, 1 = 1–2 CCI items, and 2 = 3 or more CCI items) accrued at the time of cancer development (Model 2).

Statistical significance was set at $p < .05$. The statistical analyses were carried out using IBM SPSS version 26.0.

3 | RESULTS

At study entry, SLE patients and controls were similar in age (43 years), with a marginally higher representation of females (85.1% vs. 83.4% female, $p = .038$), and Aboriginal Australians (7.8% vs. 6.0%). Additionally, SLE patients had higher odds of having accrued at least one modified CCI item (OR 4.23, 95% CI 3.85–4.64) or having ever smoked, but lower odds of prevalent cancer (Table 1 and Table S2). At time zero, SLE patients had lower odds of having ever had colorectal, breast, and skin cancer, but had high odds of hematological cancer, particularly Hodgkin's disease (Table S3).

3.1 | Association between a hospitalization for SLE with the risk of cancer development

A total of 426 (20.2%) SLE patients developed cancer compared with 3664 (17.4%) in the general population comparators (Figure 1 and Table 2). At cancer development, SLE patients were on average, 3.5 years younger (59.95 vs. 63.75 years, $p < .001$), were more often smokers (OR 1.78, 95% CI 1.44–2.18), with equivalent distributions of sex and Aboriginality. SLE patients had had substantially higher comorbidity accrual (modified CCI >0: OR 4.36, 95% CI 3.48–5.46) and more viral infections (OR 3.95, 95% CI 3.13–4.98; Table 3 and Table S4), but fewer had prevalent cancer.

Hospitalised-SLE patients had an increased risk of cancer development compared with comparators in the model matched for age, sex, Aboriginality, and temporality (hazard ratio [HR] 1.20, 95% CI 1.08–1.33; $p < .001$), but this was attenuated in the multivariate-adjusted model (adjusted HR [aHR] 1.03, 95% CI 0.93–1.14; $p = .563$) (Table 2). There were no sex-related differences in the multivariate-adjusted risk of cancer development after a SLE-related hospitalisation; however, male SLE patients had higher risk of hematological cancer development, and female SLE patients had higher risk of HPV-related cancer development (Table S5). With respect to age, in those <60 years old, a SLE-related hospitalisations increased the multivariate-adjusted risk of cancer development by 40% (aHR 1.40, 95% CI 1.23–1.60; $p < .001$), in contrast to those aged ≥70 years who had a reduced risk of cancer development. In those <40 years old, a SLE-related hospitalization increased the risk of developing hematological, non-hematological, and HPV-related cancers (Table S5). The multivariate-adjusted risk of cancer development after SLE-hospitalisation increased in the 1980–1999 period, but this attenuated in the 2000–2014 period (Table 2); this attenuation over time was seen across non-hematological and HPV-related cancers. However, the increased risk of hematological cancer development

TABLE 1 Cohort characteristics at study entry.

	SLE	Controls	OR (95% CI)	*p* value
Participants	2111	21 110		
Lookback time, median (IQR)	**7.54 (0.89, 15.34)**	**5.96 (0, 15.91)**		**<.001**
Follow-up time, median (IQR)	**13.17 (5.80, 19.64)**	**15.14 (7.00, 24.56)**	–	**<.001**
Follow-up time, sum	28 910	337 730	–	–
Demographics				
Age (y), mean ± SD	43.96 ± 17.74	43.56 ± 19.63	–	.364
Male, *n* (%)	**314 (14.9)**	**3512 (16.6)**	**0.88 (0.78, 0.99)**	**.037**
Female, *n* (%)	**1797 (85.1)**	**17 598 (83.4)**	**1.14 (1.01, 1.29)**	
Aboriginality, *n* (%)	**165 (7.8)**	**1275 (6.0)**	**1.32 (1.11, 1.56)**	**.001**
Smoking status, *n* (%)	**474 (22.5)**	**2964 (14.0)**	**1.77 (1.59, 1.98)**	**<.001**
Prevalent cancer, *n* (%)	**197 (9.3)**	**2392 (11.3)**	**0.81 (0.70, 0.94)**	**.005**
Any modCCI item > 0, *n* (%)	**943 (44.7)**	**3386 (16.0)**	**4.23 (3.85, 4.64)**	**<.001**
0 items, *n* (%)	**1168 (55.3)**	**17 724 (84.0)**	**0.26 (0.24, 0.29)†**	
1–2 items, *n* (%)	**753 (35.7)**	**2919 (13.8)**	**3.83 (3.46, 4.25)†**	**<.001**
>2 items, *n* (%)	**190 (9.0)**	**467 (2.2)**	**5.70 (1.90, 6.64)†**	
CCI score, median (IQR)	**2 (1, 3)**	**1 (1, 2)**	–	**<.001**

Note: Lookback time: the index hospitalization for any reason to time zero (date of index SLE-related hospitalization or random hospitalization for general population comparators). Follow-up time: from time zero (index hospitalization for SLE or random hospitalization for general population comparators) to study exit (date of death or 31 December 2014). modCCI: Modified Charlson Comorbidity Index, which includes all items except systemic lupus erythematosus, and cancer; Summary statistics were compared across groups with Mann–Whitney *U* test, *t* test, χ^2 test, binary logistic (odds ratio [OR] or multinomial regression [†]) with 95% confidence intervals (95% CI). Bolded results are significantly different across SLE and controls, $p < .05$.

after SLE-related hospitalization remained in the 2000–2014 period (Table S5). The risk of developing oropharyngeal, vulvo-vaginal, soft-tissue sarcoma, non-melanoma, nervous system (excluding brain), and hematological cancer, especially non-Hodgkin's lymphoma, was significantly higher in SLE patients.

3.2 | Cancer development by Aboriginality

From 1990–2015 (overall study sample, $n = 21\,958$), Aboriginal Australians had lower age- and sex-adjusted risk of incident overall cancer development (aHR 0.75, 95% CI 0.64–0.88; $p < .001$); which was underwritten by lower risk of colorectal, breast (female only), and skin cancer (Table S6). However, Aboriginal Australians had higher risk of incident cancer development of the hepatobiliary, respiratory (lung), musculoskeletal, and female reproductive systems (Table S6). Within Aboriginal Australians, a SLE-related hospitalization conferred no additional (age- and sex-adjusted) risk of cancer development from 1980–2014 (Table 2); although, we had insufficient end points to explore this association within specific cancer-types (data not shown).

3.3 | Association between a hospitalization for SLE with mortality after cancer development

After cancer development, hospitalized-SLE patients had increased multivariate-adjusted risk of mortality during follow-up (aHR 1.31, 95% CI 1.12–1.52); this association was reached by 3-years and established at 5-years (Table 3). mortality. Five-year mortality after cancer development was higher in hospitalized-SLE patients, who were <50 years-old (highest), female, non-Aboriginal Australian, or hospitalized from 1980–1999 (Table 4). Five-year mortality after cancer development was lower in hospitalised-SLE patients who were >70 years-old (Table 4).

Systemic lupus erythematosus patients had an increased risk of 5-year mortality after developing HPV-related (aHR 1.64, 95% CI 1.10–2.45; $p = .016$) and non-hematological (aHR 1.26, 95% CI 1.05–1.50; $p = .011$) cancers, as well as cancers of the genitals (female: aHR 1.78, 95% CI 1.05–3.01; $p = .033$; male: aHR 3.57, 95% CI 1.44–8.84; $p = .006$; including, prostate cancer: aHR 3.18, 95% CI 1.29–7.85 $p = .012$), and skin cancer (aHR 2.05, 95% CI 1.36– 3.11), particularly, non-melanoma of the skin (aHR 1.64, 95% CI 1.10–2.45; $p = .016$).

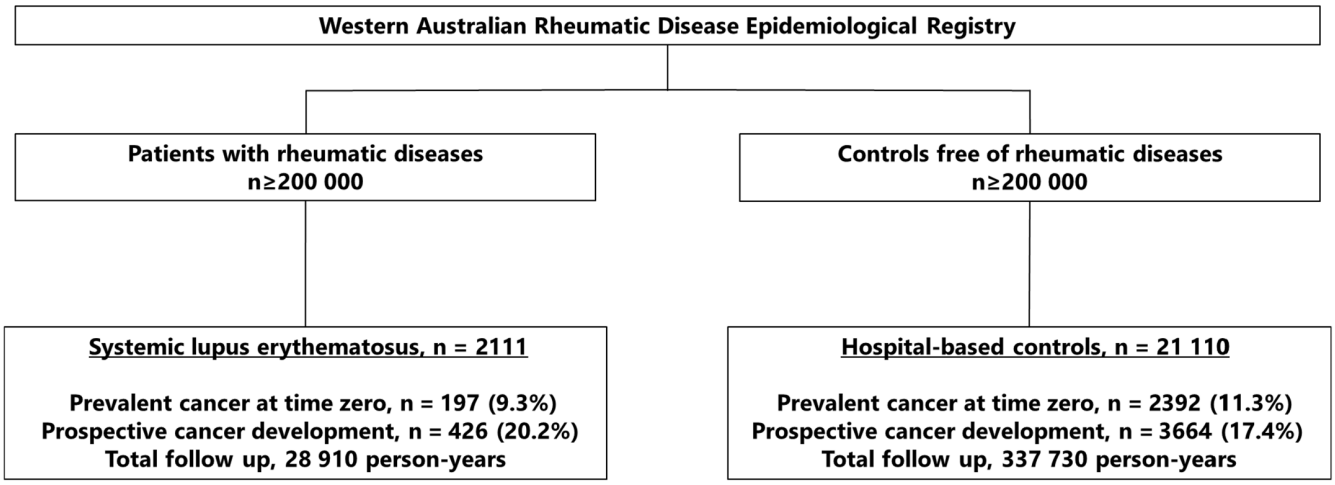

FIGURE 1 Study flowchart.

4 | DISCUSSION

In this large, population-level, data linkage, cohort study from WA, hospitalized SLE patients had an increased overall risk of cancer development, but the risk was attenuated after adjusting for smoking and comorbidity. However, SLE was independently associated with the increased risk of hematological, non-hematological, HPV-related, and site-specific cancers. After cancer development, SLE was associated with a 31% increased risk of death after 5 years compared with the general population with the highest 5-year post-cancer mortality in SLE patients <50 years old, as well as those with genital (female and male reproductive organs) or skin cancers.

The increased unadjusted (albeit matched for age, sex, Aboriginality, and temporality) risk of cancer development for SLE compared with controls, aligned with the standardized incidence rates (1.28, 95% CI 1.16–1.42) reported in the meta-analysis by Song et al.,[2] and an international multi-centered cohort study.[23] Additionally, our unadjusted findings of an increased risk of cancer in female, but not male, SLE patients, aligned with others.[2,23] However, after further adjustment for confounding risk factors the increased risk of cancer was attenuated, which aligned with other studies.[23,24] Our lower than expected SLE prevalence in female patients (85.1% vs. >90%) has been seen in other hospitalized SLE cohorts from Argentina (83.3%)[25] and Western Europe (87%),[26] and in another Western Australian population-level study with a stricter definition of SLE (≥2 ICD-10 codes at least 30 days apart),[27] and might reflect male patients having higher healthcare resource utilization for SLE-specific or comorbidity reasons, rather than a selection bias.[28] Thus, the difference between our multivariate adjusted data and the meta-analyses is explainable by the lack of adjustment for confounding factors like age, sex, environmental triggers, ethnicity, alcohol use, viral inducers, and smoking status in their aggregated results.[2]

Aboriginal Australians with SLE (7.8%) and without SLE (6.0%) were over-represented relative to the (~3%) Aboriginal Australian population of WA. This may reflect a higher prevalence or disease severity of SLE in Aboriginal Australians.[29-31] However, Aboriginal Australians have poorer access and utilization of primary and secondary healthcare services, due to complex socioeconomic, lifestyle, and geographical factors.[32-36] These barriers can result in escalation of healthcare problems to the point of needing (avoidable) hospitalization or causing premature mortality.[36,37]

Despite the Aboriginal–non-Aboriginal healthcare-gap, we found that Aboriginal Australians had a 27% lower (multivariate-adjusted) risk of developing cancer; which was underwritten by nearly higher odds of liver cancer, but lower odds of developing breast (females), colorectal, prostate, and skin cancer compared with non-Aboriginal Australians (data not shown). Data on incidence and prevalence of cancer in Aboriginal Australians are limited; our findings are in broad agreement with the WA Health cancer statistics.[38] A hospitalization for SLE in an Aboriginal Australian did not increase the risk of developing (any) cancer over time, including hepatobiliary cancer. Whereas, in non-Aboriginal Australians, SLE patients had increased risk of cancer development, including skin cancer which was driven by non-melanoma cancers. Given that Aboriginal Australians with SLE did not experience any increased frequency of skin cancer; and, that cutaneous LE disease activity is not associated with skin cancer development[39]; our data align with the literature, which indicates that SLE patients are at increased risk of developing skin cancer via mechanisms other than disease activity.

The association between SLE and risk of cancer development was modified by age, with SLE patients <40 years of age (aHR 1.51) and those 50–59 years old (aHR 1.35) being at increased risk, but those >70 years old at reduced risk, which was similar to the findings of cohort studies.[5,23] The modification of cancer risk across age groups confirms the earlier onset of hematological cancers in SLE patients;[40] the earlier onset of virus-induced, mainly HPV-related, cancers in female SLE patients[23]; the long-term exposure to medications like cyclophosphamide, azathioprine, and methotrexate[41]; and the earlier comorbidity, damage (SLICC damage index >0) accrual.[42]

A hospitalization for SLE was associated with a 31% increased (multivariate-adjusted) risk of 5-year post-cancer mortality. SLE

TABLE 2 Association between an SLE-related hospitalization with prospective cancer development from 1980 to 2014.

			Unadjusted		Model 1	
	SLE	Comparators	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Prospective cancer development, *n* (%)	426 (20.2)	3664 (17.4)	**1.33 (1.21, 1.48)**	**<.001**	1.03 (0.93, 1.14)	.563
Sex						
Male, *n* (%)	83 (26.4)	789 (22.5)	1.31 (1.05, 1.64)	.019	0.98 (0.78, 1.24)	.862
Female, *n* (%)	343 (19.1)	2875 (16.3)	**1.36 (1.21, 1.52)**	**<.001**	1.07 (0.95, 1.20)	.265
Aboriginality						
Aboriginal Australian, *n* (%)	14 (8.5)	132 (10.4)	1.06 (0.61, 1.85)	.830	0.65 (0.37, 1.14)	.130
Non-Aboriginal Australian, *n* (%)	412 (21.2)	3532 (17.8)	1.35 (1.22, 1.49)	<.001	1.05 (0.943, 1.17)	.377
Age at time zero						
<40, *n* (%)	115 (11.8)	865 (8.4)	**2.05 (1.69. 2.50)**	**<.001**	**1.58 (1.29, 1.94)**	**<.001**
40–49, *n* (%)	77 (20.1)	458 (15.8)	**1.37 (1.07, 1.74)**	**.012**	0.99 (0.76, 1.29)	.928
50–59, *n* (%)	93 (32.2)	621 (23.2)	**1.41 (1.13, 1.75)**	**.002**	**1.41 (1.137, 1.78)**	**.003**
60–69, *n* (%)	79 (32.0)	814 (31.3)	0.99 (0.78, 1.24)	.915	0.95 (0.75, 1.20)	.679
70+, *n* (%)	62 (28.2)	906 (34.3)	**0.86 (0.67, 1.11)**	**.251**	**0.78 (0.60, 1.01)**	**.064**
Year of index SLE hospitalization						
1980–1999, *n* (%)	318 (24.6)	2202 (18.6)	**1.74 (1.55, 1.96)**	**<.001**	**1.16 (1.02, 1.31)**	**.024**
2000–2014, *n* (%)	108 (13.2)	1462 (15.8)	**0.86 (0.70, 1.04)**	**.116**	0.95 (0.78, 1.15)	.580
Cancer sites						
Oral, nasal, and pharyngeal, *n* (%)	22 (1.0)	80 (0.4)	**3.14 (1.95, 5.03)**	**<.001**	**2.13 (1.30, 3.50)**	**.003**
Digestive organs and peritoneum, *n* (%)	75 (3.6)	615 (2.9)	**1.38 (1.09, 1.76)**	**.008**	0.99 (0.77, 1.26)	.902
Esophageal, *n* (%)	9 (0.4)	39 (0.2)	**2.62 (1.27, 5.42)**	**.009**	1.41 (0.66, 3.01)	.370
Stomach, *n* (%)	9 (0.4)	59 (0.3)	1.77 (0.87, 3.57)	.113	1.29 (0.62, 2.67)	.495
Colorectal, *n* (%)	39 (1.8)	396 (1.9)	1.12 (0.80, 1.55)	.517	0.88 (0.63, 1.23)	.460
Hepatobiliary, *n* (%)	11 (0.5)	60 (0.3)	**2.08 (1.09, 3.96)**	**.026**	1.29 (0.66, 2.52)	.450
Pancreatic, *n* (%)	11 (0.5)	73 (0.3)	1.69 (0.90, 3.19)	.105	1.02 (0.53, 1.95)	.965
Respiratory system, *n* (%)	51 (2.4)	297 (1.4)	**1.89 (1.40, 2.54)**	**<.001**	1.23 (0.91, 1.67)	.185
Larynx, *n* (%)	<5 (0.1)	11 (0.1)	2.83 (0.79, 10.13)	.111	–	–
Trachea, bronchus, and lung, *n* (%)	44 (2.1)	261 (1.2)	**1.85 (1.34, 2.55)**	**<.001**	0.99 (0.34, 2.92)	.990
Pleura, mesothelioma, thymus, heart, and mediastinum, *n* (%)	<5 (0.2)	30 (0.1)	1.53 (0.54, 4.35)	.426	1.94 (0.18, 20.82)	.585
Any breast (m/f), *n* (%)	40 (1.9)	635 (3.0)	**0.71 (0.52, 0.98)**	**.035**	0.80 (0.58, 1.10)	.172
Females, *n* (%)	40 (2.2)	632 (3.6)	**0.70 (0.50, 0.95)**	**.024**	0.75 (0.54, 1.04)	.083
Males, *n* (%)	0 (0.0)	<5 (0.1)	–	–	–	–
Female reproductive system, *n* (%)	44 (2.4)	390 (2.2)	**1.50 (1.09, 2.05)**	**.012**	1.09 (0.79, 1.50)	.616
Cervical, *n* (%)	28 (1.6)	212 (1.2)	1.47 (0.99, 2.17)	.058	1.43 (0.95, 2.14)	.087
Uterine, *n* (%)	<5 (0.2)	89 (0.5)	0.50 (0.18, 1.36)	.174	0.39 (0.14, 1.08)	.070
Ovarian, *n* (%)	0 (0.0)	<5 (0.0)	–	–	–	–
Fallopian tube, other uterine adnexa, *n* (%)	0 (0.0)	16 (0.1)	–	–	–	–

TABLE 2 (Continued)

	SLE	Comparators	Unadjusted		Model 1	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
Other, *n* (%)	7 (0.4)	24 (0.1)	**3.57 (1.53, 8.31)**	**.003**	**3.22 (1.34, 7.75)**	**.009**
Male genital system, *n* (%)	9 (2.9)	181 (5.2)	0.62 (0.32, 1.20)	.156	0.56 (0.28, 1.10)	.091
Prostate, *n* (%)	9 (2.9)	175 (5.0)	0.64 (0.33, 1.25)	.192	0.57 (0.29, 1.12)	.102
Testicular, *n* (%)	0 (0.0)	5 (0.1)	–	–	–	–
Urinary system, *n* (%)	20 (0.9)	163 (0.8)	1.40 (0.88, 2.23)	.156	0.96 (0.60, 1.55)	.877
Bladder, *n* (%)	15 (0.7)	115 (0.5)	1.48 (0.86, 2.54)	.155	1.02 (0.58, 1.77)	.955
Kidney, renal pelvis, and ureter, *n* (%)	8 (0.4)	55 (0.3)	1.69 (0.80, 3.54)	.169	1.31 (0.52, 2.45)	.755
Musculoskeletal, *n* (%)	12 (0.6)	47 (0.2)	**2.97 (1.57, 5.61)**	**.001**	**2.26 (1.16, 4.40)**	**.016**
Bone and joints, *n* (%)	<5 (0.1)	8 (0.0)	**4.17 (1.10, 15.73)**	**.035**	–	–
Soft tissue, *n* (%)	9 (0.4)	39 (0.2)	**2.71 (1.31, 5.61)**	**.007**	**2.15 (1.01, 4.58)**	**.049**
Skin, *n* (%)	152 (7.2)	1334 (6.3)	**1.36 (1.15, 1.61)**	**<.001**	1.18 (0.99, 1.40)	.064
Melanoma, *n* (%)	11 (0.5)	101 (0.5)	1.23 (0.66, 2.30)	.509	1.06 (0.56, 2.00)	.868
Non-melanoma of the skin, *n* (%)	150 (7.1)	1307 (6.2)	**1.37 (1.16, 1.63)**	**<.001**	**1.20 (1.01, 1.43)**	**.041**
Nervous system, *n* (%)	13 (0.6)	85 (0.4)	1.76 (0.98, 3.16)	.058	1.39 (0.76, 2.55)	.282
Brain, *n* (%)	6 (0.3)	57 (0.3)	1.20 (0.52, 2.78)	.673	0.80 (0.34, 1.89)	.607
Other nervous system, *n* (%)	7 (0.3)	29 (0.1)	**2.84 (1.24, 6.49)**	**.014**	**2.66 (1.13, 6.27)**	**.026**
Eye, *n* (%)	<5 (0.2)	8 (0.0)	**5.15 (1.55, 17.10)**	**.007**	–	–
Thyroid (plus thymus), *n* (%)	8 (0.4)	61 (0.3)	1.54 (0.73, 3.21)	.255	1.32 (0.61, 2.82)	.483
Other sites, *n* (%)	117 (5.5)	955 (4.5)	**1.36 (1.12, 1.65)**	**.002**	1.04 (0.85, 1.27)	.701
HPV-related cancer, *n* (%)	82 (3.9)	653 (3.1)	**1.41 (1.12, 1.78)**	**.003**	**1.43 (1.13, 1.80)**	**.003**
Kaposi sarcoma, *n* (%)	0 (0.0)	<5 (0.0)	–	–	–	–
Cancer—excluding hematological cancers, *n* (%)	415 (19.7)	3610 (17.1)	**1.32 (1.19, 1.46)**	**<.001**	**1.28 (1.16, 1.42)**	**<.001**
Hematological, *n* (%)	40 (1.9)	198 (0.9)	**2.25 (1.60, 3.16)**	**<.001**	**1.78 (1.25, 2.53)**	**.001**
Hodgkin's disease, *n* (%)	<5 (0.1)	9 (0.0)	3.67 (0.99, 13.60)	.052	–	–
Non-Hodgkin lymphoma, *n* (%)	25 (1.2)	103 (0.5)	**2.71 (1.75, 4.20)**	**<.001**	**2.31 (1.46, 3.64)**	**<.001**
Multiple myeloma, *n* (%)	<5 (0.2)	32 (0.2)	1.36 (0.48, 3.86)	.558	–	–
Leukemias, *n* (%)	21 (1.0)	130 (0.6)	**1.86 (1.18, 2.96)**	**.008**	1.26 (0.78, 2.03)	.351

Note: HR (95% CI), Hazard ratio with 95% confidence intervals; <5, actual numbers confidentialized to maintain patient privacy; Model 1, prevalent cancer, modified CCI items, and smoking status.

Bolded results are significantly different across SLE and controls, $p < .05$.

patients had equivalent risk of 5-year post-cancer mortality across the sexes and study period (1980–1999 vs. 2000–2014), but was higher in non-Aboriginal Australians, and those 40–49 years old. Although comparable studies are limited with respect to mortality after cancer development, our findings aligned with an SLE-specific study,[43] and a broader sample of patients with rheumatic diseases.[44] Our data suggest that virus-induced cancers,[45] especially HPV-related cancer of the oropharynx, skin, vulvo-vaginal area, and prostate, may have worse survival in SLE patients compared with controls. Although the mechanisms require further study to delineate the role of case-complexity and treatment challenges, including an increased risk of severe adverse drug reactions in SLE patients undergoing chemotherapeutic treatments, especially infection in the link between virus-induced cancers and premature mortality.

In line with the literature, we showed that SLE patients had an increased risk of developing HPV-related cancers over time.[2,46-49] This was driven by a twofold risk of developing oropharyngeal cancers, and a threefold risk of developing vulvo-vaginal cancers with risk higher compared with controls, underwritten by a higher burden of viral infections, especially herpesviruses, and risk factors

TABLE 3 Association between cancer development and 5-year mortality in SLE patients compared with general population comparators.

			Unadjusted		Model 1		Model 2	
	SLE	Controls	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Post-cancer mortality, *n* (%)								
Overall	213 (50.0)	1427 (38.9)	1.38 (1.19, 1.59)	**<.001**	**1.67 (1.44, 1.93)**	**<.001**	**1.31 (1.12, 1.52)**	**.001**
1 year	51 (12.0)	460 (12.6)	0.98 (0.73, 1.30)	.868	1.11 (0.83, 1.49)	.469	0.95 (0.70, 1.28)	.726
3 years	96 (22.5)	664 (18.1)	**1.29 (1.04, 1.60)**	**.020**	**1.48 (1.20, 1.84)**	**<.001**	**1.26 (1.01, 1.58)**	**.042**
5 years	112 (26.3)	757 (20.7)	**1.33 (1.09, 1.62)**	**.005**	**1.56 (1.28, 1.91)**	**<.001**	**1.31 (1.06, 1.61)**	**.012**
5-year post-cancer mortality, by age group, *n* (%)								
<40	6 (12.0)	17 (5.2)	**2.64 (1.04, 6.70)**	**.041**	**2.62 (1.02, 6.69)**	**.045**	1.02 (0.34, 3.00)	.978
40–49	8 (13.3)	24 (6.2)	**2.45 (1.10, 5.45)**	**.029**	**2.67 (1.19, 5.97)**	**.017**	**3.51 (1.38, 8.90)**	**.008**
50–59	19 (21.1)	64 (10.0)	**2.27 (1.36, 3.79)**	**.002**	**1.90 (1.13, 3.20)**	**.016**	1.37 (0.76, 2.46)	.293
60–69	21 (20.8)	162 (19.2)	1.02 (0.65, 1.61)	.920	0.96 (0.61, 1.52)	.876	0.80 (0.49, 1.31)	.376
70+	58 (46.4)	490 (33.5)	**1.56 (1.19, 2.05)**	**.001**	**1.60 (1.22, 2.11)**	**.001**	**1.43 (1.08, 1.89)**	**.012**
5-year post-cancer mortality, by Aboriginality, *n* (%)								
Aboriginal Australian	5 (35.7)	43 (32.6)	1.12 (0.44, 2.83)	.809	1.43 (0.56, 3.70)	.456	0.99 (0.37, 2.63)	.979
Non-Aboriginal Australian	107 (26.0)	714 (20.2)	**1.34 (1.09, 1.64)**	**.005**	**1.59 (1.29, 1.95)**	**<.001**	**1.38 (1.11, 1.70)**	**.004**
5-year post-cancer mortality, by sex, *n* (%)								
Males	28 (33.7)	212 (26.9)	1.32 (0.89, 1.96)	.163	**1.56 (1.05, 2.33)**	**.030**	1.36 (0.90, 2.05)	.142
Females	84 (24.5)	545 (19.0)	**1.35 (1.07, 1.69)**	**.011**	**1.56 (1.23, 1.96)**	**<.001**	**1.29 (1.01, 1.65)**	**.041**
5-year post-cancer mortality, by year of cancer development (after time zero), *n* (%)								
1980–1999	50 (41.7)	227 (27.8)	**1.60 (1.18, 2.17)**	**.003**	**1.78 (1.31, 2.42)**	**<.001**	**1.68 (1.21, 2.34)**	**.002**
2000–2015	62 (20.3)	530 (18.6)	1.12 (0.86, 1.46)	.383	**1.41 (1.08, 1.84)**	**.011**	1.12 (0.85, 1.47)	.431

Note: Model 1, age, sex, and year of cancer development. Model 2, Model 1 + smoking status + Charlson Comorbidity Index items (0 = 0, 1 = 1–2 items, and 2 = 3 or more items), and prevalent cancer.

Bolded results are significantly different across SLE and controls, $p < .05$.

including smoking and alcohol consumption in SLE patients.[50,51] The inclusion of smoking in the multivariate model did not attenuate the risk of HPV-related cancers herein. Given the lack of evidence to link oro-mucocutaneous or vulvar (occurring in <5% of SLE patients) disease manifestations to cancer development in SLE,[52] this would suggest that viral infections could be linked to cancer development in SLE patients.[46] In line with the literature, we found an excess 5-year mortality in SLE patients who developed HPV-related, genital and non-melanoma skin cancers.[53,54] In the context of rising prevalence of HPV-related oropharyngeal cancer in Australia[55]; and, that only 7.0% of SLE patients and 4.5% of controls herein would have qualified for the school-aged (ongoing) or community-based (ceased in 2009) rollout of the HPV vaccination program in Australia,[56] our data suggest that preventative measures, including HPV vaccination, smoking cessation, and routine screening should be recommended to reduce the risk of virus-induced, e.g. HPV-related, cancers, especially in SLE patients.

The 20% increased risk of developing non-melanoma skin cancer in SLE patients aligns the findings of a meta-analysis,[2] and confirms data from a Danish SLE cohort study from 1951 to 2006.[23] In SLE, the association of cutaneous disease activity, particularly rashes and photosensitivity, with skin cancer development is yet to be fully elucidated. Possible explanations for the increased risk of skin cancer in SLE patients, include: (a) surveillance bias, due to more regular

TABLE 4 Relative risk of 5-year mortality after cancer development in patients with systemic lupus erythematosus and general population comparators, by cancer site.

			Unadjusted	Model 1	Model 2
	SLE	Controls	HR (95% CI)	HR (95% CI)	HR (95% CI)
5-year mortality by cancer site					
Oral, nasal, and pharyngeal, *n* (%)	11 (50.0)	32 (40.0)	1.34 (0.67, 2.66)	1.61 (0.78, 3.33)	1.10 (0.51, 2.35)
Digestive organs and peritoneum, *n* (%)	41 (54.7)	368 (59.8)	0.85 (0.62, 1.17)	1.12 (0.80, 1.56)	1.09 (0.77, 1.55)
Esophageal, *n* (%)	6 (66.7)	32 (82.1)	**0.40 (0.16, 0.97)**	0.60 (0.21, 1.72)	–
Stomach, *n* (%)	5 (55.6)	41 (69.5)	0.63 (0.25, 1.59)	0.72 (0.28, 1.86)	–
Colorectal, *n* (%)	17 (43.6)	186 (47.0)	0.87 (0.53, 1.43)	1.29 (0.77, 2.15)	1.22 (0.72, 2.07)
Hepatobiliary, *n* (%)	9 (81.8)	51 (85.0)	1.27 (0.62, 2.61)	1.72 (0.81, 3.66)	1.69 (0.75, 3.83)
Pancreatic, *n* (%)	9 (81.8)	67 (91.8)	1.14 (0.56, 2.30)	1.17 (0.55, 2.50)	1.21 (0.51, 2.87)
Respiratory system, *n* (%)	38 (74.5)	250 (84.2)	0.70 (0.50, 0.98)	0.73 (0.51, 1.04)	0.72 (0.50, 1.03)
Larynx, *n* (%)	1 (33.3)	6 (54.5)	–	–	–
Trachea, bronchus, and lung, *n* (%)	34 (77.3)	220 (84.3)	0.75 (0.52, 1.08)	0.79 (0.55, 1.14)	
Pleura, mesothelioma, thymus, heart, and mediastinum, *n* (%)	3 (75.0)	29 (96.7)	–	–	–
Breast (m/f), *n* (%)	14 (35.0)	118 (18.6)	1.77 (0.86, 3.65)	1.47 (0.71, 3.06)	0.67 (0.30, 1.51)
Females, *n* (%)	14 (35.0)	117 (18.5)	1.77 (0.86, 3.65)	1.47 (0.71, 3.06)	0.67 (0.30, 1.51)
Males, *n* (%)	0 (100.0)	1 (33.3)	–	–	–
Female reproductive system, *n* (%)	19 (43.2)	114 (29.2)	1.8 (0.91, 2.40)	**2.16 (1.31, 3.54)**	**1.78 (1.05, 3.01)**
Cervical, *n* (%)	7 (25.0)	15 (7.1)	**4.58 (1.87, 11.25)**	–	–
Uterine, *n* (%)	2 (50.0)	23 (25.8)	2.87 (0.67, 12.26)	–	–
Ovarian, *n* (%)	0 (0.0)	<5 (100.0)	–	–	–
Fallopian tube, other uterine adnexa, and other, *n* (%)	0 (0.0)	9 (56.3)	–	–	–
Other, *n* (%)	5 (71.4)	6 (25.0)	–	–	–
Male genital system, *n* (%)	6 (66.7)	60 (33.1)	**2.52 (1.09, 5.84)**	**4.25 (1.72, 10.47)**	**3.57 (1.44, 8.84)**
Prostate, *n* (%)	6 (66.7)	60 (34.3)	**2.41 (1.04, 5.58)**	**3.85 (1.57, 9.45)**	**3.18 (1.29, 7.85)**
Testicular, *n* (%)	0 (0.0)	0 (0.0)	–	–	–
Other male and penis, *n* (%)	0 (0.0)	<(50.0)	–	–	–
Urinary system, *n* (%)	8 (40.0)	73 (44.8)	0.79 (0.38, 1.65)	0.97 (0.46, 2.05)	0.85 (0.39, 1.86)
Bladder, *n* (%)	6 (40.0)	54 (47.0)	0.72 (0.31, 1.66)	0.86 (0.36, 2.06)	–
Kidney, renal pelvis, and ureter, *n* (%)	5 (62.5)	23 (41.8)	1.66 (0.63, 4.37)	–	–
Musculoskeletal, *n* (%)	4 (33.3)	31 (66.0)	0.36 (0.13, 1.04)	–	–
Bone and joints, *n* (%)	2 (66.7)	5 (62.5)	–	–	–

(Continues)

TABLE 4 (Continued)

	SLE	Controls	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Soft tissue, *n* (%)	2 (22.2)	24 (61.5)	–	–	–
Skin, *n* (%)	31 (20.4)	162 (12.1)	**1.76 (1.20, 2.58)**	**2.57 (1.74, 3.80)**	**2.05 (1.36, 3.11)**
Melanoma, *n* (%)	4 (36.4)	33 (32.7)	–	–	–
Non-melanoma of the skin, *n* (%)	29 (19.3)	144 (11.0)	**1.84 (1.24, 2.74)**	**2.79 (1.86, 4.20)**	**2.18 (1.41, 3.36)**
Nervous system, *n* (%)	7 (53.8)	50 (58.8)	0.86 (0.39, 1.89)	0.85 (0.39, 1.89)	–
Brain, *n* (%)	4 (66.7)	43 (75.4)	–	–	–
Other nervous system, *n* (%)	3 (42.9)	7 (24.1)	–	–	–
Eye, *n* (%)	4 (100.0)	3 (37.5)	–	–	–
Thyroid plus thymus, *n* (%)	0 (0.0)	10 (16.4)	–	–	–
Other sites, *n* (%)	89 (76.1)	654 (68.5)	1.12 (0.90, 1.39)	**1.29 (1.02, 1.62)**	1.10 (0.86, 1.40)
HPV-related cancer, *n* (%)	32 (39.0)	178 (27.3)	**1.67 (1.15, 2.44)**	**2.35 (1.59, 3.46)**	**1.64 (1.10, 2.45)**
Kaposi sarcoma, *n* (%)	0 (0.0)	0 (0.0)	–	–	–
Cancer—excluding hematological cancers, *n* (%)	155 (37.3)	1064 (29.5)	**1.32 (1.11, 1.56)**	**1.58 (1.34, 1.88)**	**1.26 (1.05, 1.50)**
Hematological, *n* (%)	21 (52.5)	96 (49.2)	0.96 (0.60, 1.54)	1.17 (0.72, 1.89)	1.02 (0.61, 1.69)
Hodgkin's disease, *n* (%)	1 (33.3)	1 (11.1)	–	–	–
Non-Hodgkin lymphoma, *n* (%)	11 (44.0)	45 (44.1)	0.81 (0.42, 1.57)	1.28 (0.63, 2.58)	–
Multiple myeloma, *n* (%)	2 (50.0)	20 (62.5)	1.00 (0.23, 4.30)	–	–
(a)Leukemias, *n* (%)	11 (52.4)	73 (56.2)	0.87 (0.46, 1.64)	1.00 (0.52, 1.91)	0.95 (0.48, 1.89)

Note: Data represent the frequency and % of deaths per cancer site (cell denominator take from Table 3) within study groups. Model 1: age, sex, and year of cancer development. Model 2: Model 1 + smoking status + Charlson Comorbidity Index items (0 = 0, 1 = 1–2 items, and 2 = 3 or more items), and prevalent cancer.

Bolded results are significantly different across SLE and controls, $p < .05$.

patient follow up in patients with chronic diseases with cutaneous manifestations;[22] (b) immunosuppressive medication use, as seen in other immune-mediated diseases and transplant recipients[57]; and, (c) the oncogenic capabilities of HPV to induce skin (as well as other) cancer(s).[58] Additionally, as the majority of SLE patients in our research setting are of European ancestry (>67.5%, https://www.abs.gov.au/census/find-census-data/quickstats/2016/5), they would be more susceptible to skin cancer development given the very high levels of background UV radiation in WA. Importantly, SLE patients had twice the risk of 5-year mortality after skin cancer development, which conventionally has excellent 5-year survival (>95%). Therefore, the worsened 5-year mortality in SLE patients after developing skin cancer may reflect exacerbated cancer severity induced by susceptibility to viral infection or SLE-specific factors, including treatment effects, and case-complexity related to comorbidity in SLE cohorts, which requires further study. Hence, in the absence of clear evidence of an SLE-specific mechanism, clinicians should still advise their patients to practice maximum sun protection habits and have annual skin cancer screening.

Hospitalized SLE patients had similar breast cancer risk to healthy females, which aligns with other studies.[59,60] This fits with the data showing that SLE patients have some attributes that confer protection against breast cancer development, including developing fewer estrogen-receptor-negative breast cancers, which are typically under-represented in SLE patients, especially older women[61]; data which indicates that cell-penetrating autoantibodies may have some anti-cancer effects[59]; and, that increased cumulative doses of antimalarial medications may protect against breast cancer development.[62] However, as lower risk does not equate to no risk, and as breast cancer is still the second highest cause of cancer-related mortality in Australia, it is important that SLE patients undertake routine breast cancer screening.

In line with the current literature, male SLE patients had no increased risk of prostate cancer.[2] Some have suggested a reduced risk of prostate cancer in male SLE patients can be related to hypoandrogenic states and genetic factors.[63] Another hypothesis is that, heat-shock protein-27, which is implicated in prostate cancer progression and metastases, was found to be decreased among

SLE patients with autoantibodies to extractable nuclear antigens.[64] Furthermore, the long-term use of hydroxychloroquine, via osmosis into the prostate,[65] may have antitumor effects through its ability to regulate the autophagosome and induce apoptosis in cancer cells.[66] However, contrary to the good 5-year survival reported in the general population, we found that SLE patients with prostate cancer had a fourfold increased risk of 5-year mortality. Further research would need to address the role of increased comorbidity including, obesity, and the higher burden of viral infections on post-cancer survival in SLE patients.

Systemic lupus erythematosus patients had an increased risk of developing cancers of the musculoskeletal system, especially soft-tissue sarcomas ($n=9$). The existing data on these rare and heterogeneous cancers in SLE are scarce. One study reported an increased standardized incidence ratio of soft-tissue sarcomas in SLE patients, based on two events.[5] Soft-tissue sarcomas have also been linked to genetics, viruses (herpesvirus 8), Kaposi sarcoma (although we found no herein), and environmental exposures.[67] Hence, although we suspect that soft-tissue sarcomas are being driven by a higher viral infection burden in SLE patients; the mechanisms by which these rare and heterogeneous cancer types develop in SLE patients requires further study.

We showed that SLE patients had twice the risk of developing cancer of the meninges and spine, but not the brain (cerebrum/cerebellum). The lack of association between SLE and brain cancer confirms existing data,[2] but there are some data to suggest that SLE patients are susceptible to developing meningioma.[68] We did not find an increased odds of viral infections of the central nervous system at time zero. Although, it is unclear what underlies the potential mechanism between SLE and these rare cancers, future studies could investigate the role of neuropsychiatric disease activity and cancer development of the nervous system.

Hospitalized SLE patients had a 78% increased risk of developing hematological cancer, similar to a meta-analysis,[2] an international multi-centered cohort study,[23] and others.[60,69] Driving this association was the increased risk of non-Hodgkin's lymphomas. Although others have shown increased risk of lymphoma, multiple myeloma, and leukemias,[60] our study had too few end points to produce robust estimates for comparison. Although the mechanism is not fully clear, the increased risk of non-Hodgkin's lymphoma in SLE has been replicated many times[2,5,23] while the association between SLE and Hodgkin's lymphoma, multiple myeloma and leukemias, is less certain. As our data account for comorbidity, prevalent cancer, and smoking status, the mechanisms underlying the increased risk of developing lymphatic cancer may be driven by SLE-specific factors including, chronic inflammation causing carcinogenesis, uncontrolled activation of autoreactive T and B lymphocytes,[70] the defective clearance of apoptotic cells,[71] cumulative prednisone and cyclophosphamide dosages,[72] or viral inducers.[46] Further studies should investigate the association between the use of the B-cell-depleting agent (rituximab) for SLE with lymphatic and hematopoietic cancer development. Rituximab can increase B-cell-activating factor levels, which is a risk factor for lymphoma; and, reduce APRIL (a proliferation-inducing ligand) levels, which were increased in cancerous tissue.[73] Although the 5-year post-cancer mortality risk was not increased in SLE patients with lymphatic and hematopoietic cancer, we previously demonstrated that SLE patients had increased risk of 20-year hematological cancer-related mortality,[1] which aligned with other SLE studies that investigated the effect of cancer on mortality in post-hoc analyses.[74] Early-stage lymphoma and SLE share similar clinical (lymphadenopathy occurs in up to 67% of SLE patients) and hematological findings, including neutropenia, low complement, and cryoglobulinemia; and the use of cyclophosphamide and high cumulative doses of corticosteroid are risk factors for developing lymphoma.[75] Hence, persistent lymphadenopathy and/or abnormal immunophenotyping in SLE patients should prompt screening for lymphoma.

4.1 | Strengths and limitations

The limitations of this study pertain to the identification of SLE patients who required hospital services, i.e. Emergency Department presentations and hospital admissions for any reason; this meant that we might not have captured all SLE cases, especially those managed solely in the primary (community) or secondary healthcare settings, namely public or private specialist centers. Furthermore, by identifying our SLE sample from administrative health data there is a low probability that we have included patients with other immune-mediated connective-tissue diseases;[16] therefore our results may not reflect the true risk of cancer in all SLE patients in WA. Another limitation is that administrative health data are not designed to report on the conventional SLE-specific variables that are reported in cohort studies, which includes indices of disease activity and damage accrual, and reporting of medication use, especially oral glucocorticoid use. Additionally, due to the lack of laboratory data, we could not ascertain whether our patients met the classification criteria for SLE. In spite of this potential selection bias, our cancer development estimates were similar to a range of clinical, cohort, and registry studies arising from different healthcare settings. The lack of laboratory findings was also a limitation in assessing whether certain autoantibody profiles conferred protection against cancer, as previously suggested.[59] Furthermore, the WARDER does not contain medication data, in particular type and duration of treatment, which limited our ability to determine whether medications were influencing cancer development or 5-year mortality thereafter. Another limitation is the lack of available information to define the ethnicity of non-Aboriginal Australians into Asian, European, or other sub-groups of interest. The relative strength and stability of our estimates are ensured by the ability to identify a large number of SLE patients during a 35-year period, which allowed for an average of 9 years of lookback and 14 years of follow up. In addition, as less than 10% of SLE patients go without hospitalization over an 11-year period, we are likely to have captured nearly all SLE patients in our study period, which spans three decades.[17] Additionally, we ascertained complete cancer development data from the WA Cancer and Death Registries, which

captures all cancer notifications statewide and diagnoses reported on the death certificate, ensuring that we accurately identified cancer end points for all patients.

Systemic lupus erythematosus patients were at increased risk of some but not all cancer types compared with the general population. Clinicians should be particularly aware of the increased risk of virus-induced cancers, particularly of the oropharyngeal and vulvovaginal areas; as well as, the increased risk of soft-tissue sarcoma, non-melanoma skin cancer, and non-Hodgkin's lymphoma over time. SLE patients had increased risk of 5-year mortality after cancer development, with the highest risk in those under 50 years old, and those with skin or prostate cancer.

AUTHOR CONTRIBUTIONS

The authors are responsible for the content and writing of the paper. Authors (WDR, DBP, HK, CAI, JCN) had access to the data in this study and WDR takes complete responsibility for the integrity and accuracy of the data analysis.

ACKNOWLEDGEMENTS

The authors wish to thank the staff at the Western Australian Data Linkage Branch and Emergency Department Data Collection, Hospital Morbidity Data Collection, Western Australian Cancer Registry, and Death Registrations. The authors wish to thank the Australian Co-ordinating Registry, the Registries of Births, Deaths and Marriages, the Coroners, the National Coronial Information System, and the Victorian Department of Justice and Community Safety for enabling COD URF data to be used for this publication. Open access publishing facilitated by The University of Western Australia, as part of the Wiley - The University of Western Australia agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

This work was supported by an unrestricted grant from the Arthritis and Osteoporosis Foundation of Western Australia (JCN) and Arthritis Australia (WDR, DP, HK and JCN received an unrestricted Australian Project Grant). WDR received a PhD Scholarship in Memory of John Donald Stewart, the Gabrielle Vitale Memorial Fund Grant from the Lupus Group of Western Australia, and the Australian Rheumatology Association (Western Australia branch) Research & Training Scholarship.

CONFLICT OF INTEREST STATEMENT

The authors declare that they hold no conflict(s) of interest in relation to this study or its findings.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as Supporting Information.

ETHICAL APPROVAL

This study was approved by the WA Health HREC approval no. 2016/24.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Raymond WD, Preen DB, Keen HI, Inderjeeth CA, Nossent JC. Cancer development in patients hospitalized with systemic lupus erythematosus: A population-level data linkage study. *Int J Rheum Dis*. 2023;26:1557-1570. doi:10.1111/1756-185X.14784