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Comparison of breast cancer risk in women with and without systemic lupus erythematosus in a Medicare population

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Abstract

Studies have suggested a decreased breast cancer risk in women with systemic lupus erythematosus. However, these studies enrolled younger patients identified primarily from lupus clinics. We compared the 5-year incidence of breast cancer among women with and without a diagnosis of SLE in a large population-based study of Medicare beneficiaries. We used a 20 % sample to create a cohort of 3,670,138 women from 2006 Medicare claims data with and without SLE at baseline. The study had 80 % power to detect whether the 5-year breast cancer incidence in the SLE cohort was 13 % higher or lower than the non-SLE cohort. Of the 18,423 women with SLE, 21 % were African American and 53 % were ≥ 65 years. The absolute age-adjusted risk for breast cancer in women with SLE was 2.23 (95 % CI 1.94–2.55) and 2.14 (95 % CI 1.96–2.34) in controls per 100 women. The overall absolute age and race adjusted incidence rate was 1.04 (95 % CI 0.90–1.21). Among women with SLE from “Others” (Hispanic, Native American, and/or Asian), the age-adjusted risk for breast cancer was 2.44 per 100 women (95 % CI 1.07–2.18), and age-adjusted incidence rate was 1.52 (95 % CI 1.07–2.18). In contrast to prior clinic-based studies, this population-based cohort study showed that the risk of breast cancer in women with SLE was not lower than in women without SLE. Women with SLE should follow routine breast cancer screening recommendations for their age group to avoid delay in diagnosis, because the presence of SLE may affect selection of early breast cancer therapies.

Keywords

Systemic lupus erythematosus; Breast cancer risk; Medicare claims data

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem inflammatory autoimmune disease with an estimated prevalence in the United States of 161,000 and 322,000 for “definite” and “definite plus probable” cases, respectively [1, 2]. SLE predominantly affects African-American women (female:male 8:1; African American:Caucasian 4:1) between their 2nd to 4th decade. As survival rates have improved steadily in recent years (5 and 10-year survival >90 and 85 %, respectively), patients are now more at risk for comorbidities including malignancies [3–5]. Although a higher than usual risk of hematologic malignancies, lung, liver, cervix, kidney, nasopharynx, and vagina/vulva cancers have been reported in patients with SLE [5–9], controversy exists about the risk for breast cancer, which is particularly salient as most SLE patients are women [5, 10, 11].

Studies evaluating breast cancer risk among SLE patients have been either retrospective clinical reviews or cohorts assembled almost entirely from rheumatology or lupus practices. Results have varied, with a recent emphasis on registry-based studies showing a lower risk for breast cancer in SLE women [5, 6, 9, 11–14]. However, earlier studies also reported an increased risk [8, 15–17], or no risk difference for breast cancer among women with SLE compared to women in general population [7, 18–21]. Small numbers of cases likely limited the ability of these studies to generalize the breast cancer risk to the entire SLE population who may or may not be cared for in specialty clinics. Despite the controversy about breast cancer risk, breast cancer is still the most commonly diagnosed cancer among women with SLE and constitutes a large portion of their overall cancer burden. Thus understanding the true breast cancer risk among all SLE women is important because it affects breast cancer prevention. Early discovery and treatment may be particularly important in women with SLE as therapy selections may be affected by the presence of the autoimmune disease. Our study aim was to overcome the limitations of the previous studies (number of cases, study design, and ascertainment) by estimating breast cancer incidence and risk ratio among women with and without SLE identified at baseline and followed forward in a large population-based older cohort at the greatest risk of breast cancer. To the best of our knowledge, this study offers the largest population-based cohort and the largest number of SLE patients for the evaluation of the risk of breast cancer.

Methods

A randomly drawn 20 % sample of the Medicare claims dataset from 2006 was used as the primary study population source. The ascertained sample showed the same overall characteristics as the overall dataset. The SLE cohort was identified as Medicare beneficiaries with at least two carrier or hospital outpatient claims or a single inpatient claim with a diagnosis of SLE (ICD-9-CM 710.0x). The incidence of breast cancer was determined by the Chronic Condition Warehouse criteria for a breast cancer diagnosis. These criteria are similar to those used for identification of other studies of chronic diseases in administrative claims data [22]. The risk of beneficiary misclassification is low as validation studies using Medicare physician claims data reported 85 % sensitivity for SLE claims using the medical record as the gold standard [23, 24]. Beneficiaries were excluded if they were men, had a claim history of breast cancer in 2006 or during prior years, died

during 2006, or had HMO coverage at any point during 2006. This resulted in a SLE cohort of 18,423 beneficiaries (Fig. 1). The control cohort (3,651,715) consisted of women free of SLE using the same exclusions as for the SLE cohort (Fig. 1). Given the sample sizes and the cumulative incidence of breast cancer in the non-SLE cohort, a priori, this study has 80 % power to detect whether the 5-year incidence in the SLE cohort was 13 % (RR 1.13, 0.87) higher or lower, respectively, than the non-SLE cohort, with confidence intervals that do not pass unity, essentially the same as being statistically significant at the $p < 0.05$ level.

Descriptive statistics were generated for the ascertained entire cohort as well as for members of the cohort diagnosed with cancer during the study period. Incidence rates for breast cancer were defined for women meeting the Chronic Condition Warehouse criteria for a breast cancer diagnosis during any year from 2007 to 2011 (1 inpatient/skilled nursing facility or two hospital outpatient/carrier claims during a 1-year period). Crude incidence rates and the incidence ratio for breast cancer were calculated for women with SLE and control cohorts, women under age 65 years or 65 and above and by race (Caucasian, African American, and others). Negative binomial regression was used to calculate the incidence rate and ratios for SLE and control cohorts with adjustment for age and race.

Results

Of the total of 24,369 possible SLE patients in the cohort, 86 % met the carrier claims criteria with a small percentage included through the hospital outpatient (3.2 %) or inpatient (11 %) inclusion criteria. All male patients (14 %), patients with history for breast cancer (4.7 %), patients with HMO coverage (2.4 %), and patients who died in 2006 (3.6 %) were excluded to obtain the eligible SLE cohort of 18,423 women (Fig. 1).

Breast cancer incidence rate and risk ratio

Among women with SLE, the overall and age/race adjusted absolute breast cancer incidence was 2.26 (95 % CI 2.05–2.48) and 2.23 (95 % CI 1.94–2.55) per 100 women over 5 years, respectively. The overall and age/race adjusted absolute incidence rate of breast cancer for women without SLE was 2.59 (95 % CI 2.57–2.61) and 2.14 (95 % CI 1.95–2.34) per 100 women over 5 years, respectively. The age-adjusted breast cancer incidence rate for Caucasians, African Americans and Others (Asian, Hispanic, North American Native, and unknown) with SLE was 2.41 (95 % CI 2.16–2.69), 1.97 (95 % CI 1.55–2.50), and 2.44 (95 % CI 1.71–3.47) per 100 women over 5 years of follow-up, respectively. The overall age-adjusted breast cancer incidence for Caucasians, African Americans and Others (Asian, Hispanic, North American Native, and unknown) without SLE (control) was 2.54 (95 % CI 2.52–2.56), 2.18 (95 % CI 2.13–2.24), and 1.60 (95 % CI 1.46–1.75) per 100 women over 5 years, respectively (Table 1).

While the overall unadjusted risk ratio for breast cancer was 0.87 (95 % CI 0.79–0.96), after adjustment for age and race, the adjusted breast cancer risk ratio was not significant, 1.04 (95 % CI 0.90–1.21) (Table 2). When stratified by race, similar trends were seen; the unadjusted risk ratio was 0.75 (95 % CI 0.59–0.95) with an age-adjusted risk ratio of 0.90 (95 % CI 0.71–1.15) among African Americans. Among Caucasians, the unadjusted breast cancer risk ratio was 0.89 (95 % CI 0.80–0.99) and age-adjusted risk was not statistically

significant, 0.95 (95 % CI 0.85–1.06). We found an increased risk ratio for breast cancer for the ethnic group “Others” [Asian, Hispanic, North American Native, and unknown] unadjusted 1.44 (95 % CI 0.98–2.29) and age adjusted 1.52 (95 % CI 1.07–2.18). However, this smaller-sized sample category had only few breast cancer diagnoses ($N = 33$; 8 %).

We also examined breast cancer incidence rates by stratifying the data into two age groups, 65 years or older and younger than 65 years. Among women with SLE 65 years and under 65 of age, the age/race adjusted breast cancer incidence was 2.54 (95 % CI 2.14–3.01) and 1.60 (95 % CI 1.35–1.90) per 100 women over 5 years, respectively. Similarly among women without SLE (control group) 65 years and under 65 of age, the age/race adjusted breast cancer incidence was 2.54 (95 % CI 2.28–2.83) and 1.55 (95 % CI 1.47–1.64) per 100 women over 5 years, respectively. The incidence of breast cancer per 100 women over 5 years by race was also calculated for these two age groups (Table 1).

When women 65 years of age were examined, the unadjusted and age/race adjusted risk ratios for breast cancer were 0.99 (95 % CI 0.89–1.11) and 1.00 (95 % CI 0.82–1.22), respectively. Similarly, SLE women under 65 years had no difference in the risk of breast cancer than women without SLE [unadjusted risk ratio 0.98 (95 % CI 0.83–1.15); age/race adjusted risk ratio 1.03 (95 % CI 0.87–1.22)]. Interestingly, the age-adjusted higher risk ratio for breast cancer persisted for the ‘Other’ category for age group 65 years only (Table 2).

Discussion

In this large population-based cohort identified from Medicare claims data, heavily skewed toward older women who are at greater risk for breast cancer, we found that the 5-year risk of incident breast cancer among women with SLE is similar to women in the general population, in contrast to published results from recent specialty clinic-based and SLE registry cohorts. We further found that when examined across racial groups, the risk of breast cancer in women with SLE is similar to women without SLE in both Caucasian and African women. Surprisingly, we found that the risk of breast cancer may be higher in women with SLE from Hispanic, Native American, and/or Asian ethnicities. To our knowledge this is the largest population-based study that has examined the risk of breast cancer among women from Hispanic, Native American, and/or Asian ethnicities with SLE compared to women without SLE, although this comparison is low power with few cases and may not be as robust as the other subgroup analyses.

Several factors may be responsible for the discordant results between our study and previously reported clinic-based and registry studies. The clinic-based cohorts were assembled both prospectively and retrospectively by enrolling SLE patients from outpatient clinics or from hospital discharge registries. SLE patients were generally younger and not draw a priori from a general population making comparisons difficult. Valid comparable control groups for this population are notoriously difficult to define and likely come from a different underlying population distribution than the SLE patients. The largest assembled clinic-based registry cohort has consistently reported a lower risk of breast cancer in women with SLE [9], which could have profound implications for breast cancer screening among

women with lupus, or may affect an index of suspicion for breast cancer among clinicians. Interestingly results from these clinical-based studies [9] underestimated the breast cancer risk by excluding in situ breast cancers cases from the clinical cohort [25] analysis and did not note this exclusion. This made it difficult to calculate the correct expected number of cases for standardized incidence ratio (SIR) analysis. Notably, however, clinic-based SLE cohorts are limited by selection bias wherein patients (or treating physicians) self-select themselves for follow-up at a specialty clinic and may thus have different exposures or disease characteristics than those found along all SLE patients who do not seek such care. Such differences may include differences in socioeconomic status, general health care, or possibly even greater use of immunomodulators.

As noted, a major limitation of clinic-based or registry cohort is the lack of a true control group within the study population itself. Most such studies have used standardized populations with the assumption that the exposure-profile of SLE women enrolled from clinics is similar to any standardized population. Lack of ethnic diversity and utilization of data from non-population-based (non-representative) registries are among other limitations of the prior smaller clinical cohort studies.

Similar to our study, the only population-based cohort study with a sufficient number of cases of breast cancer cases reported to date (The Taiwan National Cohort) [8] did not report a protective effect of SLE on breast cancer incidence rates. They actually reported an increased risk of breast cancer (standardized incidence ratio: 1.55, 95 % 1.51–1.6) in women with SLE as compared to women without SLE [8]. The increased risk noted in Taiwan National Cohort appears to be consistent with our finding of an increased risk in women from the “Others” category in our analysis, which includes women from Asian ethnic background.

Findings from our study are also consistent with some earlier prior studies that have shown no difference in the risk of breast cancer among women with SLE as compared to general population (See Table 3) [7, 18–21]. However, these studies reported their results based on small numbers (less than 6) of breast cancer cases [7, 18, 20, 21].

Interestingly, and as expected, most (64 %) of the incident breast cancer cases observed were diagnosed among women age 65 years or above. This is to be anticipated as breast cancer risk is well known to increase with age. Medicare participants are mostly 65 years of age or older. However, even when stratifying the cohort by age, the breast cancer incidence and risk ratio were similar for women ≥65 and for those <65 years. Only one study has reported an increased risk of breast cancer in the younger age group especially among Caucasian women that may be attributed possibly to SLE disease severity [5]. Conversely we did not observe this in our younger women <65 years of age.

Women with SLE have earlier menopause (even when not exposed to cytotoxic medications), as compared with women without SLE [26]. This change in hormonal exposure could be the reason that the risk of breast cancer among women with SLE at younger ages equilibrates early to that of the general population. In specialty clinics versus population-based studies, earlier exposure to SLE modulating agents such as

hydroxychloroquine (an anti-malarial drug) may theoretically inhibit growth of breast cancer cells and result in lower rates of cancer in prior studies of younger populations [27]. However, studies investigating the relation of SLE treatment with cancer risk failed to identify/quantify such treatment effect on cancer incidence [10, 28, 29].

The main strength of our study is a very large robust population-based cohort that was ethnically enriched and large enough to evaluate breast cancer risk among women with lupus. We also believe this study provides a real-world contemporary control group. Our study also has potential limitations. Whereas we used a population-based cohort for women 65 years of age, women younger than this age were limited and were likely not representative of all US women in that age category. To address this limitation, we compared SLE women <65 years of age with controls <65 years, which should control for various Medicare-qualifying demographic, social, and clinical factors. It can be argued that as SLE is a disease of relatively younger women who are lower risk of breast cancer, a seeming protective effect of SLE on breast cancer risk may be purely a function of age distributions in lupus groups studied to date. Further, as age is such a strong predictor of breast cancer risk, theoretically it is possible that older age overwhelms any possible protective effect of SLE. However, this is an unlikely explanation because 46 % of our lupus cohort consisted of women less than age 65 and we found that younger SLE women had breast cancer risk similar to younger non-SLE women. Another limitation is that we did not have information on patient's SLE severity index or specific SLE treatment to adjust for disease severity or therapy.

In conclusion, our results support the hypothesis that the risk of breast cancer among women with SLE is not lower than the risk of breast cancer in the general population, and this is also likely to be case for younger women. These results are of great importance to both the patients and their physicians who have in recent years been exposed primarily to literature that promotes the belief that lupus has a protective effect on the breast cancer risk among women with SLE. Therefore, awareness of equivalent breast cancer risk should guide appropriate screening, follow-up care, and regular surveillance to all women, directed by clinical judgment in conjunction with population-based guidelines and regardless of any underlying diagnosis of SLE. Further evaluation is needed on whether there is a difference in the type of breast cancer and stage at diagnosis between women with and without SLE, and the extent to which specific SLE treatments may potentially reduce the incidence of breast cancer.

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Appendix

See Table 3.

Fig. 1.
Study population

Table 1

Study characteristics and breast cancer incidence risk by race and age groups

	SLE cohort (N = 18,423)				Control cohort (N = 3,651,715)			
	Cases	Total	Unadjusted incidence [95 % CI]	Age-adjusted incidence [95 % CI]	Cases	Total	Unadjusted incidence [95 % CI]	Age-adjusted incidence [95 % CI]
All ages combined								
All	416	18,423	2.26 [2.05–2.48]	2.23 [1.94–2.55] ^a	94,572	3,651,715	2.59 [2.57–2.61]	2.14 [1.95–2.34] ^a
Caucasians	315	13,231	2.38 [2.13–2.66]	2.41 [2.16–2.69]	82,062	3,058,316	2.68 [2.66–2.70]	2.54 [2.52–2.56]
African Americans	68	3839	1.77 [1.38–2.24]	1.97 [1.55–2.50]	8740	370,533	2.36 [2.31–2.41]	2.18 [2.13–2.24]
Others	33	1353	2.44 [1.68–3.41]	2.44 [1.71–3.47]	3770	222,866	1.69 [1.64–1.75]	1.60 [1.46–1.75]
Age ≥65 years								
All	264	9795	2.70 [2.38–3.04]	2.54 [2.14–3.01] ^a	84,629	3,101,399	2.73 [2.71–2.75]	2.54 [2.28–2.83] ^a
Caucasians	215	8079	2.66 [2.32–3.04]	2.49 [2.18–2.84]	74,763	2,654,412	2.82 [2.80–2.84]	2.75 [2.73–2.77]
African Americans	27	1140	2.37 [1.57–3.43]	2.18 [1.50–3.18]	6686	261,264	2.56 [2.50–2.62]	2.51 [2.45–2.57]
Others	22	576	3.82 [2.41–5.73]	3.58 [2.33–5.51]	3180	185,723	1.71 [1.65–1.77]	1.69 [1.54–1.86]
Age <65 years								
All	152	8628	1.76 [1.49–2.06]	1.60 [1.35–1.90] ^a	9943	550,316	1.81 [1.77–1.84]	1.55 [1.47–1.64] ^a
Caucasians	100	5152	1.94 [1.58–2.36]	1.60 [1.31–1.95]	7299	403,904	1.81 [1.77–1.85]	1.50 [1.45–1.55]
African Americans	41	2699	1.52 [1.09–2.06]	1.46 [1.08–1.99]	2054	109,269	1.88 [1.80–1.96]	1.58 [1.50–1.67]
Others	11	777	1.42 [0.71–2.52]	1.12 [0.60–2.08]	590	37,143	1.59 [1.46–1.72]	1.15 [0.93–1.41]

^aRace adjusted

Table 2

Breast cancer incidence ratio for SLE and control cohorts

All ages combined	Unadjusted incidence ratio	<i>p</i> value	Adjusted incidence ratio	<i>p</i> value
All	0.872 [0.793–0.959]	0.005	1.040 [0.896–1.208] ^a	0.603
Caucasians	0.887 [0.795–0.990]	0.032	0.950 [0.851–1.061]	0.366
African Americans	0.751 [0.593–0.951]	0.018	0.902 [0.710–1.146]	0.4
Others	1.442 [0.981–2.293]	0.034	1.524 [1.066–2.178]	0.021
Age ≥ 65 years				
All	0.988 [0.887–1.113]	0.839	1.000 [0.818–1.221] ^a	0.996
Caucasians	0.945 [0.828–1.078]	0.4	0.904 [0.791–1.034]	0.141
African Americans	0.925 [0.637–1.345]	0.684	0.870 [0.596–1.269]	0.469
Others	2.231 [1.479–3.365]	<0.001	2.116 [1.361–3.289]	0.001
Age <65 years				
All	0.975 [0.829–1.146]	0.755	1.032 [0.874–1.218] ^a	0.71
Caucasians	1.076 [0.881–1.313]	0.474	1.068 [0.877–1.301]	0.515
African Americans	0.805 [0.590–1.099]	0.173	0.926 [0.679–1.261]	0.625
Others	0.890 [0.488–1.622]	0.703	0.973 [0.527–1.797]	0.931

^a Race adjusted

Table 3

Studies reporting risk of overall cancer and breast cancer among women with SLE

Study author and years	Study design	Study population and size	Number of breast cancer cases	Results	Study limitations/strength/comments
Pettersson et al. [16]	Finnish cancer registry—clinical cohort consists of SLE patients from medicine clinics, who were diagnosed with ARA 1971 criteria. These patients were followed over time (total person-years at risk 2340), and breast cancer was ascertained through Finnish Cancer Registry. The comparison group for the study was sex and age-specific cancer incidence rate for overall Finnish Cancer Registry	205 total SLE patients (182 women and 23 men)—age range for the registry not provided	4 breast cancer cases out of total 13 cancer cases in women (two breast cancers were diagnosed in the same patient). Mean age of women at cancer diagnosis 55 years and overall age range 39–80 years	Overall cancer RR 2.6 (1.5–4.4) Breast cancer RR 2.7 (0.7–6.8)	Ability to evaluate the influence of cytotoxic drugs on cancer limited due to small number of cases. Only relative risk was reported
Dupla ML et al. [21]	Clinical Cohort with retrospective analysis of SLE patients at La paz Hospital, Madrid. Using ARA 1982 criteria for SLE diagnosis. Only number of cases reported without risk evaluation	96 SLE patients (84 were women). Mean age at SLE onset 30 years	One breast cancer diagnosed out of 5 total female cancer cases. Mean age of women 42 years at cancer diagnosis with age range (33–56 years)	<i>Conclusion</i> SLE patients may have the same malignancies as general population after adjustment for age and sex	Information on cytotoxic medicine reported (cyclophosphamide, azathioprine, and vincristine). Small number of cases
Sweeney et al. [17]	Clinical cohort assembled from University medical center (Allegheny county Clinical) using revised criteria ARA 1982 for SLE diagnosis. Cancer cases ascertained through postal survey and non-respondent to the survey the cancer ascertainment was done via university medical records. Expected number calculated by regional age-specific incidence from 1985 Allegheny county census data and 1987 Pennsylvania cancer incidence registry data. Person-year risk cohort was multiplied by regional age-specific incidence	219 SLE patients with age range 29–69 years	3 out of 6 cases detected with breast cancer, mean age of women with cancer 54 years, age range at dx of cancer (36–65 years)	Overall cancer SIR 1.36 (0.5–2.96) Breast cancer SIR 2.05 (0.42–5.99)	Small number but evaluated the immunosuppressive agents
Abu-Shakra et al. [18]	Clinical cohort assembled from chart review where SLE was diagnosed using ARA 1982 criteria. Patients followed prospectively for 24 years at University of Toronto Lupus Clinic for cancer. Multiple comparison groups used including (i) General population of Ontario, (ii) 1426 patient with RA and (iii) 248 patients with scleroderma	Total SLE patients 724, out of which 627 were females. Mean age at SLE 33.3 years (range 8–83.1 years) with 10 years mean follow-up	4 out of 21 cancer in women were breast cancer with mean age at cancer diagnosis 57/2 years (range 27–84 years)	Overall cancer SIR 1.08 (0.7–1.62) Breast cancer SIR 0.7 (0.19–1.8)	Small number of cases not adjusted for potential variables that could influence the disease incidence
Mellemkjaer et al. [19]	Clinical cohort of SLE patients from Danish Hospital discharge register linked to cancer registry in Denmark	SLE patients 1585 (83 % women—1315), 71 % women	14 out of 102 total cancer were in the breast. No information provided for	Overall cancer RR 1.3 (1.06–1.58)	Selection bias—hospital discharge patients and limited number

Study author and years	Study design	Study population and size	Number of breast cancer cases	Results	Study limitations/strength/comments
	for detection of breast cancer cases. Expected number of breast cancer cases calculated using national cancer incidence—ICD code used for SLE diagnosis				
Ramsey-Goldman et al. [15]	Chicago Lupus Cohort Clinical using ARA 1982 linked to tumor registry used to ascertain cancer cases. SIR estimated using age, gender, and race stratified cancer incidence from Cook County IL	616 women with lupus with mean age at SLE 35.3 years (± 17.7 SD)	8 breast cancer cases—mean age of cancer women 51.6 years (± 14.5 SD)	Overall cancer SIR 2 (1.4–2.9) Breast cancer SIR 2.9 (1.4–6.4) [among Caucasian women]	Small no of cases, single-state registry data
Sultan et al. [20]	UK Clinical cohort of SLE patients assembled using ARA 1982 that was followed prospectively. Cancer cases were detected using medical notes. SIR calculated using Southeast England population annualized age/gender specific cancer incidence rate	276 SLE patients (258 were women—93.5 % females) Mean age at SLE 34.7 years and mean time to occurrence of cancer 7.4 years	3 breast cancer out of total 10 cancer cases. No information provided for age of the patients at cancer diagnosis	Overall cancer SIR 1.16 (0.55–2.13) Breast cancer SIR 1.06 (0.21–5.9)	Treatment information provided for cyclosporine and cyclophosphamide. Out of ten cases 6 had prednisolone, 4 received azathioprine, 5 were on hydroxychloroquine and 1 had cyclophosphamide. Limited number of cases
Nived et al. [24]	Clinical cohort of SLE patients assembled from Swedish National Population registry (1981–1996) and linked to National Cancer registry. Patients were prospectively followed for development of cancer till 1998. SLE diagnosis was based on typical symptoms in at least two organ systems, the presence of typical immunological findings and lack of better diagnosis. SMR calculated based on observed frequencies from age and gender matched general population data from national cancer registry	116 SLE patients (99 were women), off these only 110 full filled four or more ACR criteria. Median age at diagnosis of SLE was 48 years	No breast cancer detected. Total 11 cancer detected (7 cases were in women). Mean age for women cancer 66 years (range 53–78 years)	Overall cancer SMR for women 1.02 (0.4–2.1)	Treatment information provided. 19 % patients used azathioprine and or cyclophosphamide and 69 % were treated at least once with steroids during the study period. No breast cancer case detected
Cibere et al. [7]	Lupus clinical cohort assembled from Saskatchewan (Canada) University-based clinic and hospital data using ARA 1982 criteria. Provincial cancer statistics was used to calculate the expected number. Tumor registry was utilized to ascertain cancers	297 SLE patients (84 % women). Mean age at SLE 36 years (range 10–80 years)	4 breast cancer cases. Mean age for all cancer 60 years (range 27–89 years)	Overall cancer SIR 1.59 (1.05–2.32) Breast cancer SIR 1.15 (0.31–2.95)	Small number of cases
Bjornadal et al. [11]	Clinical cohort based on hospitalized SLE patients from Swedish Hospital discharge register data base using ICD codes. Cases ascertained via National Swedish Cancer Register. Expected number obtained by National Swedish Cancer Register rates	5715 SLE patients (4201 were women). 59 % of women were under age 60 years	52 breast cancer cases out of total 443 cancer cases. No information provided for age at diagnosis	Overall cancer SIR 1.25 (1.14–1.37) Breast cancer SIR 0.72 (0.54–0.95)	Small number of cases, selection bias (cohort assembled from hospital discharged registry matched to Swedish Cancer Registry), acute care setting causing detection bias. No validated study for diagnostic code in hospital discharge Register. Low specificity of the SLE would resulted in underestimation of true risk
Bematsky et al. [6]	International clinical cohort of SLE patients from 23 centers where cases were determined through linkage to regional tumor registries. Expected	9547 patients (90 % female 8607)	73 breast cancer cases detected out of 431 total cancer cases. Out of 431 cases 86 % cancer were	Overall cancer SIR 1.15 (1.05–1.27)	Largest study cohort for its time. Breast cancer was the most commonly diagnosed cancer

Study author and years	Study design	Study population and size	Number of breast cancer cases	Results	Study limitations/strength/comments
Bematsky et al. [9]	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	identified through hospital medical records and confirmed histology or autopsy	Expected number calculated from Thames Cancer Registry 5-year-an	Expected number calculated from Thames Cancer Registry 5-year-an
Bematsky et al. [9]	Multicenter (30) international SLE cohort—linked to regional tumor registries-almost all clinical cohorts no population-based registry	16,409 SLE patients (90 % females)	114 breast cancer cases out of 559 female cancers (Overall total cancer cases 644–84 % cancer in women, 41 % cancer among patients age 60 plus)	Overall cancer SIR 3.02 (2.48–3.63) Overall female cancer SIR 1.15 (1.05–1.24) Breast cancer SIR 0.73 (0.61–0.88)	Large study with the largest lupus patient population. No data on the race or treatment effect evaluated. Breast carcinoma in situ excluded from the cases, no such exclusion reported for control group