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ORIGINAL ARTICLE

No association between the risk of breast cancer and systemic lupus erythematosus: evidence from a meta-analysis

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Abstract

Several studies have estimated breast cancer risk in patients with systemic lupus erythematosus (SLE) relative to the general population. However, the results have been inconclusive. Therefore, we conducted a meta-analysis to ascertain a more comprehensive conclusion. A systematic literature search of electronic databases including PubMed, Web of Science, Embase, Cochrane Library, and Scopus was conducted to identify eligible studies using multiple search strategies. Based on the degree of heterogeneity, a random-effect model was chosen to calculate the pooled standardized incidence rate (SIR) with 95% confidence interval (CI), to estimate the strength of association between SLE and breast cancer incidence risk. A total of 18 eligible studies including 110,720 patients with SLE were enrolled in this meta-analysis. The combined results showed no significant association between SLE and breast cancer incidence (SIRs = 1.012 (95% CI, 0.797–1.284)). Subgroup analysis by study type, ethnicity, follow-up years, sample size, and SLE diagnostic criteria also showed no altered risk for breast cancer incidence (the summary risk estimate of each subgroup ranged from 0.82 to 1.40 with no statistical significance). This meta-analysis suggests no direct association between SLE and risk of breast cancer incidence.

Keywords Breast cancer · Meta-analysis · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease which is characterized by the production of autoantibodies directed against almost any organ system with a heterogeneous array of clinical manifestations [1]. Recent advances in diagnosis, management, and treatment of SLE have led to a substantial increase in the survival rate of SLE patients [2]. Despite this improvement, the life expectancy in such patients remains lower than that in the general population [3]. This reduction is attributed to the fact that SLE may coexist with other chronic conditions such as infections related to immune suppression, renal failure, cardiovascular disease, joint disease, and several types of cancer which may become major causes of morbidity and mortality [4, 5].

A growing body of evidence suggested that there is an increased risk of specific kinds of malignancy, especially non-Hodgkin's lymphoma in SLE versus the general population [6, 7]. Also, an increased risk for some has been reported, including lung, liver, cervix, and vagina cancer among patients with SLE [7]. However, some studies have found a decreased risk for some hormone-sensitive cancers such as breast, ovarian, and endometrial [8].

Some studies have suggested a decreased risk of breast cancer in SLE, over the past few years [9–12]. However, there have been additional observational studies which did not confirm these results, making the interpretation difficult for available reports [13–15]. Despite more reports supporting the decreased risk of breast cancer in SLE patients, the possibility of a slight increase in risk cannot be ignored. Therefore, to investigate more subtle association between SLE and the risk of breast cancer, this meta-analysis was conducted to derive a more comprehensive conclusion.

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Methods

Search strategy

The electronic databases including PubMed, Web of Science, Embase, Cochrane Library, and Scopus were searched for relevant published English articles up to 30 August 2017. The search mesh terms and text words including "autoimmune diseases," "Lupus Erythematosus, Systemic," "SLE," "breast neoplasms," "breast cancer," and "breast tumor" were used individually or in various combinations. The reference lists of all potential eligible articles were also searched for other relevant publications not identified in the database search. In the case of studies published by the same author or overlapping study populations, only the most recent or complete study was included.

Inclusion and exclusion criteria

Publications were eligible to be included in the meta-analysis if they fulfilled the following criteria: (1) case–control or cohort study investigating the association between SLE and breast cancer risk, (2) sufficient published data for estimating the standardized incidence rate (SIR) with 95% confidence interval (CI), and (3) general population as the reference group. Reviews, editorials, letters to the editor without original data, case reports, animal studies, and all other studies that failed to meet the inclusion criteria were excluded.

Data extraction and quality control

Two authors (HMM and ST) independently extracted data from all eligible publications according to the inclusion criteria, and any disagreement was resolved through discussion and team consensus. Briefly, the following information was collected from each study: first author's name and year of publication, country, ethnicity, the number of patients, study design, covariates, study period, follow-up length, and RR/SIR with corresponding 95% CI. If data were not reported in the primary study, items were treated as "not stated." All the analyses were based on previously published studies, thus no ethical approval or patient consent was required. Quality assessment was done for each study independently by two reviewers using the Newcastle–Ottawa scale (NOS) [16]. The NOS scale uses a star rating system (a score of 0–9) to evaluate the quality of each study. Studies awarded six or more stars were of high quality.

Statistical analysis

Estimating the standardized incidence rate (SIR)/relative risk (RR) and 95% CI, as the ratio between observed and expected number of cases for an exposed population, is usually a preferred method of data presentation for cohort studies. So the strength of the association between SLE and breast cancer risk was measured using SIR/RR with 95% CIs. The statistical significance of the pooled SIR/RR was determined by the Z test and considered significant for $P < 0.05$. Statistical heterogeneity across the studies was assessed by the chi-square-based Cochran's Q and I^2 statistics. In case of significant heterogeneity ($I^2 > 50\%$,), data were analyzed using a random-effect model (the DerSimonian and Laird method). Otherwise, the fixed-effects model (the Mantel–Haenszel method) was applied as the preferred method. To access the stability of the results, sensitivity analysis was carried out by excluding specific studies. The presence of publication bias was assessed by visual inspection of funnel plots, in which the standard error of *log* (RR) of each study was plotted against *log* (RR). Egger's linear regression test was also used to statistically assess publication bias, and $P < 0.05$ was considered indicative of statistically significant publication bias. Subgroup analyses were also performed with available data. All statistical meta-analyses were performed using the software called Comprehensive Meta-Analysis, with all the P values two-sided.

Results

Characteristics of the included studies

Process flow diagram of study screening for SLE and breast cancer is given in Fig. 1. Briefly, a total of 271 articles were identified in our initial search using the defined search strategy. After simultaneous review of the titles and/or abstracts, 69 studies were excluded because of being duplicate reports or irrelevant to our study aim. In subsequent screening steps for remaining articles, 30 publications were identified for further evaluation. After full-text assessment, 12 articles were then excluded due to insufficient data and duplicated cohort of patients [5, 17–27]. Eventually, 18 cohort studies were identified eligible for meta-analysis [9–15, 28–38].

The basic characteristics of all included studies were listed in Table 1. The publication years of all studies identified ranged from 1992 to 2016 years. Thirteen studies were conducted in Europe and USA, two in Asia, and three were international multi-center cohort studied from the African-American, Asian, Hispanic, and North American Native. All together, these hospital- and/or population-based SLE cohorts included a total of 110,720 patients ranged from 172 to 30,478 subjects with the mean follow-up times from 4.8 to 32 years. The detailed data about SIRs and 95% CI and the observed and expected number of cancers in each study were listed in Table 2, if available. The results of quality assessment by the NOS scale confirmed that all cohort studies were of high quality with a score greater than 6 (Table 2).

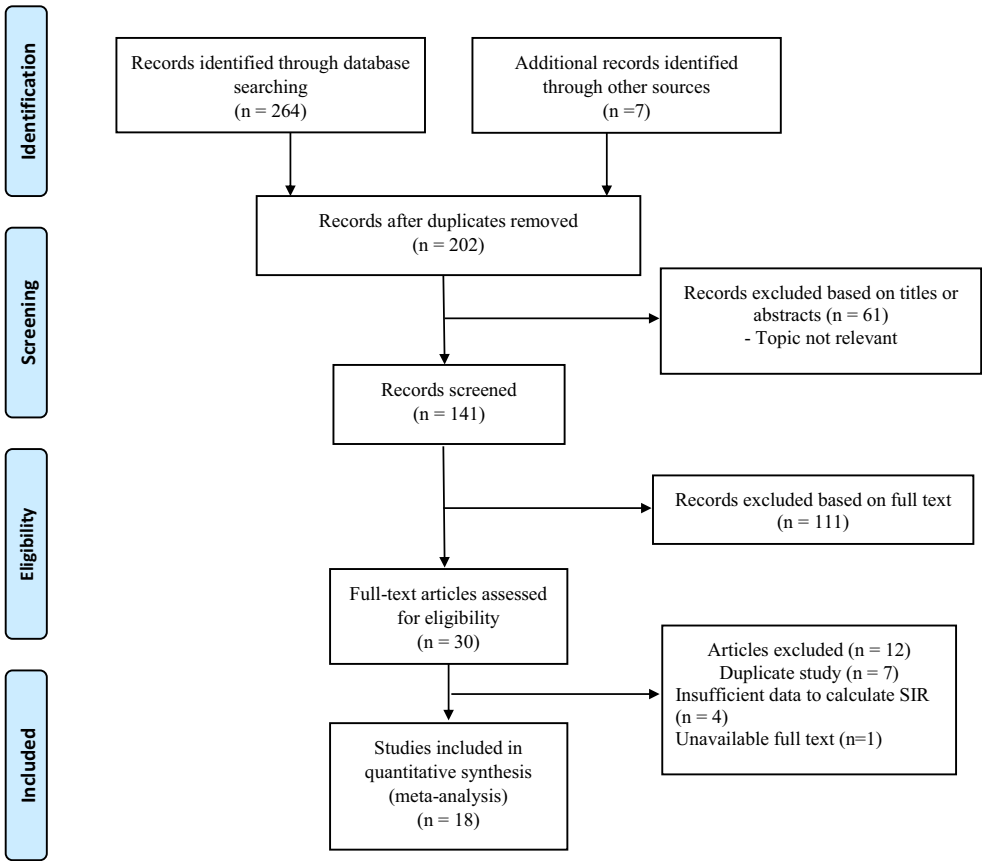

Fig. 1 Study selection process

Quantitative data synthesis

The meta-analysis of all 18 studies, comprised of 110,720 SLE patients, demonstrated no direct association between SLE and breast cancer incidence. As shown in Fig. 2, the pooled RR of all studies was 1.012 (95% CI, 0.797–1.284), with a I^2 value equivalent to 94.35% indicating a substantial heterogeneity. Data produced in our random-effect model indicated that compared with the general population, cancer occurrence in SLE patients had no different incidence rate.

To trace possible source of heterogeneity, and to identify potential effect of different factors on estimated overall SIR, we also examined the breast cancer incidence rates by stratifying data into various subgroups, based on study type, ethnicity, follow-up years, sample size, and SLE diagnostic criteria. The results of subgroup analyses were shown in Table 3. The summary risk estimate of each subgroup ranged from 0.82–1.40, indicating that these factors do not change the risk trends for overall breast cancer incidence. Taken together, all subgroups produced substantial heterogeneity ($I^2 > 60\%$), but in the heterogeneity observed in hospital-based ($I^2 = 60.89\%$), Caucasian ($I^2 = 69.54\%$), follow-up ≥ 10 years ($I^2 = 77.66\%$), and sample size < 1000 subjects ($I^2 = 75.31\%$), subgroups were slightly moderate compared with corresponding subcategories (Table 3).

According to the results of sensitivity analysis, in which one study was omitted at a time, the corresponding pooled risk estimates were not significantly altered, suggesting stability and reliability of the results (Fig. 3). In the case of publication bias, both Egger's test and visual assessment of Begg's funnel plot indicated no significant publication bias in this meta-analysis ($P = 0.12$; Fig. 4).

Discussion

Since the first publication reporting a malignancy developing in a patient with SLE, by Camarata et al. in 1963, several studies were conducted to investigate the risk of malignancy development in autoimmune diseases and to identify which types of cancer were more likely to occur [39]. Given that cohort studies are the best design to determine the incidence rate of a specific outcome in a defined group of SLE patients compared to the general population, several small or large cohort studies have been conducted to investigate this hypothesis. The results of most publications revealed large difference for malignancy occurrence in SLE that ranged from increased frequency for some types of cancers including hematologic cancers to an unclear risk for other cancers such as breast, ovarian, and endometrial. As these types of cancer appear at

Table 1 Characteristics of selected SLE cohort studies

Study, published year	Ref	Study design	Race	*N*	Age	Diagnostic criteria	Mean time of follow-up years	Covariates
Abu-Shakra, 1996	30	PB	Caucasian	724	33.3	ACR	24	Age and sex
Bernatsky, 2013	11	PB	Caucasian, African-American, and others	16,409	NR	ACR	7.4	Age, sex, calendar year, specific cancer rates, and summing overall person years
Bjornaîal, 2002	9	HB	Caucasian	5715	Under age 60 years	NR	15	Sex, age, and calendar period
Chen, 2010	14	PB	Asian	11,763	34.73	ACR (1982)	6.1	Age at diagnosis, sex, and years
Cibere, 2001	33	PB	Caucasian	297	60	ACR	12	Age, sex, and calendar year of follow-up
Dey, 2013	12	PB	Caucasian	595	33.5	NR	32	Age, sex, ethnicity, and disease duration
Dreyer, 2011	15	HB	Caucasian	576	33	ACR (1982)	13.2	Age and sex
Gadalla, 2009	38	PB	USA (various)	172	76.0	ICD-9	NR	Age, year of selection, race, mammography, region of residence, income, and immunosuppressive therapy
Khaliq, 2015	36	HB	African-American, Asian, Hispanic, and North American Native	24,369	NR	NR	Over 5 years	Age and race
Mellemkjaer, 1997	31	HB	Caucasian	1585	NR	ACR	15	Sex, age, and calendar time
Parikh-Patel, 2008	10	HB	Caucasian	30,478	NR	CCR	5.1	Sex, race/ethnicity, and 5-year age
Pettersson, 1992	28	HB	Caucasian	205	NR	ACR (1971)	21	Sex, age, and drug use
Ragnarsson, 2003	34	PB	Caucasian	238	43.2	ARA (1982)	12.8	Age and sex
Ramsey-Goldman, 1998	13	PB	Caucasian women	616	NR	ACR (1982)	10	Age, sex, and race
Sweeney, 1995	29	PB	Caucasian	219	NR	ACR (1982)	5.2	Age and sex
Sultan, 2000	32	HB	Caucasian	276	34.7	ARA	4.8	Sex, age, data of diagnosis, time of follow-up, and immunosuppressive therapy
Tarr, 2007	35	PB	Caucasian	860	33	ACR (1982)	13.4	Age, sex, and calendar year match cancer rate
Yu, 2016	37	PB	Asian	15,623	35.34	ACR	Up to 15 years	Age, sex, and duration of follow-up

PB, population-based study; *HB*, hospital-based study; *ACR*, revised American College of Rheumatology criteria; *ARA*, 1971 criteria of American Rheumatism Association; *N*, number of patients with SLE; *NR*, not reported, *Ref*, reference

Table 2 SIRs and 95% CI for breast cancer among SLE patients, defined as the ratio of the observed to the expected number of cancers in each study

Study, published year	SLE patients (*n*)	Observed (*n*)	Expected (*n*)	SIR 95% (CI)	Assessment score
Abu-Shakra, 1996	724	4	5.71	0.7 (0.19–1.8)	8
Bernatsky, 2013	16,409	114	155.2	0.73 (0.61–0.88)	9
Bjornadal, 2002	5715	52	72.2	0.72 (0.54 0.95)	8
Chen, 2010	11,763	45	29.03	1.55 (1.51–1.6)	8
Cibere, 2001	297	4	3.46	1.15 (0.31–2.95)	7
Dey, 2013	595	5	10.5	0.48 (0.35–0.64)	9
Dreyer, 2011	576	7	9.1	0.8 (0.4–1.6)	7
Gadalla, 2009	172	–	–	0.99 (0.78–1.24)	7
Khaliq, 2015	18,423	416	400	1.04 (0.90–1.21)	7
Mellemkjaer, 1997	1585	14	14	1.00 (0.55–1.68)	8
Parikh-Patel, 2008	30,478	237	311.9	0.76 (0.67–0.86)	9
Pettersson, 1992	205	4	1.5	2.7 (0.7–6.8)	9
Ragnarsson, 2003	238	7	4.38	1.6 (0.65–3.23)	8
Ramsey-Goldman, 1998	616	8	2.88	2.9 (1.4–6.4)	7
Sultan, 2000	276	3	2.83	1.06 (0.21–5.9)	7
Sweeney, 1995	219	–	–	2.05 (0.70–5.99)	7
Tarr, 2007	860	11	17.9	0.62 (0.31–1.10)	9
Yu, 2016	15,623	–	–	1.20 (0.96, 1.51)	8

SIR, standardized incidence rate; *CI*, confidence interval

a lower frequency, it was difficult to perform a robust statistical evaluation.

Although some published studies have claimed a decreased risk of breast cancer in women with SLE [9–12], review of the other available literature reported no difference or even a very small increased risk [13–15, 34–36], indicating inconclusive results probably due to limited predictive power with relatively small sample sizes. For this reason, a comprehensive meta-analysis of all available literature related to SLE and breast cancer risk was conducted to provide a more precise risk

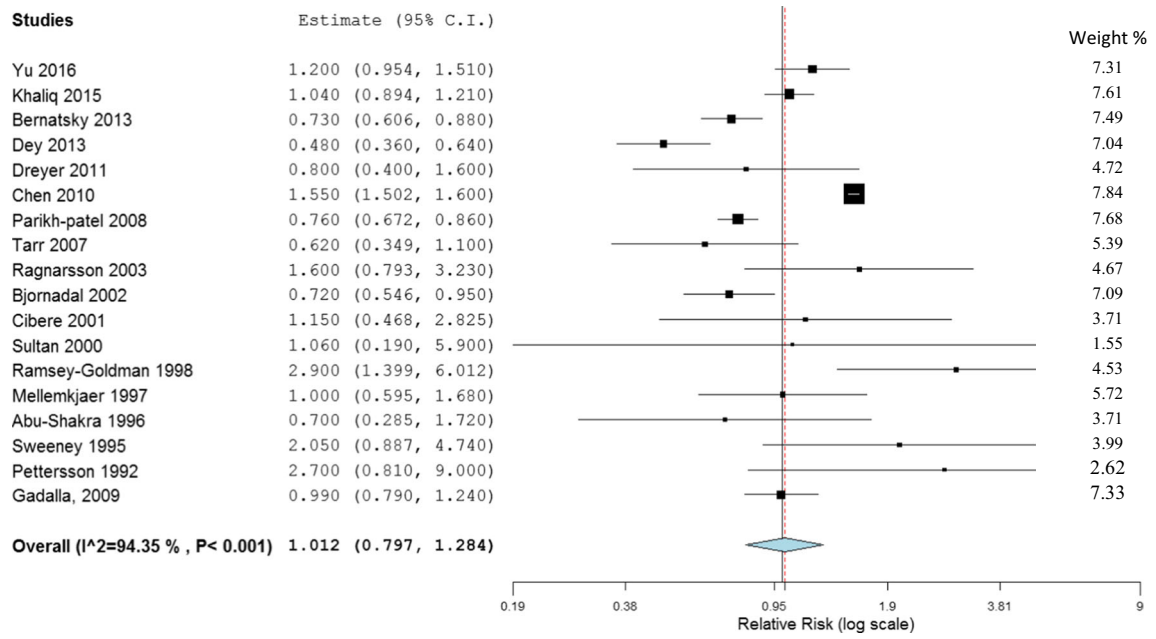

Fig. 2 Relative risk of breast cancer in patients with SLE compared with the general population. The squares and horizontal lines correspond to the study-specific RR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled RR and 95% CI

Table 3 Stratified analyses of pooled relative risks of breast cancer in patients with SLE

Subgroups		Number of studies	References	*N*	Pooled RR or RR (95% CI)	Heterogeneity	
						I^2 (%)	*P* value
Study type	HB	7	[9, 10, 15, 28, 31, 32, 36]	63,204	0.88 (0.72–1.08)	60.89	0.018
	PB	11	[11–14, 29, 30, 33–35, 37, 38]	47,516	1.06 (0.77–1.46)	93.47	0.001
Ethnicity	Caucasian	13	[9, 10, 12, 13, 15, 28–35]	42,384	0.94 (0.72–1.21)	69.54	< 0.001
	Multisite	3	[11, 36, 38]	40,950	0.91 (0.73–1.14)	77.30	0.012
	Others	2	[14, 37]	27,386	1.40 (1.10–1.79)	79.62	0.031
Follow-up years	≥ 10 years	11	[9, 12, 13, 15, 28, 30, 31, 33–35, 37]	27,034	0.98 (0.72–1.35)	77.66	< 0.001
	< 10 years	6	[10, 11, 14, 29, 32, 36]	83,514	1.05 (0.74–1.49)	97.04	< 0.001
Sample size	≥ 1000 subjects	7	[9–11, 14, 31, 36, 37]	105,942	0.97 (0.70–1.34)	97.26	< 0.001
	< 1000 subjects	11	[12, 13, 15, 28–30, 32–35, 38]	4778	1.07 (0.75–1.55)	75.31	< 0.001
SLE diagnostic criteria	ACR, 1982	12	[11, 13–15, 29–35, 37]	49,186	1.14 (0.85–1.52)	87.26	< 0.001
	Other	6	[9, 10, 12, 28, 36, 38]	61,534	0.82 (0.64–1.031)	84.10	< 0.001

PB, population-based study; *HB*, hospital-based study; *ACR*, revised American College of Rheumatology criteria; *ARA*, 1971 criteria of American Rheumatism Association; *N*, number of patients with SLE; *RR*, relative risk; *CI*, confidence interval

estimate. Data from 16 eligible cohort studies were combined to evaluate the presence of breast cancer in SLE patients to obtain a comprehensive conclusion.

In the present meta-analysis, the obtained results demonstrated that the overall incidence of breast cancer in lupus patients and general population is not different. Similar results were observed in subgroup analysis by study design, follow-up duration, ethnicity, SLE diagnostic criteria, and sample size. Hence, the results observed in this meta-analysis suggest that the clinicopathological features of SLE patients may not play a role in susceptibility to breast cancer, compared to the general population. The non-altered occurrence of breast cancer in SLE patients compared to the general population should be interpreted in the context of significant heterogeneity among published cohorts that resulted from variation in patient population size, ethnicity, number of events, the relatively short follow-up time, and also strong association between breast cancer and hormonal and reproductive factors.

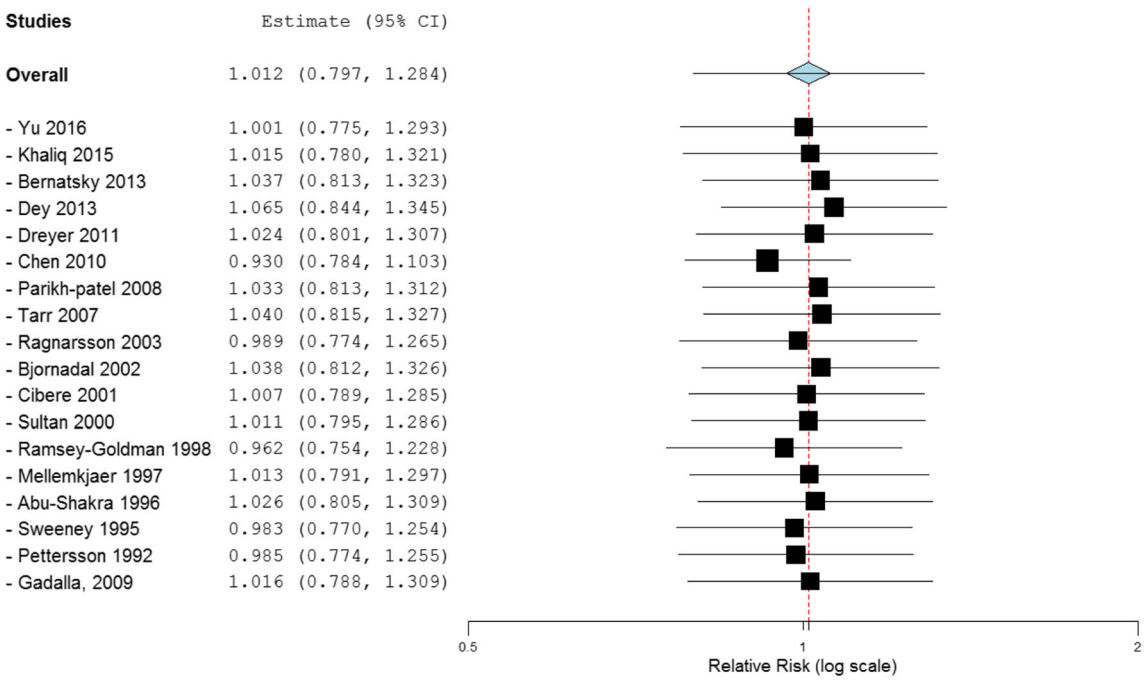

Fig. 3 Sensitivity analysis on the association between SLE and breast cancer. The squares and horizontal lines correspond to the leave-one-out pooled RR and 95% CI

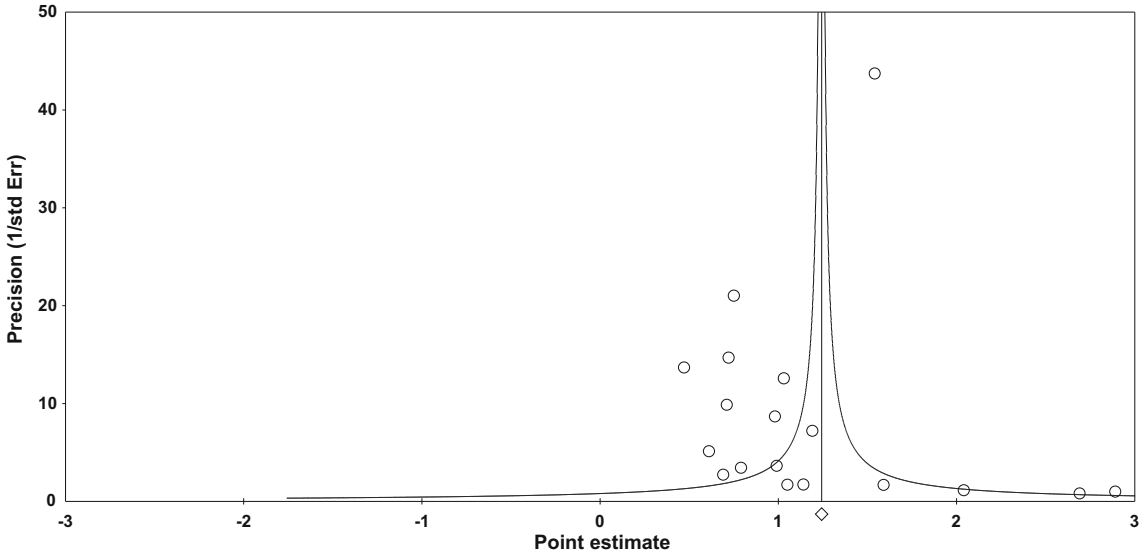

Fig. 4 Begg's funnel plot of publication bias on the association between SLE and breast cancer. The funnel plot displays log RR against its standard error for each individual study

Regarding the findings of those previous studies which clearly pointed towards a decreased risk of breast cancer in SLE, Bernatsky et al. recently conducted a study to evaluate the hypotheses that breast cancer risk in SLE may be influenced by demographic and clinical characteristics including drug exposures (non-steroidal anti-inflammatory drugs, NSAIDs, anti-malarial drugs, etc.) or autoantibody profiles [27]. However, they found no considerable evidence to support that breast cancer risk in SLE patients may strongly be derived by any of the studied clinical factors. Also, their results obtained from a genome-wide association study (GWAS), focused on 10 single nucleotide polymorphisms (SNPs) highly associated with SLE, revealed that breast cancer risk in SLE is not influenced by genetic profiles in comparison with the general population [40]. These findings may support our meta-results indicating no significant difference for breast cancer risk in SLE patients compared to the general population was observed.

Therefore, the results of available cohort studies that investigated breast cancer risk among patients with SLE are variable. Variation in the number of breast cancer cases in different cohorts ranged from 1 to 237 [10, 32]. Also, the lack of a real control group would result in a wide confidence interval, a limited power of statistical estimation, and an extreme heterogeneity among different studies. However, this meta-analysis with some advantages including a well-designed methodological issue and enrolling all available eligible studies has shed some additional light on the previous inconclusive findings and led to an overall conclusion regarding the breast cancer risk in SLE patients. In conclusion, the present meta-analysis on 110,720 SLE patients does not indicate an obvious association between SLE and breast cancer.

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Compliance with ethical standards

Disclosures None.

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