Clinical Rheumatology (2019) 38:3109–3116
https://doi.org/10.1007/s10067-019-04660-9

ORIGINAL ARTICLE

# Risk of pancreatic cancer in patients with systemic lupus erythematosus: a meta-analysis

Min-Seok Seo[1,2] · Jina Yeo[3] · In Cheol Hwang[4] · Jae-Yong Shim[2]

Received: 11 February 2019 / Revised: 21 June 2019 / Accepted: 25 June 2019 / Published online: 3 July 2019


## Abstract

**Object** Accumulating evidences suggest that the incidence of several cancers is higher in systemic lupus erythematosus (SLE) than in general population. However, the finding on pancreatic cancer risk is inconsistent. This meta-analysis aimed to determine whether SLE patients are at risk for pancreatic cancer.

**Methods** We searched PubMed, Embase, and the Cochrane database to screen the studies meeting our criteria. The hazard ratios (HRs) and its 95% confidence interval (CIs) were calculated from a meta-analysis.

**Results** Eleven cohort studies were included in the final analysis. Overall, patients with SLE had an increased risk of pancreatic cancer (HR = 1.42, CI = 1.32–1.53). In subgroup analysis, hospital-based (HR = 1.43, CI = 1.32–1.54), retrospective (HR = 1.42, CI = 1.32–1.54), over 10 years followed (HR = 1.44, CI = 1.33–1.55), and low-quality studies (HR = 1.42, CI = 1.31–1.53) remained robust. Significant publication bias was not observed among the studies ($p = 0.533$).

**Conclusions** The synthesized evidence from our meta-analysis demonstrated that SLE was associated with increased risk for pancreatic cancer. A well-designed, long-period followed study is needed to confirm this association.

**Key Points**
- *Cancer incidence in SLE patients is increasing, but the data concerning pancreatic cancer remains inconclusive.*
- *Our meta-analysis indicated that the risk of pancreatic cancer was significantly increased in SLE patients.*
- *A well-designed, long-period followed study is needed to confirm the association.*

**Keywords** Association · Meta-analysis · Pancreatic cancer · Systemic lupus erythematosus

## Introduction

Pancreatic cancer is the 12th most common malignancy which an estimated 367,000 patients were newly diagnosed worldwide in 2015. It has a high mortality and remained the 7th most prevalent cause of cancer-related death with 359,000 deaths in 2015 [1, 2]. Pancreatic ductal adenocarcinoma expected to be the 2nd leading cause of death in adult by 2030 in the USA [3]. The extremely poor prognosis of pancreatic cancer is explained by late diagnosis, aggressive feature, and intolerable to conventional modality, resulting in < 7% of overall 5-year survival rate [4]. The etiology of pancreatic cancer contains multiple factors, such as old age, tobacco smoking, heavy alcohol drinking, obesity, low physical activity, diet, diabetes, and hereditary conditions [2]. Even though there is no consensus of reliable screening guideline in general population, careful approach in high-risk population might be beneficial. Interestingly, there are some evidences addressing chronic

Min-Seok Seo and Jina Yeo share equal contribution as first authors.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10067-019-04660-9) contains supplementary material, which is available to authorized users.

✉ In Cheol Hwang
spfe0211@gmail.com

[1] Department of Family Medicine, The Catholic University of Korea Incheon St. Mary's Hospital, Incheon, South Korea

[2] Yonsei University Graduate School of Medicine, Seoul, South Korea

[3] Division Rheumatology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea

[4] Department of Family Medicine, Gil Medical Center, Gachon University College of Medicine, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, South Korea

inflammation and immune response that contribute to develop pancreatic cancer [5]. Thus, there is increasing concern about the possibility to develop malignancy in patients with co-morbid diseases having chronic inflammatory properties.

Systemic lupus erythematosus (SLE) is a chronic inflammatory, progressive, systemic autoimmune disorder which usually affects reproductive-aged women. It is characterized by production of autoantibodies directed against nuclear and cytoplasmic antigens, complement system activation, and immune complex deposition. This immunologic process results in chronic, widespread tissue and multiple vital organ damage before clinical manifestations [6]. Then with earlier diagnostic approach and more appropriate application of medication, there has been a dramatic improvement in the overall morbidity and mortality among patients with SLE [7].

Overall, mortality rate of SLE patients is 2~3 fold higher than the general population [8]: their leading causes of death were infection, renal disease, and cardiovascular disease [9]. A growing body of evidence suggests that incidence rate of malignancies in SLE patients is steeply increasing [9, 10], but the data concerning pancreatic cancer remains inconclusive [11, 12]. Recently, Song et al. reported that the risk of pancreatic cancer was not associated with SLE [13]. However, their study has a crucial limitation with duplicated and missed data. Therefore, in order to explore the cause of different result of previous meta-analyses and ascertain the risk of pancreatic cancer in SLE patients with adding recent published literatures, more comprehensively, we conducted an updated meta-analysis.

## Methods

### Publication selection

We followed the guideline in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. A systematic literature search was conducted to identify all the studies documenting pancreatic cancer in SLE. A rigorous search was independently performed to find all relevant articles in Pubmed, Embase, and Cochrane database by two authors (Seo and Yeo). Relevant articles were identified by using the following terms: systemic lupus, autoimmune disease, rheumatic disease, or SLE with cancer, carcinoma, neoplasm, malignancy, malignant, malignancies, tumor, tumour. There were no restrictions of language in our study. The last search was updated on August 31, 2018. A manual search was also performed on reference lists from extracted articles and reviews. Decisions on trials to include were taken by all four authors after thorough discussion.

### Inclusion and exclusion criteria

The inclusion criteria for the studies were as below: (a) cohort, case-control or observational study or (b) study provided standardized incidence rate (SIR)/hazard ratio (HR)/relative risk (RR)/odds ratio (OR) with 95% confidence intervals (CI) of pancreatic cancer in SLE patients. The exclusion criteria were as below: (a) letters, editorials, reviews, expert opinions, case reports; or (b) overlapping or duplicate publications based on the same study population. There was no restriction of language.

### Data extraction and synthesis

To minimize bias and improve reliability, the following data was independently extracted from all the eligible researches by two authors (Seo and Yeo); the first author, published year, country, data source (diagnosis for SLE and pancreatic cancer), study design, total number of SLE patients, study period, follow-up duration, enroll type, observed/expected number, standardized incidence rate with 95% confidence interval, and adjustment for covariates. Any discrepancy was resolved by discussion and consensus with all four authors. We assessed the methodological quality of all studies using the Newcastle-Ottawa scale [15], and any discrepancies were resolved by consensus.

### Statistical methods

This investigation aimed to assess whether there is an increased risk of pancreatic cancer among SLE patients compared with control subjects. Subgroup meta-analyses were performed which consider the following factors: data source, study design, median follow-up period, and study quality. Pancreatic cancer risk was evaluated as HR for each included publication. The heterogeneity of pooled results was estimated using Higgins' *I*-squared statistics. $I^2$ ranged from 0 to 100%, where $I^2$ values of $> 50\%$ and $< 25\%$ were defined as significant heterogeneity and insignificant heterogeneity, respectively [16]. When substantial heterogeneity ($I^2 > 50\%$) was observed, random-effects model (DerSimonian-Laird method) was used to calculate the pooled SIRs [17]. Otherwise, a fixed-effects model (Mantel-Haenszel method) was applied [18]. Begg's rank correlation test was applied to evaluate publication bias in the literature at the $p$ value $< 0.05$ of significance. All statistical analyses were conducted with Stata software version 12.1 (StataCorp, College Station, TX, USA).

## Results

### Study selection and characteristics

The detailed screening process for the identification of eligible studies is shown in Fig. 1. Following our screening strategy, 1011 articles were initially retrieved. The duplicates ($n = 430$) and articles that were not relevant based on title ($n = 447$) were excluded. After reviewing the abstract of 134 articles, a total of 123 articles were excluded for the following reasons: thirty-six articles were not original articles, twenty-eight articles did not focus on cancer risk, fifty-nine articles were not pertaining to pancreatic cancer. Then, we fulfilled the full test review of eleven articles met our eligible criteria. Three articles were subsequently excluded for overlapping groups of participants. After adding three articles identified through manual searches, a total of eleven articles were included in the meta-analysis.

The basic characteristics of the included studies are shown in Table 1. Two studies were performed in Canada, Denmark, and the UK, whereas one each in Finland, Taiwan, USA, and Sweden. There was one international multicenter study from the USA. These studies included population- and hospital-based SLE cohorts that ranged from 205 to 30,478 and had mean follow-up period from 5.1 to 25.7 years. All studies were adjusted for age and sex ($n = 11$). One study was controlled for race additionally and another for alcohol, smoking, hypertension, hyperlipidemia, BMI, Charlson index score, and use of prednisolone [27].

### Quality scale

The results of the quality assessment are shown in Supplementary Table 1. All studies included in the meta-analysis were cohort. The items to consider included patient selection, comparability, and outcome. The NOS scores range from 5 to7. The methodological quality of all studies was generally good. Four studies were deemed to be high quality (NOS score ≥ 7) and the left seven studies were to be moderate

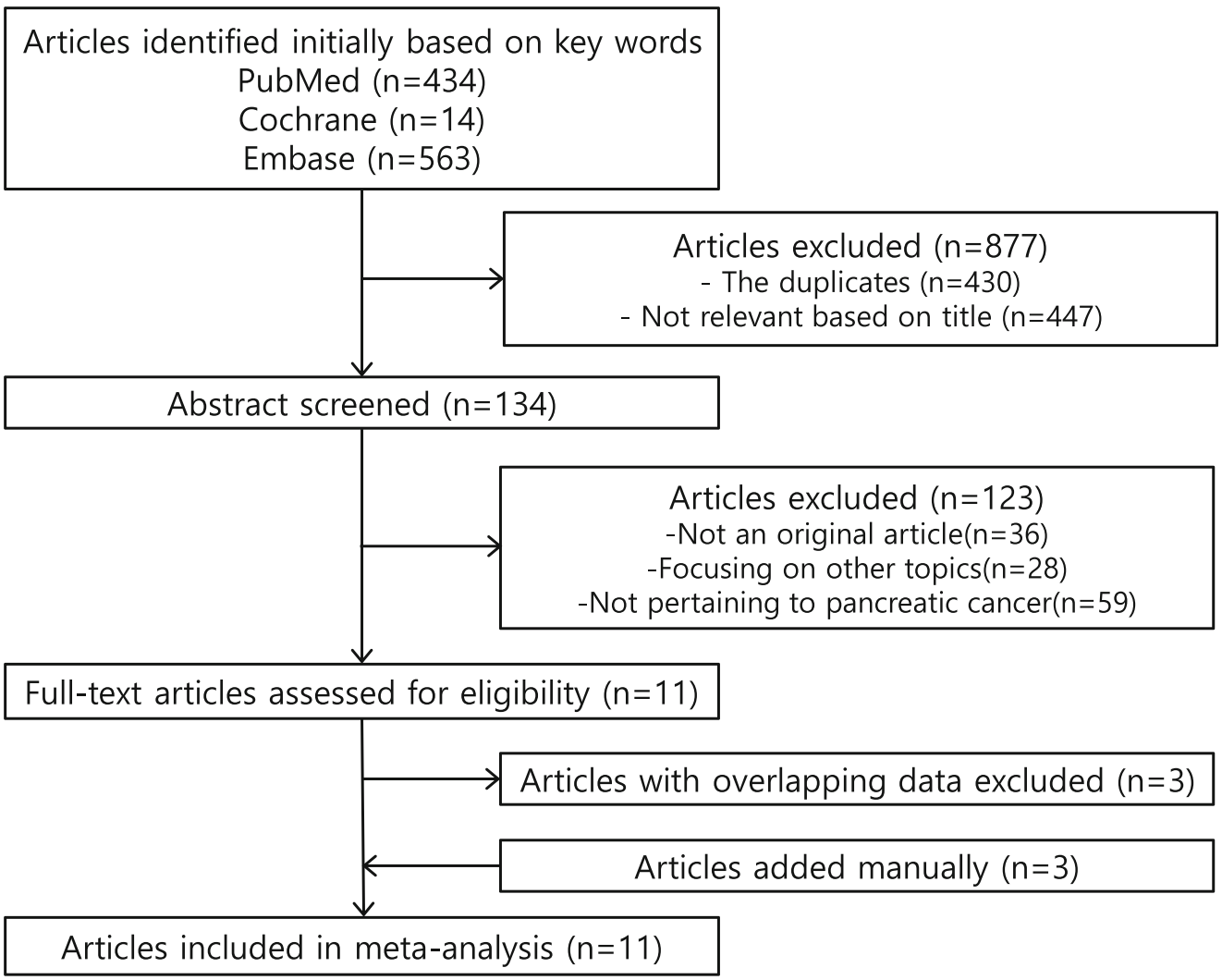


**Fig. 1** Flow diagram for identifying relevant articles

**Table 1** Characteristics of studies included in the meta-analysis

| Study | Year | Country | Data source | Design | SLE (female/male) | Follow-up (years) | HR (95% CI) | Adjusted variates other than age and sex |
|---|---|---|---|---|---|---|---|---|
| Abu-Shakra [19] | 1996 | Canada | Hospital | Prospective | 724 (627/97) | 10 | 6.15 (0.75–22.2) | |
| Mellemkjaer [20] | 1997 | Denmark | Hospital | Retrospective | 1585 (1308/227) | 6.8 | 0.5 (0–2.5) | |
| Cibere [21] | 2001 | Canada | Hospital | Retrospective | 297 (250/47) | 12 | 3.44 (0.04–19.18) | |
| Björnådal [22] | 2002 | Sweden | Hospital | Retrospective | 5715 (4201/1514) | 8.8 | 1.26 (0.7–2.07) | |
| Parikh-Patel [23] | 2008 | USA | Statewide | Retrospective | 30,478 (27,133/3345) | 5.1 | 1.13 (0.73–1.67) | Race |
| Dreyer [24] | 2011 | Denmark | Hospital | Retrospective | 576 (508/68) | 13.2 | 1.4 (0.2–9.9) | |
| Bernatsky [25] | 2013 | International | Hospital | Prospective | 16,409 | 7.4 | 0.9 (0.43–1.65) | |
| Dey [26] | 2013 | UK | Hospital | Retrospective | 595 | 14.7 | 1.4 (0.2–9.9) | |
| Rees [27] | 2016 | UK | Nationwide | Retrospective | 7732 (6634/1098) | 8.4 | 1.92 (0.74–5.00) | Alcohol, smoking, body mass index, hypertension, Charlson index score, dyslipidemia, prednisolone |
| Yu [28] | 2016 | Taiwan | Nationwide | Retrospective | 15,623 (13,693/1930) | 7.9 | 1.5 (0.68–3.35) | |
| Tallbacka [29] | 2018 | Finland | Hospital | Prospective | 205 (182/23) | 25.7 | 3.91 (0.81–11.4) | |

*SLE*, systemic lupus erythematosus; *HR*, hazard ratio; *CI*, confidence interval

quality ($4 \leq$ NOS score $< 7$). The mean NOS score for eleven studies was 6.18.

## Meta-analyses

The combined HR for pancreatic cancer was 1.42 (95% CI 1.32–1.53), suggesting a statistically significant increased risk of pancreatic cancer in individuals with SLE as shown in Fig. 2. One study among 11 articles had an unduly large influence on the results [26]. In subgroup analysis of 10 articles exempt Dey's study, the pooled HR was 1.31 (95% CI 1.01–1.68). When we stratified the analysis by data source, SLE was not associated with risk of pancreatic cancer (HR 1.27, 95% CI 0.90–1.80) in the three studies based on nation- or state-wide data, but not in the eight studies based on hospital data (HR 1.43, 95% CI 1.32–1.54). In subgroup analysis stratified by study design, the combined HR was 2.36 (95% CI 0.66–8.51) for prospective studies, but not significant. Compared with prospective studies, the association was lower among retrospective studies (HR 1.42, 95% CI 1.32–1.53), but remained significant. When we restricted each analysis to mean follow-up duration, the pooled HR was 1.44 (95% CI 1.33–1.55) among five studied followed over 10 years and 1.19 (0.92–1.56) six studies below 10 years, respectively. The studies with a high NOS score conferred a higher risk to develop pancreatic cancer (HR 2.06, 95% CI 0.89–4.73) than the studies with a low NOS score did (HR 1.42, 95% CI 1.31–1.53), but not significant (Table 2). The Funnel plot did not show marked asymmetry among studies ($p = 0.533$, Fig. 3).

## Discussion

An association between SLE and malignancy has long been observed by several researches. The risk of hematologic malignancies, particularly non-Hodgkin's lymphoma, was increased in patient with SLE. A number of studies have reported these results similarly [19, 20, 30]. However, in the case of a solid tumor, the results were somewhat inconsistent. The results of our meta-analysis, including eleven studies with 79,939 SLE cases, revealed that the incidence of pancreatic cancer increased in patient with SLE compared with the general population. Recently, some meta-analyses investigated the incidence of all cancer in SLE patients, which results were different in pancreatic cancer. Cao et al. have reported that the risk of pancreatic cancer in SLE patient was increased, but not significant [11]. Their meta-analysis consisted of seven articles until 2014. Subsequent meta-study including eight articles until 2015 by Mao et al. was reported [12]; the association between SLE and pancreatic cancer was significant. In our study, we are able to find the different results between two meta-studies by one study's large influence (Dey et al). In our subgroup analysis to exclude the unduly large effect of Dey's study, which was consisted of articles included in Cao's meta-analysis and recent three articles, the association between SLE and pancreatic cancer risk was still significant. The most recent meta-analysis about the risk of pancreatic cancer in patients with SLE was reported by Song et al. in 2018

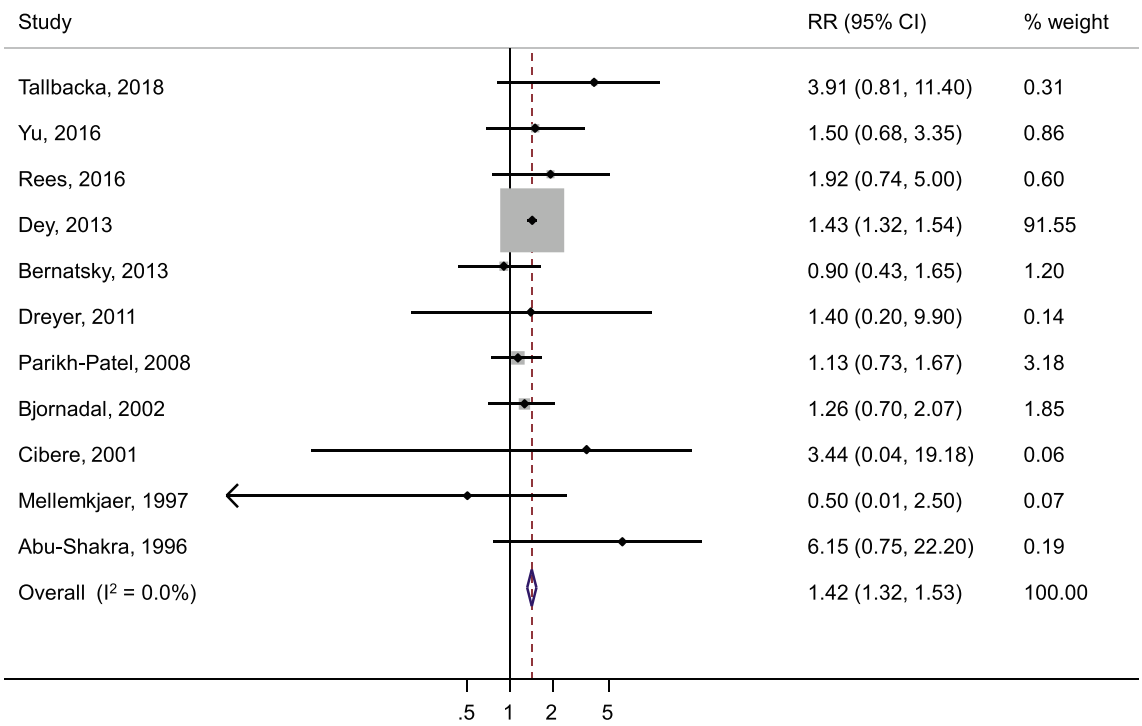


**Fig. 2** Forest plot showing the effect of SLE on risk of pancreatic cancer. SLE, systemic lupus erythematosus; RR, relative risk; CI, confidence interval

[13]. The risk of pancreatic cancer was not associated with SLE in their study. However, we identified some critical limitation to select data in Song's study. The multicenter study by Bernatsky et al. in 2013 is updated result of the study in 2005. We suggest that it is proper to exclude Bernatsky's study in 2005. Another important problem is that Song et al. missed some relevant studies by Rees et al., Dey et al., and Mellemkjaer et al. [20, 26, 27]. Considering several limitations of the study by Song et al., our meta-analysis provides more accurate estimates without duplicated and missed data.

The studies using hospital-based data did reach the statistical significance, in contrast to those using nation- or state-wide data. It might be caused by quality of diagnosis in nation or statewide data. Population-based studies usually have a limitation of coding and keying errors despite

**Table 2** Risk of pancreatic cancer in patients with SLE

| | No. of studies | HR (95% CI) | $I^2$ | Model |
|---|---|---|---|---|
| Overall | 11 | 1.42 (1.32–1.53) | 0% | Fixed-effect |
| Exclude Dey et al.'s study | 10 | 1.31 (1.01–1.68) | 1.2% | Fixed-effect |
| Data source | | | | |
| Hospital-based | 8 | 1.43 (1.32–1.54) | 12.1% | Fixed-effect |
| Nation- or state-wide | 3 | 1.27 (0.90–1.80) | 0% | Fixed-effect |
| Cohort | | | | |
| Prospective | 3 | 2.36 (0.66–8.51) | 71.0% | Random-effect |
| Retrospective | 8 | 1.42 (1.32–1.53) | 0% | Fixed-effect |
| Mean follow-up | | | | |
| ≥ 10 years | 5 | 1.44 (1.33–1.55) | 25.3% | Fixed-effect |
| < 10 years | 6 | 1.19 (0.92–1.56) | 0% | Fixed-effect |
| Study quality | | | | |
| High (NOS ≥ 7) | 4 | 2.06 (0.89–4.73) | 57.9% | Random-effect |
| Low (NOS < 7) | 7 | 1.42 (1.31–1.53) | 0% | Fixed-effect |

*SLE*, systemic lupus erythematosus; *HR*, hazard ratio; *CI*, confidence interval; *NOS*, Newcastle-Ottawa Scale
$I^2$ means heterogeneity of model

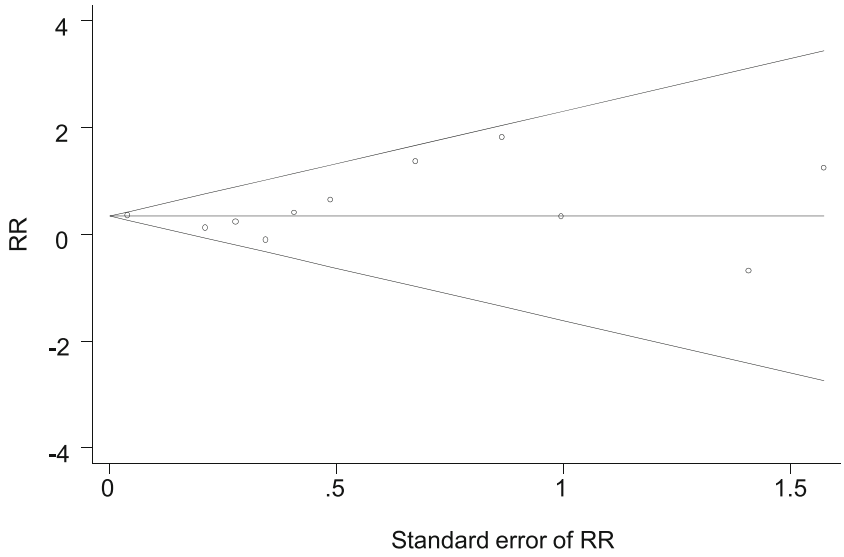


**Fig. 3** Begg's funnel plot with 95% confidence limits for pancreatic cancer among the included studies. RR, relative risk

all their efforts to minimize data errors. In the case of study design, we found that prospective cohort studies were not shown statistical significance unlike retrospective. Similar results were shown in subgroup analysis according to study quality: high-quality studies did not have significance, and only low-quality studies remained significant. Overall significance was led by retrospective studies or low-quality studies. Thus, to confirm the association between SLE and pancreatic cancer more exactly, additional prospective cohort studies with high quality are needed.

For the follow-up duration, significant results were only observed in studies with over 10-year follow-up. It shed light on clinical significance to manage the patient with SLE. Most patients were diagnosed with SLE at young and middle age. Actually, mean age at diagnosis of SLE among included studies in our meta-analysis was the thirties and forties. Co-morbid malignancies were mostly detected within 1~2 years after SLE diagnosis. Some studies have identified that the risk of malignancy in SLE patient gradually decreased over time during short-term following period [25, 31]. In contrast with SLE, almost 90% of pancreatic cancer are diagnosed at over 55 years of age, and peak incidence was shown in the seventies and eighties [4]. Given the discrepancy in peak age between SLE and pancreatic cancer, further studies with longer follow-up duration that affect the risk of very late-occurring cancer including pancreatic cancer in SLE patients are needed.

Underlying mechanism for the increased risk of pancreatic cancer in SLE patient remains unclear. One feasible explanation for pathophysiology is chronic inflammation which was known as a major risk factor for several cancers. Chronic inflammation might promote production of pro-inflammatory cytokines such as tumor necrosis factor α, interleukin-6, and leptin, resulting in cancer development and growth [5]. Increasing evidences have reported that pancreatic cancer risk is higher in metabolic disorders including type 2 diabetes, obesity, and nonalcoholic fatty liver disease [32–34]. These metabolic disorders shared chronic inflammation with pancreatic cancer. Interestingly, pancreatic cancer risk decreased by anti-inflammatory food such as curcumin and flavonoids [35]. Some medications having properties to reduce inflammation was also reported to reduce the risk of pancreatic cancer. In a meta-analysis of aspirin, aspirin use decrease the risk of pancreatic cancer by 20% compared with non-users [36]. Other non-steroidal anti-inflammatory drugs (NSAIDs) have shown similar results in the reduction of pancreatic cancer incidence [35]. Melatonin, as a potent tissue protector against inflammation, is suggested to have the protective potential on pancreatic cancer [37]. Several studies have implied that statins used for the treatment of hyperlipidemia have potential benefit for reduction of cancer risk including pancreatic cancer. An anti-inflammatory effect as well as immune modulatory effect of statin was considered crucial mechanism of chemoprevention for cancer [38]. Thus, chronic inflammatory pathway is linked to increased risk of pancreatic cancer in SLE. Because NSAIDs use is not really recommended in SLE patients due to harmful effect on the kidney, its use to reduce pancreatic cancer risk is cautious. However, considering long-lasting process of SLE, strategy to reduce chronic inflammation is beneficial to prevent the development of pancreatic cancer.

Another possible mechanism is excess autoantibody effect. A number of evidences have demonstrated that SLE-related autoantibodies were associated with DNA damage and impairment of DNA repair in several cancers except certain hormone-sensitive malignancies such as prostate, breast, and ovarian cancer [39]. Ro60/SSA antigen is related to autoimmune response which is found in systemic autoimmune

diseases including SLE and Sjogren's disease. Liu et al. reported that Ro60/SSA was upregulated in pancreatic cancer tissue and knockdown of Ro60/SSA antigen inhibited tumor growth [40]. Thus, overexpressed antigen and autoantibody reaction in SLE patient might influence the increased risk of cancer. In addition, immunosuppressive drug use, immune dysregulation, and shared genetic susceptibility were supposed to be a possible mechanism underlying the association between SLE and several cancers [10]. Further studies are warranted to clarify the mechanism linking SLE and pancreatic cancer.

Our meta-analysis has some limitations. First, aggressive surveillance for cancer after SLE diagnosis might overestimate the incidence of pancreatic cancer. Even though almost studies have excluded cancer cases diagnosed within 1~2 year after SLE diagnosis to minimize detection bias, more regular health checkup is likely to lead a detection bias. Second, most studies were conducted in North American and European countries. An incidence of SLE is varying worldwide. The highest incidence was shown in North America, whereas European countries had a lower incidence. Asia and Australia had a higher incidence than in European countries [41]. Several evidences have revealed that SLE patients in Asia had severe clinical feature and poorer prognosis compared with Caucasians [42]. Considering different incidence and outcome according to geography, more studies in other regions such as Asia, Australia, and Africa should be performed in the future. Third, we could not evaluate potential confounding variables such as smoking, alcohol drinking, BMI, immunosuppressive drugs, and concurrent chronic disease.

In conclusion, despite these limitations listed above, our study support that SLE was associated with increased pancreatic cancer risk. Although there is no reliable screening strategy in the general population, several researchers have concerned about screening test for high-risk group of pancreatic cancer. Additional well-designed and long-period followed studies are needed to confirm the association between SLE and risk of pancreatic cancer. Also, physicians dealing with SLE should pay close attention to pancreatic cancer risk from the time of SLE diagnosis, and where appropriate, they should do the efforts to find pancreatic cancer early with appropriate screening test.

**Author contributions** Seo, Yeo, and Hwang designed the study and wrote and edited the manuscript.

All four authors searched literature and extracted the data.

Hwang coordinated the study.

All four authors interpreted and discussed the results, revised manuscript, and approved the final version.

## Compliance with ethical standards

**Disclosures** None.

## References


1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
2. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV et al (2016) Pancreatic cancer. Nat Rev Dis Primers 2:16022
3. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM (2014) Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 74:2913–2921
4. Ilic M, Ilic I (2016) Epidemiology of pancreatic cancer. World J Gastroenterol 22:9694–9705
5. Abbruzzese JL, Andersen DK, Borrebaeck CAK, Chari ST, Costello E, Cruz-Monserrate Z, Eibl G, Engleman EG, Fisher WE, Habtezion A, Kim SK, Korc M, Logsdon C, Lyssiotis CA, Pandol SJ, Rustgi A, Wolfe BM, Zheng L, Powers AC (2018) The interface of pancreatic cancer with diabetes, obesity, and inflammation: research gaps and opportunities: summary of a National Institute of Diabetes and Digestive and Kidney Diseases workshop. Pancreas 47:516–525
6. D'Cruz DP, Khamashta MA, Hughes GR (2007) Systemic lupus erythematosus. Lancet 369:587–596
7. Mak A, Cheung MW, Chiew HJ, Liu Y, Ho RC (2012) Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. Semin Arthritis Rheum 41:830–839
8. Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA (2014) Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res (Hoboken) 66:608–616
9. Lee YH, Choi SJ, Ji JD, Song GG (2016) Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus 25:727–734
10. Choi MY, Flood K, Bernatsky S, Ramsey-Goldman R, Clarke AE (2017) A review on SLE and malignancy. Best Pract Res Clin Rheumatol 31:373–396
11. Cao L, Tong H, Xu G, Liu P, Meng H, Wang J, Zhao X, Tang Y, Jin J (2015) Systemic lupus erythematous and malignancy risk: a meta-analysis. PLoS One 10:e0122964
12. Mao S, Shen H, Zhang J (2016) Systemic lupus erythematosus and malignancies risk. J Cancer Res Clin Oncol 142:253–262
13. Song L, Wang Y, Zhang J, Song N, Xu X, Lu Y (2018) The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther 20:270
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
15. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25:603–605
16. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
18. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
19. Abu-Shakra M, Gladman DD, Urowitz MB (1996) Malignancy in systemic lupus erythematosus. Arthritis Rheum 39:1050–1054
20. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH (1997) Non-Hodgkin's lymphoma and other cancers among a

cohort of patients with systemic lupus erythematosus. Arthritis Rheum 40:761–768
21. Cibere J, Sibley J, Haga M (2001) Systemic lupus erythematosus and the risk of malignancy. Lupus 10:394–400
22. Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A (2002) Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 31:66–71
23. Parikh-Patel A, White RH, Allen M, Cress R (2008) Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control 19:887–894
24. Dreyer L, Faurschou M, Mogensen M, Jacobsen S (2011) High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis Rheum 63:3032–3037
25. Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, Zoma A, Manzi S, Urowitz MB, Gladman D, Fortin PR, Ginzler E, Yelin E, Bae SC, Wallace DJ, Edworthy S, Jacobsen S, Gordon C, Dooley MA, Peschken CA, Hanly JG, Alarcón GS, Nived O, Ruiz-Irastorza G, Isenberg D, Rahman A, Witte T, Aranow C, Kamen DL, Steinsson K, Askanase A, Barr S, Criswell LA, Sturfelt G, Patel NM, Senécal JL, Zummer M, Pope JE, Ensworth S, el-Gabalawy H, McCarthy T, Dreyer L, Sibley J, St. Pierre Y, Clarke AE (2013) Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 42:130–135
26. Dey D, Kenu E, Isenberg DA (2013) Cancer complicating systemic lupus erythematosus–a dichotomy emerging from a nested case-control study. Lupus 22:919–927
27. Rees F, Doherty M, Grainge M, Lanyon P, Davenport G, Zhang W (2016) Burden of comorbidity in systemic lupus erythematosus in the UK, 1999-2012. Arthritis Care Res (Hoboken) 68:819–827
28. Yu KH, Kuo CF, Huang LH, Huang WK, See LC (2016) Cancer risk in patients with inflammatory systemic autoimmune rheumatic diseases: a nationwide population-based dynamic cohort study in Taiwan. Medicine (Baltimore) 95:e3540
29. Tallbacka KR, Pettersson T, Pukkala E (2018) Increased incidence of cancer in systemic lupus erythematosus: a Finnish cohort study with more than 25 years of follow-up. Scand J Rheumatol:1–4
30. Azrielant S, Tiosano S, Watad A, Mahroum N, Whitby A, Comaneshter D, Cohen AD, Amital H (2017) Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. Immunol Res 65:464–469
31. Chen YJ, Chang YT, Wang CB, Wu CY (2010) Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. Am J Med 123:1150 e1–1150 e6. https://doi.org/10.1016/j.amjmed.2010.08.006
32. Lee DY, Yu JH, Park S, Han K, Kim NH, Yoo HJ, Choi KM, Baik SH, Kim NH, Seo JA (2018) The influence of diabetes and antidiabetic medications on the risk of pancreatic cancer: a nationwide population-based study in Korea. Sci Rep 8:9719
33. Xu M, Jung X, Hines OJ, Eibl G, Chen Y (2018) Obesity and pancreatic cancer: overview of epidemiology and potential prevention by weight loss. Pancreas 47:158–162
34. Chang CF, Tseng YC, Huang HH, Shih YL, Hsieh TY, Lin HH (2018) Exploring the relationship between nonalcoholic fatty liver disease and pancreatic cancer by computed tomographic survey. Intern Emerg Med 13:191–197
35. Benzel J, Fendrich V (2018) Chemoprevention and treatment of pancreatic cancer: update and review of the literature. Digestion 97:275–287
36. Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y, Lu Z (2018) Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer 18:288
37. Tamtaji OR, Mirhosseini N, Reiter RJ, Behnamfar M, Asemi Z (2019) Melatonin and pancreatic cancer: current knowledge and future perspectives. J Cell Physiol 234:5372–5378. https://doi.org/10.1002/jcp.27372
38. Chen MJ, Tsan YT, Liou JM, Lee YC, Wu MS, Chiu HM, Wang HP, Chen PC (2016) Statins and the risk of pancreatic cancer in type 2 diabetic patients–a population-based cohort study. Int J Cancer 138:594–603
39. Noble PW, Bernatsky S, Clarke AE, Isenberg DA, Ramsey-Goldman R, Hansen JE (2016) DNA-damaging autoantibodies and cancer: the lupus butterfly theory. Nat Rev Rheumatol 12:429–434
40. Liu D, Qian W, Li D, Kong L (2018) Ro60/SSA levels are increased and promote the progression of pancreatic ductal adenocarcinoma. Biochem Biophys Res Commun 495:2519–2524
41. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W (2017) The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 56:1945–1961
42. Jakes RW, Bae SC, Louthrenoo W, Mok CC, Navarra SV, Kwon N (2012) Systematic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: prevalence, incidence, clinical features, and mortality. Arthritis Care Res (Hoboken) 64:159–168