Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

EXTENDED REPORT

Primary Sjögren's syndrome and malignancy risk: a systematic review and meta-analysis

Yan Liang, Zaixing Yang, Baodong Qin, Renqian Zhong

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2013-203305).

Department of Laboratory Diagnostics, Changzheng Hospital, Second Military Medical University, Shanghai, China

Correspondence to
Dr Yang Zaixing and Professor Renqian Zhong, Department of Laboratory Diagnostics, Changzheng Hospital, Second Military Medical University, 415 Fengyang Road, Shanghai 200003, China; yangzaixingdiyi@163.com and rqzhong@yahoo.com

YL, ZY and BQ contributed equally.

Accepted 14 April 2013
Published Online First 17 May 2013

ABSTRACT

Objective To investigate the association between primary Sjögren's syndrome (pSS) and the risks of malignancy including overall malignancy and site-specific malignancies through a systematic review and meta-analysis.

Methods We searched Pubmed before January 2013, with a restriction to English language publications. Studies were included if they met the following criteria: (1) a cohort or observational study; (2) pSS as one of the exposure interests; (3) cancer as an outcome of interest; (4) relative risk (RR) or standardised incidence rate (SIR) with 95% CIs. We used a random or fixed effects model to calculate the pooled RR according to the heterogeneity test.

Results Fourteen studies involving more than 14 523 patients with pSS were included. Compared with the general population, patients with pSS had significantly increased risks of overall cancer (pooled RR 1.53; 95% CI 1.17 to 1.88), non-Hodgkin lymphoma (NHL) (pooled RR 13.76; 95% CI 8.53 to 18.99) and thyroid cancer (pooled RR 2.58; 95% CI 1.14 to 4.03). A significant association was found in various subgroup meta-analyses for NHL but, for overall malignancy, a significant association was only found in some groups. Additionally, the number of studies exploring the association of pSS with the risk of solid malignancies was so small that we could not carry out subgroup meta-analyses.

Conclusions This meta-analysis indicates that pSS is significantly associated with increased risks of overall malignancy, NHL and thyroid cancer. However, it is not yet known whether the apparent increased risk of overall malignancy in patients with pSS is due to the relatively high prevalence of NHL in that group.

Primary Sjögren's syndrome (pSS) with a female preponderance is a systemic autoimmune disorder with secretory gland dysfunction characterised by dryness of the main mucosal surfaces including the mouth, eyes, nose and vagina.[1] The disease is one of the three most common autoimmune disorders.[2]

Since Kassan *et al*[3] first reported an increased risk of non-Hodgkin lymphoma (NHL) in patients with pSS, an increasing number of studies have explored this association. In 2005 the first meta-analysis preliminarily confirmed that pSS is closely associated with an increased risk of NHL development.[4] However, the number of studies included in the previous meta-analysis was small (only five) and, since 2005, more studies have been published. Moreover, some studies also investigated the association between pSS and the risk of cancers other than NHL, although the results remained inconclusive. To obtain a better estimation of cancer risk in pSS, we carried out the present meta-analysis of all available cohort studies relating pSS to the risks of various cancers.

MATERIALS AND METHODS

PubMed was searched (updated to 31 December 2012) for English language articles by combinations of the following terms: 'Sjögren's syndrome', 'SS' and 'cancer', 'malignancy', 'neoplasm', 'tumour', 'carcinoma', 'lymphoma' and 'relative risk', 'RR', 'standardised incidence rate', 'SIR'. All eligible articles were retrieved and their references were reviewed to identify additional relevant studies.

Studies were included if they fulfilled the following inclusion criteria: (1) a cohort or observational study; (2) pSS as one of the exposure interests; (3) cancer as one outcome of interest; (4) relative risk (RR) or standardised incidence rate (SIR) with 95% CIs available (or with data to calculate them). Studies were excluded if the effect size could not be calculated according to these studies.

All articles were retrieved and assessed independently by two reviewers (YL and ZY) who extracted data including authors, publication date, country of origin, characteristics of the study population including sex, age, diagnostic criteria for pSS, mean follow-up in years and other details of adjustment. Any disagreement was resolved by consensus.

Data extraction and statistical analysis

Publications that used established diagnostic criteria (table 1) for pSS and that reported RR or SIR with corresponding 95% CIs were selected for inclusion in the meta-analysis. The detailed method for calculating SIR and 95% CI has been described in a previous study.[5 6]

Heterogeneity of effects across studies was assessed using the χ^2 test statistic and quantified by I^2, which represented the percentage of total variation across studies that was attributable to heterogeneity rather than chance.[7] The pooled RR was estimated by a fixed effect model when there was no heterogeneity, otherwise a random effect model was used. If statistical heterogeneity was present, the Galbraith plot was used to detect potential sources of heterogeneity.[8] Subgroup analyses were carried out according to region, diagnostic criteria for pSS, study design, mean age and mean duration of follow-up. A sensitivity analysis was performed to evaluate stability by sequential omission of individual studies. Publication bias was tested by the

To cite: Liang Y, Yang Z, Qin B, *et al*. *Ann Rheum Dis* 2014;**73**:1151–1156.

Table 1 Characteristics of cohort studies on primary Sjögren's syndrome and risk of malignancies

Study	Region	Study period	Number of pSS patients	Sex	Mean age at study entry (years)	Malignancies (n)	Mean years of follow-up (years)	Estimate of relative risk	Diagnostic criteria	Adjustment for covariates
Kassan *et al*[3]	USA	1954–1976	142	F/M	NA	All (15), non-lymphoma (8), NHL (7 women)	8.1	SIR	Clinical, laboratory, and histological evidence of keratoconjunctivitis sicca and xerostomia	Age, calendar year of diagnosis
Landgren *et al*[10]	USA	1969–1996	NA	M	NA	Mouth (20), colon (12)	NA	RR	ICD	Age, calendar year, race, number of hospital visits, latency, alcoholism
Thomas *et al*[11]	UK	1981–1996	682	F/M	60.95	All (48)	4.7	SIR	ICD	Sex, age
Valesini *et al*[12]	Italy	NA	331	F/M	49.9	NHL (9), Waldenstrom's macroglobulinaemia, monoclonal gammopathy of undetermined significance	5.95	SIR	Preliminary European criteria	Sex, age, calendar year of diagnosis
Kauppi *et al*[13]	Finland	1970–1993	1385	F/M	NA	All (59), haematological malignancies (25), NHL (16), Hodgkin's disease (2), leukaemia (4), myeloma (3), other malignancies (63)	6.92	SIR	NA	Sex, age, calendar year of diagnosis
Pertovaara *et al*[14]	Finland	1977–1996	110	F/M	62	All (8), NHL (3), myeloma (1), Hodgkin's disease (0)	9	SIR	Modified Californian criteria and preliminary European criteria	Sex, age, calendar year of diagnosis
Davidson *et al*[15]	UK	1981–1988	100	F/M	NA	NHL	>10 (median)	SIR	Fox's and European criteria	Sex, age, calendar year of diagnosis
Lazarus *et al*[16]	UK	1979–2003	112	F/M	53.6	All (22), lymphoma (11), non-lymphoma (13)	10.8	SIR	Preliminary European criteria	Sex, age, calendar year of diagnosis
Theander *et al*[17]	Sweden	1984–2002	286	F/M	NA	All (33), NHL (11), lung (4), mouth and throat (1), gastrointestinal (8), skin/non-melanoma (2), melanoma (0), breast (3), female reproductive system (6), kidney/urinary tract (1), thyroid gland (1), myeloma (1), Mb Hodgkin (0), leukaemia (0), prostate/testis (2), brain (0), connective tissue (1)	8	SIR	AECG	Sex, age, calendar year of diagnosis
Zhang *et al*[18]	China	1990–2005	1320	F/M	39	All (29), lymphoma (8), multiple myeloma (2), non-haematological tumour	4.2	SIR	AECG	Sex, age, calendar year of diagnosis
Solans-Laqué *et al*[19]	Spain	1988–2008	244	F/M	57.8	NHL	8.6	SIR	Preliminary European criteria	Sex, age
Johnsen *et al*[20]	Norway	1980–2009	443	F/M	53(median)	NHL	8 (median)	SIR	AECG	Sex, age
Hemminki *et al*[21]	Sweden	1964–2008	1516	F	NA	Breast (16), cervical (2), endometrial (6), ovarian (2)	11	SIR	ICD	Age, region, socioeconomic status
Weng *et al*[22]	Taiwan, China	2000–2008	7852	F/M	54	All (227), NHL (26), liver (23), lung (29), mouth (3), nasopharynx (3), stomach (10), colon (3), rectum (5), pancreas (3), skin/non-melanoma (4), breast (37), cervix uteri (7), ovary (6), bladder (6), kidney (5), thyroid gland (14), multiple myeloma (5), prostate (7)	3.5	SIR	AECG	Sex, age

AECG, American-European Consensus Group; ICD, International Classification of Diseases; NA, not available; NHL, non-Hodgkin lymphoma; RR, relative risk; SIR, standardised incidence rate.

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

Egger linear regression test for funnel plot asymmetry and the Begg–Mazumdar test.[9] All analyses were performed with STATA V.11.0 software.

RESULTS

Characteristics of included studies

Of the 591 publications initially identified in PubMed, 14 studies were included in the meta-analysis (figure 1),[3 10–22] 8 involving 11 889 patients for overall malignancy, 11 involving 12 325 patients for NHL and 5 involving 10 953 patients for myeloma. Two studies were from Asia, two from the USA and 10 were from Europe (table 1).

pSS and risk of overall malignancy

Owing to significant heterogeneity, we used the random effect model. The result indicated that pSS was associated with a 53% increased risk for overall malignancy (table 2). The Galbraith plot showed that three studies might be major sources of heterogeneity (figure 2), two of which were conducted in Asia[18 22] and one in Europe.[16] Subgroup analysis showed that there was significant heterogeneity between the two studies in Asia but no heterogeneity in Europe (table 3). Only one study which gave a SIR of 2.23 (95% CI 1.25 to 3.67) was conducted in the USA.[3] Furthermore, pSS was significantly associated with an increased risk of overall malignancy in Europe but not in Asia.

We also performed a subgroup analysis by diagnostic criteria for pSS. The results indicated that only patients with pSS diagnosed by other criteria had an increased risk of overall malignancy (pooled RR 1.38; 95% CI 1.12 to 1.63), but those diagnosed by preliminary European criteria and the criteria of the American-European Consensus Group (AECG) did not. Additionally, subgroup analysis on study design produced large and moderate heterogeneity for hospital-based studies and population-based studies, respectively. The pooled RR was larger in hospital-based studies (pooled RR 2.25; 95% CI 1.27 to 3.22) than in population-based studies (pooled RR 1.12; 95% CI 1.00 to 1.23). Subgroup analysis showed a significant association in studies in which the mean duration of follow-up was >6.9 years but not for those with a mean follow-up of ≤6.9 years. Furthermore, significant heterogeneity was found for studies with a mean follow-up of ≤6.9 years but not for those with a mean follow-up of >6.9 years. Of note, subgroup analysis by mean age could not produce a significant result because some studies did not report the mean age of patients with pSS at entry (table 3).

pSS and NHL risk

Eleven studies explored the association of pSS and NHL risk and all showed that pSS was significantly associated with an increased risk of NHL. The pooled RR was 13.76 (95% CI 8.53 to 18.99) for NHL in a random effect model for patients with pSS compared with the general population. The possible major source of heterogeneity could not be found by the Galbraith plot because too many of the studies were outliers (figure 3). Subgroup analyses by region, diagnostic criteria for pSS, study design, mean age and mean duration of follow-up showed that patients with pSS had a significantly increased risk of NHL in various subgroups. Subgroup analysis showed significant heterogeneity among studies in Asia, population-based studies, studies on patients with pSS diagnosed by AECG criteria, with mean age ≤54 years and with shorter mean duration of follow-up (≤7.6 years) (tables 2 and 3).

pSS and other malignancy risks

The pooled RRs for other malignancies are summarised in table 2. The results showed that pSS was significantly associated with an increased risk of thyroid cancer (pooled RR 2.58; 95% CI 1.14 to 4.03) but not with other malignancy risks.

Sensitivity analysis and publication bias

No significant change in pooled RRs was found by sequential omission of individual studies, indicating that our results are stable and reliable.

Since funnel plots may be of no use in meta-analyses containing fewer than five studies,[23] funnel plots and Egger tests were used to evaluate publication bias only for meta-analyses of pooling five or more individual studies. There was no obvious funnel plot asymmetry. All the p values of the Egger tests were

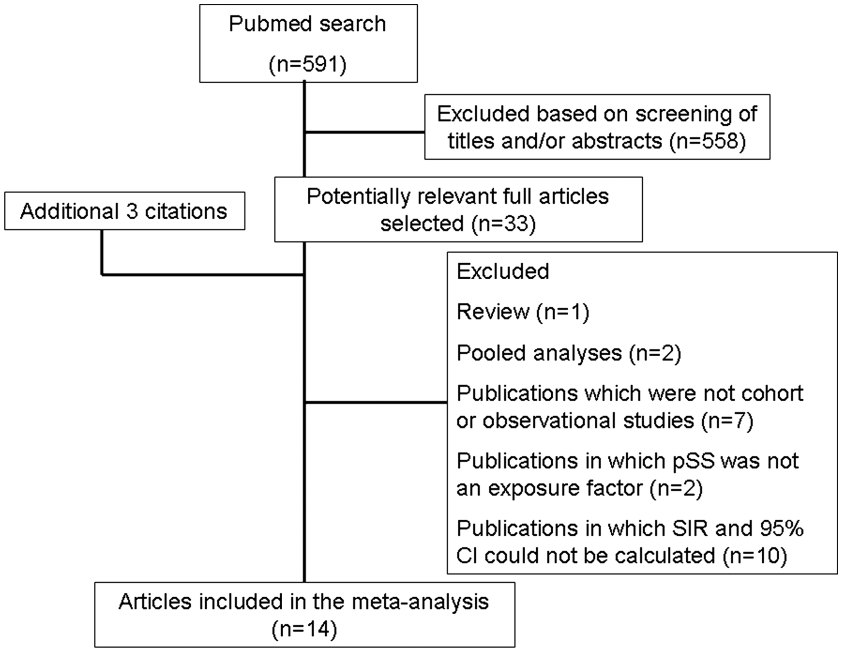


Figure 1 Flowchart of study selection.

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

Table 2 Pooled relative risks of various malignancies

Malignancies	Number of studies	References	Number of patients	Pooled RR or SIR (95% CI)	Heterogeneity	
					I^2 (%)	p Value
Overall cancer	8	3, 11, 13–14, 16–18, 22	11889	1.53 (1.17 to 1.88)	74.8	0.000
NHL	11	3, 12–20, 22	12325	13.76 (8.53 to 18.99)	58.8	0.007
Myeloma	5	13, 14, 17, 18, 22	10953	4.67 (0.85 to 8.48)	0	0.821
Mouth and throat	3	10, 17, 22	>8138	1.42 (0.80 to 2.04)	0	0.931
Lung cancer	2	17, 22	8138	1.38 (0.87 to 1.88)	0	0.393
Gastrointestinal cancer	2	17, 22	8138	0.70 (0.39 to 1.00)	59.4	0.117
Colon cancer	2	10, 22	>7852	0.56 (−0.19 to 1.30)	79.2	0.028
Skin non-melanoma	2	17, 22	8138	1.64 (0.06 to 3.22)	0	0.849
Breast cancer	3	17, 21, 22	9654	0.67 (0.27 to 1.06)	69.4	0.038
Cervical cancer	2	21, 22	9368	0.67 (0.16 to 1.18)	0	0.824
Ovary cancer	2	21, 22	9368	0.61 (0 to 1.21)	50.5	0.155
Thyroid cancer	2	17, 22	8138	2.58 (1.14 to 4.03)	0	0.659
Kidney/urinary tract cancer	2	17, 22	8138	1.08 (0.04 to 2.12)	0	0.742
Leukaemia	1	13	1385	3.6 (0.8 to 10.6)	–	–
Endometrial cancer	1	21	1516	0.72 (0.26 to 1.58)	–	–
Liver cancer	1	22	7852	1.08 (0.68 to 1.62)	–	–
Connective tissue malignancy	1	17	286	7.14 (0.18 to 39.80)	–	–

NHL, non-Hodgkin lymphoma; RR, relative risk; SIR, standardised incidence rate.

>0.05, suggesting that publication bias was not evident in various meta-analyses (see online supplements 1–3).

DISCUSSION

To our knowledge, this is the first meta-analysis to assess pSS and malignancy risks. We found that pSS is significantly associated with increased risks of overall malignancy, NHL and thyroid cancer.

Some studies examined the association between pSS and overall malignancy risk but no consistent conclusion was drawn.[3 11 13 14 16–18 22] The present meta-analysis with more strong evidence confirmed that pSS is closely associated with an increased overall risk of malignancy. Patients with pSS may have an increased risk of overall malignancy of about 53%. However, this association seemed to be influenced by different diagnostic criteria for pSS. Patients with pSS diagnosed by preliminary European criteria and AECG criteria did not show a significant association. Therefore, when exploring the association between pSS and overall malignancy risk, the diagnostic criteria must be considered. Admittedly, the number of studies included in our various subgroup analyses was too small to draw firm conclusions and the association remains to be further investigated in patients with pSS by various diagnostic criteria. In addition, this significant association must be confirmed in both population-based and hospital-based studies. The RR from hospital-based studies is far higher than that from population-based studies. The reason may be that hospitalised patients with pSS have more severe disease, which suggests that more severe pSS is more likely to develop into malignancy. Subgroup analysis by region showed that the association could only be confirmed in European populations. However, a larger number of studies are needed to investigate the association in regions other than Europe. In addition, our subgroup analyses indicated that the association is also influenced by follow-up duration. If the mean duration of follow-up is not long enough (≤6.9 years), pSS may not show an association with the risk of overall malignancy. This may be because of the possibility of overlooking cases of pSS-associated malignancy that developed later in the disease process.

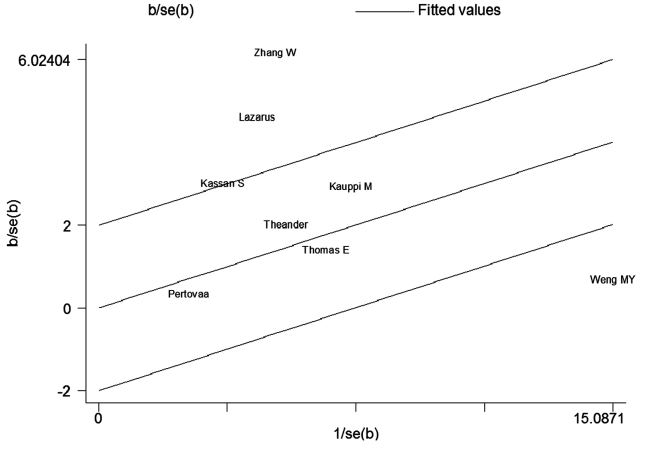


Figure 2 Galbraith plots of association between pSS and risk of overall malignancy.

Several studies have shown a significantly increased risk of NHL in patients with pSS, particularly in women and in mixed sex groups of patients. Our meta-analysis confirmed this result with a more precise estimate. Similar results were found in various subgroup analyses. However, there are three noteworthy points to address. First, the number of studies in regions other than Europe is too small so further studies are needed in other regions. Second, the RR from hospital-based studies is much higher than from population-based studies, suggesting that the severity of pSS is significantly associated with an increased risk of NHL. Third, only one study examined the risk of NHL in male patients with pSS and found that pSS is not associated with NHL risk.[22] It is therefore essential to investigate the association in men with pSS, although this is difficult due to the large predominance of women in pSS.

The present meta-analysis of five studies without between-study heterogeneity confirmed that pSS has no association with the risk of myeloma, which at least partly suggests that the aetiology between NHL and myeloma may be different. In addition, we carried out meta-analyses on the association of pSS with risks of several solid tumours and our results suggested

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

Table 3 Stratified analyses of pooled relative risks of overall malignancy and NHL in patients with primary Sjögren's syndrome (pSS)

Stratified analysis	Number of studies	Number of pSS patients	Pooled RR or SIR (95% CI)	Heterogeneity	
				I^2 (%)	p Value
Overall cancer					
Region					
Europe	5	2575	1.39 (1.16 to 1.61)	34.5	0.192
Asia	2	9172	1.07 (0.93 to 1.20)	92.2	0.000
USA	1	142	2.23 (1.25 to 3.67)	–	–
Diagnostic criteria					
Preliminary European criteria	2	222	1.82 (0.32 to 3.31)	77.8	0.034
AECG	3	9458	1.66 (0.86 to 2.45)	86.3	0.001
Other	3	2209	1.38 (1.12 to 1.63)	30.0	0.24
Study design					
Population-based	4	10205	1.12 (1.00 to 1.23)	50.6	0.108
Hospital-based	4	1684	2.25 (1.27 to 3.22)	69.2	0.021
Mean age (years)					
≤54	3	9284	2.22 (0.68 to 3.76)	90.1	0.000
>54	2	792	1.20 (0.87 to 1.53)	0	0.799
Unknown	3	1813	1.50 (1.20 to 1.80)	0	0.469
Mean duration of follow-up (years)					
≤6.9	3	9854	1.47 (0.87 to 2.06)	85.2	0.001
>6.9	5	2035	1.52 (1.25 to 1.80)	35.2	0.186
NHL					
Region					
Europe	8	3011	12.41 (8.70 to 16.13)	33.1	0.164
Asia	2	9172	6.38 (3.87 to 8.89)	79.6	0.027
USA	1	142	44.4 (16.70 to 118.40)	–	–
Diagnostic criteria					
Preliminary European criteria	4	797	19.27 (11.69 to 26.86)	36.5	0.193
AECG	4	9901	11.01 (3.31 to 18.72)	63.0	0.044
Other	3	1627	9.51 (4.14 to 14.87)	5.6	0.347
Study design					
Population-based	5	10297	9.68 (4.98 to 14.38)	52.8	0.076
Hospital-based	6	2028	18.90 (11.68 to 26.12)	26.8	0.234
Mean age (years)					
≤54	5	10058	19.30 (7.04 to 31.57)	76.0	0.002
>54	2	354	14.99 (6.46 to 23.53)	0	0.800
Unknown	4	1913	10.85 (6.12 to 15.58)	6.5	0.361
Mean duration of follow-up (years)					
≤7.6	4	10888	11.49 (3.54 to 19.43)	71.0	0.016
>7.6	7	1437	14.77 (9.72 to 19.82)	6.0	0.382

AECG, American-European Consensus Group; NHL, non-Hodgkin lymphoma; RR, relative risk; SIR, standardised incidence rate.

that pSS is significantly associated with an increased risk of thyroid cancer but not with other solid tumours. However, we have to acknowledge that the number of studies on the association between pSS and the risk of solid tumours is too small to draw firm conclusions and more studies are needed.

The fact that some studies could have mixed populations of primary and secondary SS must also be addressed and may profoundly influence the final results. Among our included studies, only one on the risk of NHL and two on the risk of overall malignancy may have had mixed populations of patients. Sensitivity analysis by omitting these studies confirmed that they had no impact on the results (data not shown). For studies on other cancer risks, sensitivity analysis could not be carried out due to the small number of studies (only two or three).

Some limitations must be addressed. First, some studies that failed to provide data from which SIR could be calculated were not included in the meta-analysis. The exclusion of such studies may reduce the power of our analysis but is unlikely to bias our results. Second, several variables such as body mass index, smoking, alcohol consumption and immunosuppressive therapy cannot be excluded because of an inherent flaw in these included studies which might bias the results. Third, as described in a previous study, we were unlikely to completely exclude potential publication bias even though no significant publication bias was found by funnel plot analysis in this study. This is because small studies with null results tend not to be published.[24] Fourth, some information such as age and duration of follow-up was not available from some studies so subgroup meta-analyses could only be conducted based on mean values, which may have had an impact on the estimated accuracy. Finally, data regarding pSS and the risk of solid malignancies were extremely sparse, limiting our ability to draw firm conclusions.

In summary, this meta-analysis shows that pSS is significantly associated with the increased overall risk of malignancy,

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com

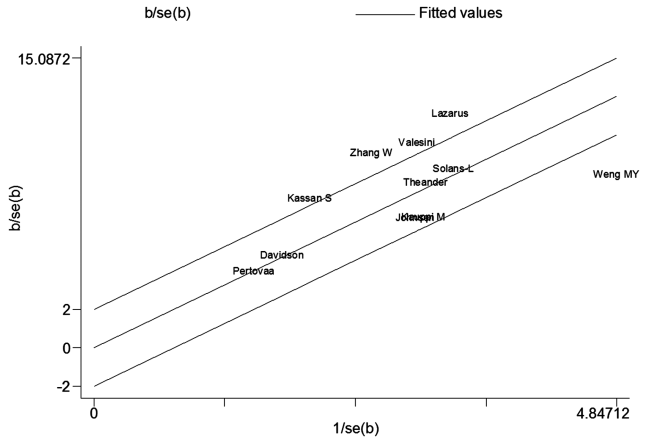


Figure 3 Galbraith plots of association between pSS and NHL risk.

especially NHL. However, it remains undetermined whether the association between overall malignancy and pSS is due to excess occurrence of NHL. Only one study investigated the association between pSS and the risk of malignancy other than NHL and did not find a significant association (SIR 1.53, 95% CI 0.89 to 2.63).[16] Two studies examined the association of pSS with the risk of non-haematological tumours rather than non-NHL tumours; one found a positive result (SIR 2.12, 95% CI 1.27 to 3.31)[18] but the other did not (SIR 1.1, 95% CI 0.8 to 1.5).[13] We therefore cannot conduct a meta-analysis to evaluate whether the increased risk of overall malignancy with pSS is due to the presence of NHL and further studies are required. A significant association might also exist between pSS and the risk of thyroid cancer, but this needs to be confirmed by further studies.

Contributors ZY initiated the study design and wrote the manuscript. YL performed the analysis. BQ and RZ checked it. All authors saw and approved the final manuscript.

Funding This study was supported by two grants from the China National Natural Science Foundation Council (81001333 and 81102262) and Changzheng Hospital Funds for Young Scholar (2011CZQN06).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, *et al*. Primary Sjogren syndrome. *BMJ* 2012;344:e3821.
2 Fox RI. Sjögren's syndrome. *Lancet* 2005;366:321–31.
3 Kassan SS, Thomas TL, Moutsopoulos HM, *et al*. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978;89:888–92.
4 Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005;165:2337–44.
5 Liang Y, Yang Z, Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012;56:1409–17.
6 Taeger D, Sun Y, Keil U, *et al*. A stand-alone Windows application for computing extract person-years, standardized mortality ratios and confidence intervals in epidemiological studies. *Epidemiology* 2000;11:607–8.
7 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:589–624.
8 Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med* 1988;7:889–94.
9 Egger M, Davey SG, Schneider M, *et al*. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
10 Landgren AM, Landgren O, Gridley G, *et al*. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million US male veterans. *Cancer* 2011;117:1163–71.
11 Thomas E, Brewster DH, Black RJ, *et al*. Risk of malignancy among patients with rheumatic conditions. *Int J Cancer* 2000;88:497–502.
12 Valesini G, Priori R, Bavoillot D, *et al*. Differential risk of non-Hodgkin's lymphoma in Italian patients with primary Sjögren's syndrome. *J Rheumatol* 1997;24:2376–80.
13 Kauppi M, Pukkala E, Isomäki H. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). *Cancer Causes Control* 1997;8:201–4.
14 Pertovaara M, Pukkala E, Laippala P, *et al*. A longitudinal cohort study of Finnish patients with primary Sjögren's syndrome: clinical, immunological, and epidemiological aspects. *Ann Rheum Dis* 2001;60:467–72.
15 Davidson BK, Kelly CA, Griffiths ID. Primary Sjögren's syndrome in the North East of England: a long-term follow-up study. *Rheumatology (Oxford)* 1999;38:245–53.
16 Lazarus MN, Robinson D, Mak V, *et al*. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. *Rheumatology (Oxford)* 2006;45:1012–15.
17 Theander E, Henriksson G, Ljungberg O, *et al*. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006;65:796–803.
18 Zhang W, Feng S, Yan S, *et al*. Incidence of malignancy in primary Sjogren's syndrome in a Chinese cohort. *Rheumatology (Oxford)* 2010;49:571–7.
19 Solans-Laqué R, López-Hernandez A, Bosch-Gil JA, *et al*. Risk, predictors, and clinical characteristics of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum* 2011;41:415–23.
20 Johnsen SJ, Brun JG, Gøransson LG, *et al*. The risk of non-Hodgkin lymphoma in primary Sjögren's syndrome, a population-based study. *Arthritis Care Res (Hoboken)*. Published Online First 8 Nov 2012. doi:10.1002/acr.21887.
21 Hemminki K, Liu X, Ji J, *et al*. Effect of autoimmune diseases on risk and survival in female cancers. *Gynecol Oncol* 2012;127:180–5.
22 Weng MY, Huang YT, Liu MF, *et al*. Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjogren's syndrome in Taiwan. *Ann Rheum Dis* 2012;71:524–7.
23 Sterne J, Becker B, Egger M. The funnel plot. In: Rothstein H, Sutton A, Borenstein M. eds. *Publication bias in meta-analysis. Prevention, assessment and adjustments*. Chichester: Wiley, 2005:75–98.
24 Ma Y, Zhang P, Wang F, *et al*. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol* 2011;29:3775–82.

Downloaded from http://ard.bmj.com/ on September 15, 2016 - Published by group.bmj.com



Primary Sjögren's syndrome and malignancy risk: a systematic review and meta-analysis

Yan Liang, Zaixing Yang, Baodong Qin and Renqian Zhong

Ann Rheum Dis 2014 73: 1151-1156 originally published online May 17, 2013
doi: 10.1136/annrheumdis-2013-203305

Updated information and services can be found at:
http://ard.bmj.com/content/73/6/1151

These include:

Supplementary Material Supplementary material can be found at:
http://ard.bmj.com/content/suppl/2013/05/16/annrheumdis-2013-203305.DC1.html

References This article cites 22 articles, 9 of which you can access for free at:
http://ard.bmj.com/content/73/6/1151#BIBL

Email alerting service Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections Articles on similar topics can be found in the following collections

Immunology (including allergy) (5101)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/