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Original Article

Thyroid cancer in systemic lupus erythematosus: a meta analysis

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Abstract: Objective: Considering inconclusive and heterogenous results, the aim of this study was to investigate the risk of thyroid cancer in systemic lupus erythematosus (SLE) by a quantitatively systematic review with meta-analysis. Methods: Electronic database of PubMed was searched for studies characterizing the associated risk of thyroid cancer in patients with SLE. The meta-analysis procedure was used to combine standardized incidence rates (SIRs) with 95% confidence intervals (CIs) to evaluate the association. Results: Seven cohort studies fulfilled the inclusion criteria and were subjected to the final analysis in the meta-analysis. Homogeneity was confirmed across the included studies. The pooled SIR based on a fixed-effect model was 2.22, with a 95% CI of 2.11-2.34. Sensitivity analyses suggested that the summary statistics obtained should approximate the actual average. Conclusion: Findings from this meta-analysis revealed the positive association between thyroid cancer and SLE risk. Individuals with SLE have a heightened risk of developing thyroid cancer.

Keywords: Meta-analysis, systemic lupus erythematosus, standardized incidence ratio, thyroid cancer

Introduction

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease characterized by chronic inflammation, autoantibodies production, complement activation and immune-complex deposition, resulting in tissue and organ damage. SLE is observed predominantly in women of childbearing age with the female: male ratio of 10:1 [1]. Though survival of SLE has improved in recent decades, the incidence and mortality of SLE patients remain higher compared with the general population, not only for all-cause mortality but also for mortality from cancer. Therefore, investigating the relationship of cancer risk in SLE has gained much attention. Thyroid cancer is a malignant neoplasm originating from follicular or parafollicular thyroid cells, which is three times more common in women than in men. Thyroid cancer, in 2010, resulted in 36,000 deaths globally up from 24,000 in 1990 [2]. The most effective management of aggressive thyroid cancer is surgical removal of thyroid gland (thyroidectomy) followed by radioactive iodine ablation and TSH-suppression therapy. Chemotherapy or radiotherapy may also be used in cases of distant metastases or advanced cancer stage. Current literatures reporting malignancies incidence in SLE varies widely, and therefore an accurate and weighted analysis of the standardized incidence rate (SIR) is of importance. The objective of this systematic review and meta-analysis of published data is to provide an accurate overview of the current risk of thyroid cancer in SLE.

Materials and methods

To identify studies characterizing the risk of thyroid cancer in patients with SLE, a searching of databases by PubMed was performed using the search terms “systemic lupus erythematosus” or SLE or lupus, and “thyroid cancer” or cancer or malignancy or neoplasm and “Standardized incidence rate” or SIR or “standardized morbidity rate” or SMR with English-language up to August 31, 2013. Studies considered in this meta-analysis should fulfill the following criteria: (1) observational-type study design including prospective, retrospective, epidemiologic, database, survey, registry, and cohort of SLE patients diagnosed according to well-defined criteria, (2) providing enough information to

Table 1. Characteristics of cohort studies included in this meta-analysis

First author	Year	Population	Cohort	No. of pts.	Person-years	Observed/Expected events for thyroid cancer
Bernatsky S	2013	Multi-centre	Multi centre clinical	16409	121 283 years	24/13.7
Bjornadal L	2002	Swedish	Administrative data-based	5715	50 246 years	1/3.5
Chen YJ	2010	Taiwan	National Health Insurance Research Database	11763	--	14/6.26
Dreyer L	2011	Danish	Central Population Register	576	7 803 years	1/0.3
Kang KY	2010	Korea	Kangnam St. Mary's hospital	914	5 716 years	1/1.03
Parikh-Patel A	2008	California	Statewide patient discharge data	30478	157 969 years	30/16.4
Ragnarsson O	2003	Icelandic	Icelandic SLE database	238	2 774 years	1/0.58

Table 2. Summary results of thyroid cancer in SLE

First author	SIR	95% CI
Bernatsky S	1.76	1.13-2.61
Bjornadal L	0.29	0.01-1.60
Chen YJ	2.24	2.12-2.36
Dreyer L	3.50	0.50-25.20
Kang KY	0.98	0.00-3.85
Parikh-Patel A	1.83	1.24-2.62
Ragnarsson O	1.22	0.06-9.40
Summary	2.22	2.11-2.34

Table 3. Sensitivity analysis by omitting each study at a time

Excluded Studies	SIR (95% CI)
Bernatsky S	2.23 (2.11-2.35)
Bjornadal L	2.22 (2.10-2.34)
Chen YJ	1.77 (1.35-2.33)
Dreyer L	2.21 (2.11-2.34)
Kang KY	2.22 (2.11-2.34)
Parikh-Patel A	2.23 (2.11-2.35)
Ragnarsson O	2.22 (2.11-2.34)

obtain a SIR with its 95% confidence interval (CI). We attempted to avoid overlap by excluding studies for which updated manuscripts were available.

The SIR accompanied by a 95% CI was extracted from individual study. When these statistical variables were not provided, they were calculated from the observed and expected incidence rates presented in the study (SIR = number of observed thyroid cancer per number of expected thyroid cancer), and a 95% CI was determined assuming that the frequency of observed cases followed a Poisson distribution.

Heterogeneity test across studies was determined with the chi-squared based Q-test. Summary estimates were calculated based on a fixed-effect model (Mantel-Haenszel method) [3]. Potential publication bias was sought by the methods of Egger et al. [4] and Begg et al. [5]. All analyses were carried out using STATA software version 9.0 (Stata Corp., College Station, TX).

Results

A total of seven studies were identified that met the inclusion criteria [6-12]. Characteristics of the included studies are summarized in **Table 1**. In brief, one study was from a multi-centre cohort, one from Sweden, one from Taiwan, one from Denmark, one from Korea, one from California, and one from Iceland. The seven studies together include 66,093 patients with SLE, and totally 72 patients with thyroid cancer were observed after SLE diagnosed.

Data were pooled by use of the fixed effects model as the heterogeneity test was insignificant (Q = 5.30, df = 6, P = 0.506), and the pooled estimate revealed a significantly increased overall SIR for thyroid cancer in SLE of 2.22 (95% CI: 2.11-2.34) (**Table 2**). Sensitivity analysis was performed by omitting each study at a time to assess the stability of the meta-analysis. When any single study was removed, the corresponding pooled SIRs were not substantially altered (**Table 3**), suggested that the summary statistics obtained should approximate the actual average.

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. There was no indication of publication bias from either Egger's (P = 0.548) or Begg's (P = 0.082) tests.

Discussion

In recent years, several epidemiological studies have attempted to characterize the incidence of thyroid cancer in SLE patients. However, the findings from different studies are inconsistent due to the inconsistent of methodology and sample sources. Bernatsky et al. [6] showed an increased incidence of thyroid cancer in SLE in an international multi-centre cohort study, and other two studies from Chen et al. [8] and Parikh-Patel et al. [11] also noted an elevated risk for thyroid cancer. However, other studies [7, 9, 10, 12] failed to suggest an association between SLE and thyroid cancer.

Meta-analysis is a widely accepted tool in which individual study findings on the same topic are statistically integrated and analyzed. Therefore, we quantitatively combined seven cohort studies including 66,093 patients with SLE in this systematic review, and totally 72 patients with thyroid cancer were observed after SLE diagnosed. Summary SIR indicated a significantly increased risk of thyroid cancer in patients with SLE.

SLE patients, by virtue of their disease, have basic defects in immune cell function, resulting in immune dysregulation. These defects could also be potentiated by immunosuppressive therapy and lend further concern that this population may be at increased risk for developing cancer [13]. Other factors including exposure to medication and vital agents might play a critical role in the development of cancer in SLE cases [14].

Why was a higher risk of thyroid cancer observed in SLE? Few studies have attempted to determine the potential pathogenesis. Several reports have suggested the association of SLE and thyroid autoimmunity. Autoimmune thyroid diseases could cause thyroid inflammation, which is associated with an increased risk of thyroid cancer [15]. Furthermore, an association between thyroid cancer and chronic thyroiditis has been observed in many studies [16].

Several limitations should be noted in this paper. Due to the limited literature, our analyses are just based on fewer studies. Thus, the results should be interpreted with caution. We did not have enough information about confounding factors, such as age, environmental triggers, and an adjusted estimates could not be obtain.

In summary, the published data to date support an increased risk of thyroid cancer in patients with SLE. Further studies focusing on the underlying mechanisms between SLE and cancer risk are needed.

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Disclosure of conflict of interest

None.

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