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The risk of cancer development in systemic sclerosis: A meta-analysis

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ABSTRACT

Objectives: Systemic sclerosis is a multi-system disorder of connective tissue characterized by Raynaud's phenomenon and fibrosis of various organs. The risk of development of cancer in systemic sclerosis (SSc) has been extensively investigated with inconclusive results. To shed some light on the controversy, we conducted a meta-analysis of all published articles linking SSc to the risk of cancer development. *Methods*: Relevant electronic databases were searched for English-language studies characterizing the association of cancers in patients with SSc. Standardized incidence rate (SIR) with its 95% confidence interval (CI) of each study was combined using a fixed/random effect model. *Results*: A total of seven papers including 7183 SSc patients were identified, of which 7 reported the SIR for lung cancer, 4 for non-Hodgkin's lymphoma (NHL) and 4 for hematopoietic cancer and 7 for breast cancer. Compared with the general population, the combined SIR was 3.14 (95% CI: 2.02–4.89), 2.68 (95% CI: 1.58–4.56), 2.57 (95% CI: 1.79–3.68) and 1.09 (95% CI: 0.86–1.38), respectively. Significant heterogeneity was observed in lung cancer group ($Q = 26.13$, $P < 0.001$, $I^2 = 77\%$). Potential publication bias was absent. *Conclusions*: This present meta-analysis demonstrated an increased risk of lung, non-Hodgkin's lymphoma and hematopoietic cancers among patients with SSc, but not for breast cancer. However, some of the available data were several decades old, and future studies taking new treatment strategies into account are required.

1. Introduction

Systemic sclerosis (SSc) is a multi-system disorder of connective tissue with unknown etiology, characterized by excessive fibrosis in the skin and various internal organs such as the lung, kidney and heart. SSc is generally divided into two categories based on the extent of skin fibrosis: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) [1,2]. SSc is observed predominantly in black females, with a peak of incidence between 45 and 64 years of age [3]. Incidence rates and prevalence estimates vary wildly, which Europe, United States, Australia, and Argentina suggest a prevalence of 150–300 cases per million with a lower prevalence noted in Scandinavia, Japan, the UK, Taiwan, and India [4].

Risk factors of cancer such as smoking and a family history of cancer were more commonly observed in the SSc patients who developed cancer, suggesting a multifactorial pathogenic mechanism involving both genetic contributions as well as other defined cancer risk factors [5]. Besides, researches suggested that underlying mechanism of carcinogenesis in some types of cancers in patients with systemic sclerosis is persistent inflammation, the immunosuppressive mechanism of the disease, or treatments [6]. Studies have indicated that the risk of cancer is elevated in SSc patients, and SSc is probably associated with cancers of the breast, hematological and lung cancer. The four selected cancer are most commonly described in recent studies. But the results from different studies are inconsistent. Chatterjee et al. [7] did not find statistical evidence of an increased incidence of cancer in SSc patients, except for liver cancer. The cancer incidence in lcSSc patients showed an odds ratio of 1.98 as compared with patients with dcSSc, which was significant difference ($P = 0.042$). Whereas, Hill et al. [8] found that dcSSc had a highest relative risk of cancer in contrast to lcSSc. In a recent nationwide population study in Taiwan, Kuo et al. [9] found SSc patients were at high risk of developing cancer, especially of the lung, oral cavity and pharynx,

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Table 1
Characteristics of studies of systemic sclerosis and cancer incidence.

Source (country)	Calendar period	No. of patients	Duration of follow-up (year)	SSc patients ascertainment	Tumor type (O/E): SIR (95% CI)
Chatterjee et al. [7] (Detroit)	1973–2004	538	NA	From Michigan Scleroderma Registry According to the American Rheumatology Association criteria	Lung cancer (10/8.16): All: 1.23 (0.59–2.25) Male: 2.33 (0.48–6.80) Female: 1.29 (0.52–2.65) Breast cancer (9/11.17): Female: 0.81 (0.37–1.53) NHL (2/1.69): All: 1.18 (0.14–4.28) Female: 1.61 (0.20–5.83)
Hill et al. [8] (South Australia)	1993–2000	441	Male: 5.5 years Female: 6.1 years	From the South Australian Scleroderma Registry. According to the American Rheumatology Association criteria	Lung cancer (12/2.03): All: 5.9 (3.05–10.31) Male: 9.32 (4.02–18.37) Female: 3.41 (0.93–8.72) Breast cancer (8/4.94): Female: 1.62 (0.70–3.19) Hematopoietic (2/1.74): All: 1.15 (0.14–4.14) Male: 0.00 (0.00–7.98) Female: 1.56(0.19–5.64)
Rosenthal [14] (Sweden)	1965–1983	917	8.07 years, 7403PY	From the Swedish inpatient discharge registry According to the seventh revision of the International Classification of Diseases code up to 1968 and the eighth revision for the years 1969–1983	Lung cancer (15/3.06): All: 4.9 (2.8–8.1) Male: 4.5 (1.9–8.9) Female: 5.5 (2.2–11.3) Hematopoietic (7/3.04): All: 2.3 (0.9–4.8) Male: 2.6 (0.5–7.5) Female: 2.2 (0.6–5.5) NHL(4/1.38): All: 2.9 (0.8–7.4) Male: 1.9 (0–10.7) Female: 3.5 (0.7–10.2) Breast cancer (8/7.27): Female: 1.1 (0.5–2.1)
Derk [5] (USA)	1987–2002	769	4.9 years, 3775PY	From the Scleroderma Center According to the American Rheumatology Association criteria	Lung cancer (10/6.45): All: 1.55 (0.54–2.56) Male: 3.29 (0.43–7.01) Female: 1.47 (0.29–2.65) Breast cancer (25/25.25): Female: 0.99 (0.41–1.57) NHL (7/0.37): Male: 19.04 (0.38–37.7)
Olesen et al. [6] (Danish)	1977–2006	2040	6.4 years, 16,003.1PY	From the Danish National Registry of Patients According to the American Rheumatology Association criteria	Lung cancer (29/13.8): All: 2.1 (1.4–3.0) Male: 2.5 (1.2–4.8) Female: 2.0 (1.2–3.0) Hematopoietic (18/7.2): All: 2.5 (1.5–4.0) Male: 5.5 (2.5–10.4) Female: 1.6 (0.8–3.1) NHL (10/4): All: 2.5 (1.2–4.6) Male: 3.4 (0.7–10.0) Female: 2.2 (0.9–4.6) Breast cancer (26/26): Female: 1.0 (0.7–1.5)
Kuo [9] (Taiwan)	1996–2008	2053	Male: 6.3 years Female: 5.7 years	From the Taiwan National Health Insurance Research Dataset and the National Death Registry	Lung cancer (21/5): All: 4.20 (2.67–6.42) Male: 5.00 (2.54–8.91) Female: 3.67 (1.93–6.37) Breast cancer (11/8): Female: 1.38 (0.72–2.39) Hematopoietic (7/2): All: 3.50 (1.53–6.92) Male: 1.00 (0.05–4.93) Female: 6.00 (2.43–12.48)
Hashimoto [15] (Japan)	1973–2008	405	4787PY	From Kitasato University Hospital According to the American Rheumatology Association criteria	Lung cancer(10/1.75): All: 5.73 (2.18–9.29) Female: 6.48 (2.46–10.50) Breast cancer(4/3.92): 1.02 (0.02–2.02)

NHL, non-Hodgkin's lymphoma; PY, person-years; SIR, standardized incidence rate; CI, confidence interval.