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Review

Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature

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ABSTRACT

Conflicting data have been published regarding the risk of cervical lesions among women with systemic lupus erythematosus (SLE). We systematically reviewed the evidence for an association of SLE with cervical precancerous lesions (high-grade squamous intraepithelial lesions, HSIL), and performed a meta-analysis to determine the risk of HSIL in SLE patients. Observational studies identified up to February 2013 from the Medline, Embase and Cochrane databases were selected if they assessed the prevalence of HSIL in female SLE patients versus healthy female controls and included in a meta-analysis with pooled effect estimates obtained using a random-effects model. Of 235 citations retrieved, 7 studies met inclusion criteria. The pooled odds ratio for the risk of HSIL in SLE patients ($n = 416$) versus female controls ($n = 11{,}408$) was 8.66 (95% CI: 3.75–20.00), without significant heterogeneity across studies. Cumulative meta-analysis according to year of study publication revealed a slight increase in the risk of HSIL in the 2001–2011 period and then a stabilization afterwards. This meta-analysis shows that the risk of HSIL is significantly increased in SLE patients, compared to healthy female controls. This suggests that women with SLE may benefit from HPV vaccines and specific cervical cancer screening.

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1. Introduction

The prognosis of systemic lupus erythematosus (SLE) has improved constantly over the last decades, due to advances in therapeutic modalities and more judicious use of existing therapies, in particular steroids and cytotoxic agents. However, patients with SLE still carry a heavy burden of morbidity owing to organ damage as well as a significant mortality due to infections and cancer. Compared to the general population, the risk of cancer is increased by 15% in SLE [1,2] and the incidence of virus-induced cancer appears to be particularly high in SLE patients [3]. In a prospective Canadian cohort study [4], the risk of cervical cancer, which was mainly carcinoma in situ, was increased with a standardized incidence ratio (SIR) of 8.15 (95%CI: 1.63–23.81). The causal role of HPV infection in cervical cancers has been firmly established and HPV types 16 and 18 are considered as the causative agents of 70% of cervical cancers [5]. It is therefore crucial to decide whether SLE patients should benefit from a specific gynecological follow-up, including either HPV vaccines against HPV types 16 and 18 or cervical cancer screening, or both. Few studies, mostly performed on small samples, have evaluated the rate of HPV-related cervical lesions among women with SLE and conflicting results have been reported [1,2]. Here, we conducted a systematic review of the literature and a meta-analysis to quantify the risk for high-grade squamous intraepithelial lesions (HSIL), the precancerous cervical lesions [5,6] in patients with SLE compared to a healthy control population. We used the cytological criteria of HSIL, rather than the histological one of high grade cervical intraepithelial neoplasia, since cervical cancer screening is performed through cytological screening [7]. We believe that these data may provide useful guidance to clinicians and policymakers for implementing primary prevention through HPV vaccination and specific screening guidelines in women with SLE.

2. Methods

This meta-analysis was performed in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group [8].

2.1. Literature search

Two main investigators (E.Z. & L.A.) searched EMBASE (1974-February 2013), MEDLINE (1966-January 2013) and the Cochrane Database of Systematic Reviews (The Cochrane Library, 2013, issue 1) for original articles without language restrictions. The search strategy combined free text search, exploded MESH/EMTREE terms and all synonyms of the following Medical Subject Headings terms: *systemic lupus erythematosus, human papillomavirus, cervical dysplasia, squamous intraepithelial lesions, cervical intraepithelial neoplasia, carcinoma in situ, cervical cancer,* and *vaginal smears* (see the detailed search strategy in appendix A). We also searched for additional articles from the reference list of relevant papers obtained from the electronic search. In addition, the grey literature was explored by hand-searching the conference abstracts of the American College of Rheumatology and the European League Against Rheumatism until January 2013.

2.2. Study selection

Selection criteria were determined before data collection. Observational studies were considered if they included female patients with SLE, and if a 2×2 table could be constructed based on the prevalence of HSIL (in accordance with the Bethesda classification system [6]), in SLE patients versus healthy female controls. Reviews, editorials, guidelines, case reports, articles on different outcomes and sub-studies of eligible studies were excluded. Whenever disagreement in study selection occurred, it was resolved by discussion between the two main investigators until a consensus was reached. A log of reasons for rejection of citations identified from the searches was kept. When we identified patients that had been included in multiple papers [9,10], the analysis was limited to the study with the largest number of patients in order to avoid duplications.

2.3. Data extraction, disease definitions and management of duplicate patients

The data were simultaneously and independently extracted by the two main investigators. The recorded information for each selected

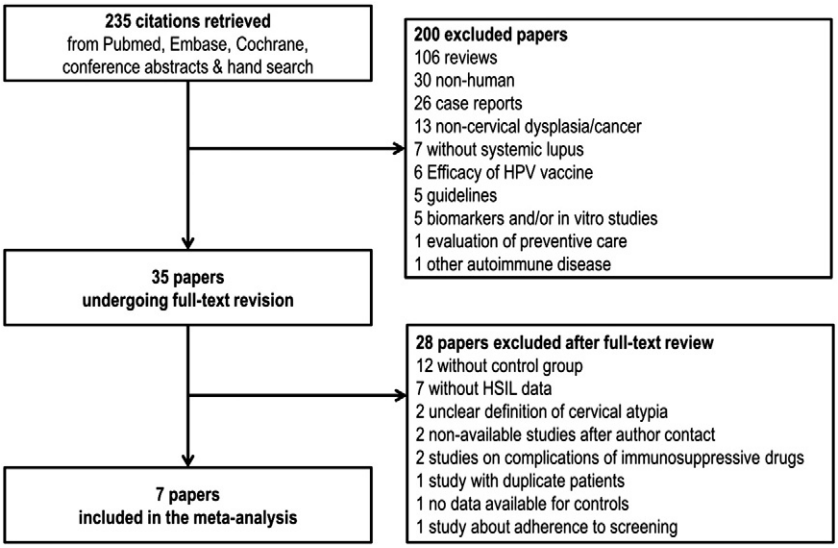

Fig. 1. Flow-chart for study selection.