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ORIGINAL ARTICLE

Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review

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Abstract The purpose of this study was to review and evaluate systematically the scientific evidence on the relationship between systemic lupus erythematosus (SLE), human papillomavirus (HPV) infection, pre-cancerous cervical abnormalities, and cervical cancer. Establishing strict inclusion and exclusion criteria, we performed an extensive search for studies in MEDLINE and BIREME databases to assess the studies that evaluated the frequency of HPV infection, pre-cancerous cervical abnormalities, and cervical cancer in women with SLE. Secondary references were additionally obtained from the included articles. Thirty-three articles met the criteria previously established. Fifteen out of 18 studies that performed cytological analysis showed a higher frequency of squamous intraepithelial lesions in SLE patients compared with normal women. Moreover, three studies found a higher frequency of high-grade squamous intraepithelial lesions. Additionally, it was observed that women with SLE had a higher frequency of HPV infection, confirmed by molecular biology techniques. Curiously, despite the above findings, no increased frequency of cervical cancer was observed in the majority of the studies which addressed this issue. Five studies observed a relationship between cervical abnormalities and previous use of immunosuppressive drugs. This review suggests that SLE patients seem not to be at increased risk for developing cervical cancer; however, they should be considered at higher risk for HPV infection and cervical dysplasia than the general population. Thus, gynecological visits at shorter intervals seem to be a reasonable approach for those patients.

Keywords Cancer · Cervical intraepithelial neoplasia · Dysplasia · Human papillomavirus · Squamous intraepithelial lesion · Systemic lupus erythematosus

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Introduction

Human papillomaviruses (HPVs) are a group of DNA viruses that can cause benign and malignant lesions in the skin and mucous membranes.

At least 15 HPV types are associated with malignancy (high-risk HPV): HPV 16, 18, 31, 35, 39, 45, 51, 52, 56, 59, 66, 68, 69, 73, and 83 [1]. The types 16 and 18 are the most common types found in cervical squamous cell carcinoma, accounting for more than 70% of cases [2]. While the most common low-risk types are 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81. In general, more than 90% of the anogenital warts are associated with HPV 6 and 11 [3].

Several epidemiological and laboratory studies showed that persistent infection with HPV is strongly associated with squamous cell carcinoma and adenocarcinoma of the cervix [4]. Carcinogenesis secondary to HPV infection is due to viral integration into the host genome and the deletion of regulatory gene E2, resulting in the over-expression of E6 and E7 genes. The proteins encoded by these genes are capable of binding to tumor suppressor proteins, disrupting the cell cycle, and apoptosis [5].

Systemic lupus erythematosus (SLE), the prototype of the autoimmune disease is a chronic inflammatory, multisystemic disease of unknown cause. Most patients present clinical periods of exacerbation and periods of reduced activity of the disease [6]. SLE, as well as other immunological conditions, by itself or in combination with immunosuppressive therapy, theoretically may predispose the development of proliferative diseases [7–13].

A possible association between SLE and increased frequency of HPV infection, squamous intraepithelial lesions, and cervical cancer is not well defined. The aim of this study is to review and evaluate the scientific evidences on the relationship between SLE, HPV infection, pre-cancerous cervical lesions, and cervical cancer.

Methods

Inclusion criteria of the studies This review included cross-sectional, case-control, retrospective, and prospective cohort studies that evaluated frequency of HPV infection, cervical abnormalities, and cervical cancer in patients with SLE.

Exclusion criteria of the studies Review articles and studies that include self-reported diagnoses were excluded.

Search strategy MEDLINE database and Biblioteca Regional de Medicina (BIREME, a specialized center of PAHO/WHO) database were searched using the following keywords: *Systemic lupus erythematosus, human papillomavirus 16, human papillomavirus 18, papillomaviridae, papillomavirus, uterine cervical neoplasm, dysplasia, neoplasia, neoplasm, intraepithelial, NIC (neoplasia intraepithelial cervical), HPV, pap smears, cervix carcinoma, cancer, malignancies.* MeSH, the US National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE was used. There was no restriction regarding the time of publication or language. Secondary references were additionally obtained from the included articles.

Methodology used for review After the search for articles was made, the authors independently evaluated whether the articles analyzed could be included in the review. The full articles were assessed, with the exception of five studies that were in abstract form from international meetings [14–18]. The following data were extracted: study design, sample size, number of controls, diagnostic criteria, measures of frequency of HPV infection, cervical neoplasia, cervical cancer, and the association with immunosuppressive drugs.

Classification of cervical lesions We kept the original nomenclature for cervical lesions used in each article. The cytological findings observed in Pap smear are presented as cervical dysplasia, cervical intraepithelial neoplasia (CIN), or squamous intraepithelial lesion (SIL). Currently, the 2001 Bethesda system classified the squamous epithelial lesions into two groups: low-grade squamous intraepithelial lesions (LGSIL or LSIL), which correspond to CIN I and high-grade squamous intraepithelial lesions (HGSIL or HSIL) corresponding to CIN II and III [19].

Results

From the primary search, 30 articles were selected and analyzed. Secondary search performed in these studies, resulted in the inclusion of 26 articles, ending up with 56 articles. Of these, 33 articles met the criteria previously established. The types of studies selected were with 24 cohorts (nine prospective and 15 retrospective), six cross-sectional, and three case-control.

Five studies performed diagnostic techniques of molecular biology for the detection of HPV infection [15, 16, 20–23]. Nath et al. found that SLE patients as well as patients without SLE with abnormal smears had a higher prevalence of infection with HPV compared with those individuals with normal smears without SLE (15/30 in the SLE group, 37/67 in abnormal smears group, and 0/15 with normal smear) [22]. Tam et al. observed a higher prevalence of infection with multiple HPV types in SLE patients compared with healthy control group (4.7% vs. 1.1%). Moreover, the group of SLE patients showed 10.6% of high-risk HPV infection compared with 4.2% in the control group [20].

Conversely, Berthier et al. found no significant difference between latent HPV infection in the group of SLE patients compared with controls, although this may be justified by the small sample size evaluated in the SLE group [23]. Sayag-Boukris et al. showed 3/66 cases of latent infection by HPV in the SLE group and 6/122 cases in the control group, which was not statistically significant [16].

A higher frequency of abnormal cervical pre-malignant lesions in SLE was observed in 15 out of 18 studies that evaluated this issue (Table 1). A higher frequency of HGSIL in patients with SLE was described by Barros et al., who found 5/76 cases of HGSIL in the SLE patients and no cases in 80 control patients [24]. Similarly, Tam et al. observed 3.5% of HGSIL in a group of 85 patients with SLE compared with 0.5% in the 2,080 healthy women group [20] as well as Dhar et al., who found 13/321 cases of HGSIL or cervical cancer in the SLE group and 9/747 cases in the control group [25]. Moreover, Tam et al. noted that previous diagnosis of SLE was an independent predictive factor for abnormal Pap smears, after logistic regression analysis [20]. In a prospective cohort with a 3-

Table 1 Main features of studies on HPV infection and cervical pre-malignant lesions in SLE

Reference, author (year)	Origin	Study design	Number of women with SLE	Control (women)	Outcome	Association between immunosuppressive treatment and cervical dysplasia/ HPV infection
Nyberg et al. [38] (1981)	Sweden	Retrospective cohort	80 (18 treated with cytotoxic drugs)	80 healthy	SLE group: 19/80 cases of cervical dysplasia; Control group with 9/80 cases. $P<0.05$ SLE group treated with cytotoxic drugs with cervical dysplasia in 9/18 cases (17 in current or previous treatment with Aza); Healthy control group with 2/18 cases. $P<0.05$	(Yes) Aza
Russomano et al. [18] (1986)	Brazil	Prospective cohort	48	–	SLE group with 11/48 (37.5%) of CIN.	–
Russomano et al. [42] (1989)	Brazil	Prospective cohort	70	8,804 healthy	SLE group with 10/70 cases of CIN; Control group with 65/8,804 cases. RR=22.4 (CI=13.66–36.6)	No
Blumenfeld et al. [39] (1994)	Israel	Prospective cohort	39	100 healthy/122 sterile	SLE group with 14/39 cases of cervical dysplasia Healthy group with 5/100 cases Young sterile group: 6/122 cases $P<0.01$	No
Dhar et al. [17] (1996)	USA	Retrospective cohort	29	747 healthy	SLE group with 9/29 of SIL (six LGSIL and three HGSIL); Control group with 72/747 cases (63 LGSIL and nine HGSIL). SIL with $P<0.0001$	No
Sayag-Boukris et al. [16] (1996)[a]	France	Cross-sectional	66	122 healthy	SLE group with 3% of HGSIL; 3/66 cases of latent HPV infection (one HPV16; one HPV31; one not typeable HPV); Control group with 0.8% of HGSIL; 6/122 cases of latent HPV infection (three HPV16; three not typeable HPV). Not statistically significant	–
Lima et al. [15] (1998)[a]	Brazil	Cross-sectional	83	49 healthy	SLE group with 10/83 cases of SIL (nine LGSIL and one HGSIL); 9/10 cases of HPV infection; Control group with 1/49 case of SIL; 0/1 case of HPV infection. SIL with $P=0.04$ HPV infection with $P=0.02$	–
Berthier et al. [23] (1999)[ab]	France	Cross-sectional	11	10,000 healthy	SLE group with 18% of cervical dysplasia; Control group with 3%. $P<0.01$	No
Bateman et al. [21] (2000)[a, b]	USA	Case-control	61 treated with Cyc	49 SLE not treated with Cyc	SLE group previously treated with 10/61 cases of cervical dysplasia (one carcinoma in situ/two CIN III/one CIN II/ six CIN I/three HPV+) SLE not previously treated with 2/49 cases (two CIN II/one	Yes (Cyc)

Table 1 (continued)

Reference, author (year)	Origin	Study design	Number of women with SLE	Control (women)	Outcome	Association between immunosuppressive treatment and cervical dysplasia/ HPV infection
					HPV+). P=0.03 Mean dose in the previously treated SLE group with dysplasia=19.6 mg. Mean dose in the previously treated SLE group without dysplasia=6.9 mg. Not statistically significant	
Dhar et al. [40] (2001)	USA	Retrospective cohort	29	747 healthy	SLE group with 7/29 cases of cervical dysplasia (one HGSIL and 6 LGSIL) Control group with 72/747 cases (nine HGSIL and 63 LGSIL). P<0.021	–
Ognenovski et al. [37] (2004)	USA	Prospective cohort	38 treated with cytostatics (four with Pred+Aza; eight with Pred+Cyc; 26 with Pred+Aza+Cyc)	23 SLE treated with Pred	Pred group (baseline) with 0/23 cases of CIN; Pred+Aza group with 0/4 cases; Pred+Cyc group (mean dose of Cyc=17.4 g) with 2/8 cases (two LGSIL) (P=0.0132); Pred+Aza+Cyc (mean dose of Cyc=13.9 g) with 4/26 cases in (three LGSIL and 1 HGSIL) (P=0.0497). Relationship between the cumulative dose of Cyc and increased risk of CIN Each gram with 13% increased risk	Yes (Cyc)
Tam et al. [20] (2004)[a, b]	China	Cross-sectional	85	2080 healthy	SLE group with 11.8% of SIL (8.2% of LSIL and 3.5% of HGSIL); 10.6% of high-risk HPV infection; 4.7% of multiple HPV types. Control group with 2% of SIL (1.5% of LSIL and 0.5% HGSIL); 4.2% of high-risk HPV infection; 1.1% of multiple HPV types. SIL with OR=6.6 (CI=3.2–13.7) High-risk HPV infection with OR=2.7 (CI=1.3–5.6); Multiple HPV types with OR=4.6 (CI=1.6–13.7)	No
Dhar et al. [25] (2005)	USA	Retrospective cohort	321	747 healthy	SLE group with 13/321 cases of HGSIL and/or cancer; Control group with 9/747 cases. OR=3.46 (P<0.0003)	–
Barros et al. [24] (2007)[b]	Brazil	Cross-sectional	76	80 healthy	SLE group with 7/76 cases of cervical dysplasia (two LGSIL and 5 HGSIL) Control group with 1/80 cases (one LGSIL) P=0.03	No
Nath et al. [22] (2007)[a]	UK	Cross-sectional	30	67 with abnormal smear and 15	SLE group with 15/30 cases of HPV+; Abnormal smear group with 37/67 cases;	No

				with normal smear	Normal smear group with 0/15 cases; $P<0.05$	
Febronio et al. [27] (2007)[b]	Brazil	Case-control	52	52 healthy	JSLE group with 1/52 cases of LGSIL; Control group with 2/52 cases. Not statistically significant	No
Mercado et al. [41] (2009)	Mexico	Retrospective cohort	62	1719 healthy	SLE group with 13/62 SIL (eight LGSIL and 5 HGSIL); Control group with 27/1719 cases (11 LGSIL and 16 HGSIL) SIL with OR=44.7 (CI=5.6–958)	No
Tam et al. [26] (2009) [a, b]	China	Prospective cohort	144	–	Increased in the cumulative prevalence of HPV infection (12.5% at baseline to 25% after 3 years) (P=0.006), high-risk HPV infection (11.1% at baseline to 20.8% after 3 years) (P=0.02) and multiple HPV infection (6.9% at baseline to 16.7% after 3 years) (P=0.009).	No

HPV human papillomavirus, *SLE* systemic lupus erythematosus, *JSLE* juvenile systemic lupus rrythematosus, *Pred* prednisone, *Aza* azathioprine, *Cyc* cyclophosphamide, *CIN* cervical intraepithelial neoplasia, *SIL* squamous intraepithelial lesion, *LGSIL* low-grade squamous intraepithelial lesion, *HGSIL* high-grade squamous intraepithelial lesion, *OR* odds ratio, *RR* relative risk, *CI* confidence interval

[a] Studies that performed molecular biology techniques

[b] Studies that did not utilize histophathologic techniques

year follow-up, Tam et al. observed an increasing in the cumulative prevalence of HPV infection, high-risk HPV infection, and multiple HPV infection following-up 144 patients [26]. Only Febronio et al. did not find an increased frequency of cervical dysplasia in the SLE group, compared with control (1/52 vs. 2/52) [27].

Regarding the association between SLE and cancer, it was found that there was no increased frequency of cervical cancer in patients with SLE in 14 out of 15 articles which evaluated this association (Table 2) [7, 9–12, 14, 28–35]. Bernatsky et al. found 431 cases of malignancies being 14 of cervical cancer in a multicenter, multinational, retrospective cohort where 9,547 patients were included. This figure was similar to the normal population [32]. Likewise, four other studies found no cases of cervical cancer during the follow-up of 434, 238, 116, and 39 patients with SLE, respectively [28, 29, 31, 33]. Curiously, Parikh-Patel et al. observed a reduction in the standardized incidence rate (SIR) of cervical cancer in the lupus group, compared with the expected frequency in the normal population (SIR=0.55; CI=0.39–0.75) [34]. Only one study showed a higher incidence of cervical cancer in SLE comparing to the population without lupus. Cibere et al. following a cohort of 297 SLE patients, identified three cases of cervical cancer, while the incidence expected in the normal population was 0.36 cases (SIR=8.15; CI=1.63–28.81) [36].

Three studies found a positive association between prior use of cytostatics and higher frequency of cervical abnormalities. Bateman et al. observed a higher frequency of cervical dysplasia and HPV infection in the group of SLE patients treated with intravenous cyclophosphamide as compared with the group of SLE patients without previous use of this agent: 10/61 (three positive cases of HPV infection) and 2/49 (one positive case of HPV infection), respectively. It was also observed that patients using a higher dose of this drug had a higher frequency of dysplasia. Furthermore, patients using cyclophosphamide developed cervical dysplasia in a shorter time [21]. Similarly, Ognenovski et al. found a higher incidence of CIN in the group of lupus patients treated with intravenous cyclophosphamide and prednisone and the group treated with cyclophosphamide, azathioprine, and prednisone compared with the group treated with prednisone alone (2/8 cases, 4/26 cases versus 0/23 cases). A direct relationship between the cumulative dose of cyclophosphamide and risk of cervical dysplasia was also identified. Over the initial 3-year period of follow-up, a 13% increase in risk of progression from normal to CIN was observed for each gram administered [37]. Also, Nyberg et al. showed a higher incidence of cervical dysplasia in the group of SLE patients treated with cytotoxic drugs as compared with healthy control group. It was observed that 9/18 cases of cervical dysplasia in the group treated with chemotherapy

Table 2 Main features of the studies on cervical cancer and SLE

Reference, author (year)	Origin	Study design	Number of women with SLE	Control	Cancer ascertainment	Outcome	Association between immunosuppressive treatment and cervical cancer
Black et al. [28] (1982)	Australia	Retrospective cohort	39	Matched general population	Chart review	No case of cervical cancer.	–
Pettersson et al. [9] (1992)	Finland	Retrospective cohort	182	Matched general population	Tumor registry	1/182 case of cervical cancer. Not statistically significant	No
Pryor et al. [14] (1993)	USA	Case-control	85 treated with Cyc	85 not treated with Cyc	–	1/85 case of cervical cancer Not statistically significant Gynecologic cancer was more common among Cyc users	Yes (Cyc)
Abu-Shakra et al. [7] (1996)	Canada	Prospective cohort	627	Matched general population, 1,426 patients with RA and 248 patients with SS	Chart Review	1/627 cases of cervical cancer. Not statistically significant	–
Ramsey-Goldman et al. [11] (1998)	USA	Retrospective cohort	616	Matched general population	Tumor registry	4/616 cases of cervical cancer. Not statistically significant	–
Cibere et al. [36] (2001)	Canada	Prospective cohort	297 (84% of women)	Matched general population	Chart review and tumor registry	3/297 cases of cervical cancer. SIR=8.15 (CI=1.63–28.81)	–
Sultan et al. [10] (2000)	UK	Prospective cohort	276 (93.5% of women)	Matched general population	Chart review	1/276 cases of cervical cancer. Not statistically significant	No
Nived et al. [29] (2001)	Sweden	Retrospective cohort	116	Matched general population	Tumor registry	No case of cervical cancer.	–
Bjornadal et al. [30] (2002)	Sweden	Retrospective cohort	5.715	Matched general population	Tumor registry	10/5.715 of cervical cancer. Not statistically significant	–
Ragnarsson et al. [31] (2003)	Iceland	Retrospective cohort	238	Matched general population	Chart review	No case of cervical cancer.	–
Bernatsky et al. [32] (2005)	Canada; USA; UK; Iceland; Sweden; South Korea	Retrospective cohort	8.607	Matched general population	Tumor registry	14/8.607 cases of cervical cancer. Not statistically significant	–
Chun et al. [33]	South Korea	Retrospective cohort	434	Matched general population	Chart review	No case of cervical cancer.	–
Tarr et al. [12] (2006)	Hungary	Retrospective cohort	771	Matched general population	Chart review	5/771 cases of cervical cancer. Not statistically significant	–
Parikh-Patel et al. [34] (2008)	USA	Retrospective cohort	27.133	Matched general population	Tumor registry	38/27.133 cases of cervical cancer. SIR=0.55 (CI=0.39–0.75)	–
Kang et al. [35] (2009)	South Korea	Prospective cohort	914	Matched general population	Chart review	5/914 cases of cervical cancer. Not statistically significant Cyc therapy contributes to increase risk of global cancer	Yes (Cyc)

SLE systemic lupus erythematosus, *Cyc* cyclophosphamide, *RA* rheumatoid arthritis, *SS* systemic sclerosis, *SIR* standardized incidence rate, *CI* confidence interval

compared with 2/18 cases in the control group. Seventeen among the 18 patients were in current or previous use of azathioprine, and one woman had also taken cyclophosphamide [38].

Pryor et al. observed that general gynecologic cancer was more common among cyclophosphamide users [14]. Kang et al. showed that cyclophosphamide therapy contributes to increased risk of global cancer.

On the other hand, other studies did not evaluate or find statistically significant association between cervical abnormalities and previous use of immunosuppressive drugs for the control of SLE [15–18, 20, 22–25, 39–42].

Discussion

The findings of the present systematic review suggest that SLE predisposes to SIL, which are considered to be the lesions that precede cancer, as all studies evaluating cervical changes confirmed the increased frequency of SIL in women with SLE. Even when possible confounding factors were excluded by logistic regression as it occurred in the study by Tam et al. [20], it was found that the diagnosis of SLE directly increases the risk of developing cervical lesions as revealed by Pap smear. Additionally, studies that utilized molecular biology technology for the detection of HPV were in agreement in terms of a higher frequency of HPV infection and persistence of this virus in the cervix.

There was a disagreement among different studies regarding the role of immunosuppressive drugs as a predisposing factor for these cervical abnormalities. On one side, the majority of the studies showed no association between the use of immunosuppressive agents and increased frequency of cervical abnormalities, while two others have suggested the participation of intravenous cyclophosphamide [18, 22] on the development of this complication. Nyberg et al. observed an increased incidence of cervical dysplasia in the group of SLE patients treated with azathioprine compared with the patients not treated with this drug [20]. Additionally, Kay et al. in another study—not included in the present review as it was not related to SLE—found an increased frequency of cervical dysplasia in women using azathioprine as immunosuppressive therapy after kidney transplantation [43]. The difference in the results can be explained by the small sample size evaluated in most of these studies.

A very intriguing finding from the present review was that, despite the increase in the frequency of HPV infection and cervical dysplasia in SLE patients, the frequency of cervical cancer in SLE in all studies but one was not different from the expected frequency in the normal population. Cibere et al. found an increased incidence of cervical cancer in a group of 297 SLE patients followed-up in Canada, in contrast to all other authors that evaluated the relationship between SLE and cancer. This can be explained by the smaller sample size compared with other studies and the possible increase in the search for comorbidities inherent to studies with prospective design.

The risk for other individual malignancy types such as squamous cell skin [31] and non-Hodgkin's lymphoma [32] seems to be higher in SLE. These conflicting results may be partially understood if one assumes that, once the SLE patient has the diagnosis of HPV infection or cervical abnormality, she may seek more frequently intense medical care than the normal population avoiding the development of the cancer. Additionally, few studies have utilized molecular biology techniques to determine the types of HPV to which these patients are more susceptible.

The FDA have recently approved, in the USA, two prophylactic HPV vaccines to women aged 9 to 26 years: a quadrivalent Gardasil® (MSD), which induces immune response against HPV 6, 11, 16, and 18, and a bivalent Cervarix® (GSK), directed to HPV 16 and 18 [44]. This vaccine could not be considered an efficient prophylactic alternative to SLE patients, in spite of the possible diminished immunologic response developed by these patients against this virus.

Based on the present review, women with SLE seem not to be at elevated risk for developing cervical cancer; however, they should be considered at higher risk for HPV infection and cervical dysplasia than the general population. Thus, these patients could benefit from gynecological visits at shorter intervals.

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