

# Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review

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## ABSTRACT

An association between immune-mediated diseases and cervical pre-malignant and malignant lesions is described, having the human papillomavirus (HPV) infection a causal role. Related studies have been generally focused on systemic lupus erythematosus (SLE) patients, but relatively to other diseases, such as rheumatoid arthritis (RA), Sjögren's syndrome (SS) and systemic sclerosis (SSc), data has not been systematically evaluated.

We conducted a systematic review analysis of the literature in PubMed, including articles published until March of 2015, in patients with RA, SS, SLE and SSc, to evaluate the frequency of HPV infection, cervical dysplasia and cervical cancer, and associated factors, with particular interest on the role of glucocorticoids and immunosuppressive treatment. Moreover, safety and efficacy of HPV vaccines in these patients was investigated. Of 476 articles identified, 27 were finally included.

The studies showed an increased prevalence of cervical dysplasia and cancer, with the HPV infection being an important associated factor, in particular in SLE patients. The data relatively to other rheumatic diseases was very scarce, but an increased prevalence of smear abnormalities was also found in RA. Patients exposed to glucocorticoids and to long-term immunosuppression, particularly cyclophosphamide, have increased risk of presenting more pre-malignant lesions than the general population. The available vaccines seem to be generally safe and immunogenic in the short- period evaluation, but long-term follow-up is required to evaluate the impact of the vaccine in the protection against HPV infection and occurrence of high-grade cervical lesions.

**Keywords:** Human papillomavirus; Cervical lesions; Rheumatic diseases; Review.

## INTRODUCTION

Rheumatic systemic inflammatory diseases are conditions that can affect women in their childbearing age. Among these, rheumatoid arthritis (RA), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), are the most prevalent and less commonly systemic sclerosis (SSc)<sup>1,2</sup>. Such autoimmune disorders are associated with the activation of autoreactive T and B-lymphocytes and with the release of proinflammatory cytokines that can possibly increase the risk of cancer<sup>3</sup>. Moreover, the immunosuppressive drugs commonly used in these conditions can be responsible for a reduction in the host immune-surveillance against malignancy<sup>4</sup>. Infection risk is also increased in these patients<sup>2</sup>.

Human papillomavirus (HPV), the most common sexually transmitted infection, is thought to be the principal causal agent for cervical uterine cancer worldwide and responsible for the largest cause of mortality in women due to cancer in most developing countries<sup>5</sup>. Smoking, younger age at first intercourse, high number of sexual partners, history of sexual transmitted infections and hormonal contraception are risk factors for cervical HPV infection. The majority of HPV infections are transient and spontaneously resolve in less than one year, but persistence of the virus in the cervix and high-risk HPV types, in particular HPV type 16 and 18, are associated with progression of cervical dysplastic lesions<sup>1</sup>. Persistent HPV infection is related with older age, HPV genotype, coexisting infections, immunosuppression and inflammation<sup>1,6</sup>.

In immunocompromised hosts, the risk of HPV infection was reported to be much greater than the general population due to high-load and persistent in-

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fection with oncogenic HPV genotypes<sup>7</sup>.

An increased risk of cervical pre-malignant and malignant lesions is described in SLE patients while fewer data are available for other systemic autoimmune diseases<sup>8,9</sup>.

Early detection of pre-malignant lesions has decreased morbidity and mortality in the general population and population-based screening programs have significantly contributed to early recognition and treatment<sup>10</sup>.

Despite the increased risk, no specific recommendations have been developed for patients with systemic autoimmune diseases.

HPV vaccination is also an emerging issue in these patients; in healthy young women, the HPV vaccine is safe and immunogenic, inducing a high degree of protection against HPV16/18 serotypes in bivalent vaccine and also HPV 6/11 in the quadrivalent vaccine and their associated premalignant lesions<sup>11,12-14</sup>. In immunocompromised patients there are very few data on safety and immunogenicity related to HPV vaccines.

The aim of this study is to systematically review the available evidence to evaluate (i) the frequency of HPV infection, cervical dysplasia and cervical cancer in patients with RA, SS, SLE and SSc, (ii) if the immunosuppressive (IM) treatment is a risk factor for HPV infection, cervical dysplasia and cervical cancer and (iii) safety and immunogenicity of HPV vaccine in these patients.

## METHODS

All the steps of the present systematic literature review were performed following the Cochrane methodology<sup>15</sup> and reported according to the PRISMA statement<sup>16</sup>. Literature search was conducted in March 2015 in MedLine; studies were searched by including MeSH terms, text words, and subheadings “lupus erythematosus systemic”, “rheumatoid arthritis”, “systemic sclerosis”, “Sjögren syndrome”, “rheumatic diseases”, “autoimmune diseases”, “cervical dysplasia”, “cervical cancer”, “human papillomavirus”, “cervical intraepithelial neoplasia”, “pap smear” and “human papillomavirus vaccine”.

Searches were limited to articles on human adult patients and included only studies on RA, SS, SLE and SSc. Although no language restrictions were imposed initially, for the full-text review and final analysis we only included Portuguese, Spanish or English articles. The

reference lists of retrieved articles were also browsed to search more relevant studies to be included.

Since a systematic literature review of studies in SLE patients was already published by Santana *et al* in 2010, for this topic an update including the studies published in the last five years was performed<sup>8</sup>.

Titles and abstracts of all the studies retrieved were reviewed to identify relevant studies for inclusion. Selected articles were systematically reviewed and relevant data was collected. Articles that did not fulfill all the inclusion criteria, juvenile population, case-reports, reviews or that had insufficient data for analyses were excluded from the systematic review.

The number of patients of each rheumatic disease and controls, age, length of follow-up, type of study, cytopathologic study of cervical smear or colposcopy, DNA isolation and typing of HPV, IM treatment, the incidence or prevalence of cervical dysplasia or cancer among all patients and associated factors were extracted and summarized in the evidence tables.

Relatively to HPV vaccines in rheumatic diseases, due to very few data in this population, the authors decided to include all available data, including juvenile patients, which include the evaluation of safety and immunogenicity of HPV vaccines.

## RESULTS

We identified 476 articles from our search, of which 46 were found to be potentially relevant. Twenty-seven studies were finally included in the review.

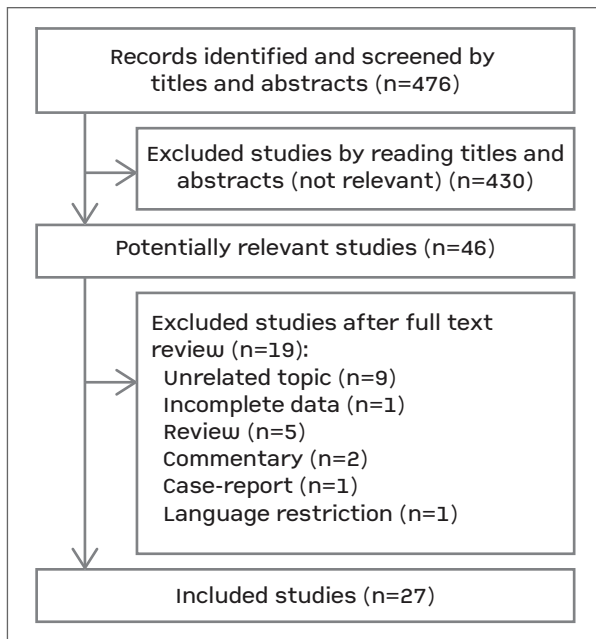
The characteristics of the studies included in the review are shown in Table I and II (available online at <http://www.actareumatologica.pt/>).

Included studies were 6 case-control studies, 11 cross-sectional studies and 10 cohort studies. The publication period runs from 2007 to 2015. Thirteen studies were from America, 7 from Europe and 7 from Asia.

Twenty-three studies reported data on frequency of HPV infection, cervical dysplasia or cervical cancer<sup>4,7,17-37</sup>. Eleven studies reported data on the role of immunosuppressants<sup>4,7,17,20,24,26,28,30-32</sup> and 4 studies focused in safety and immunogenicity of HPV vaccines in patients with rheumatic diseases<sup>11,38-40</sup>.

## FREQUENCY OF HUMAN PAPILLOMAVIRUS INFECTION AND ASSOCIATED FACTORS

Rojo-Contreras *et al.* performed two cross-sectional studies about the prevalence of cervical HPV in RA and



**FIGURE 1.** Flow-chart for study selection

SLE<sup>26</sup> and only in RA patients<sup>25</sup>. They did not find a significant difference with healthy subjects. In the first study, no association between disease activity in SLE patients and the presence of the HPV was observed<sup>26</sup>. In the second study, the factors associated with HPV infection adjusted to RA were: more than one sexual partner (OR = 5.8), more than one sexual intercourse weekly (OR = 6.7) and circumcised sexual partner (OR = 9.0)<sup>25</sup>.

Waisberg *et al.* evaluated HPV and *Chlamydia trachomatis* infections in 50 RA patients, aged matched with 50 controls, pre- and post-six months of anti-TNF treatment. A trend of lower frequency of HPV infection was observed in RA patients pre-anti-TNF compared with controls (14 vs. 30 %,  $p = 0.054$ ). HPV positive RA patients before anti-TNF therapy showed higher frequency of sexual intercourses (100 vs. 48 %,  $p = 0.014$ ), higher median number of sexual partners (1 vs. 0,  $p = 0.032$ ) and higher frequency of abnormal cervical cytology (43 vs. 7 %,  $p = 0.029$ ) than HPV negative. The age, disease duration, disease parameters and treatments were similar in both groups<sup>24</sup>.

Only one study was performed in women with Sjögren syndrome who were evaluated using cervical cytology, colposcopic examination and HPV-DNA tests, and no significant differences were observed between them and the control group<sup>27</sup>.

Relatively to SLE patients, five additional studies

evaluated HPV infection by polymerase chain reaction (PCR)-based assays for detection of HPV DNA. DNA testing showed a variable prevalence of HPV infection between 20.2% and 80.7% in the Brazilian study performed by Lyrio *et al.*<sup>7,28,31-33</sup>, comparing with a prevalence of 7.3-35.7% in healthy women (30,32). The prevalence of high-risk HPV infection was between 13.5- 72%<sup>8,29,32</sup> and 13.5% for  $\geq 2$  HPV types detected by polymerase chain reaction in a Mexican population<sup>32</sup>.

The presence of HPV infection, multiple infections, high-risk HPV types and persistent infection were associated with the development of squamous intraepithelial lesions (SIL) over a period of 3 years in the study of Tam *et al.*, but the presence of persistent high-risk HPV infection was identified as independent risk factor for the incident SIL (OR=26.9)<sup>28</sup>.

Other variables associated with HPV infection among SLE patients were  $\geq 4$  lifetime sexual partners, previous HPV infection, previous sexually transmitted disease<sup>31</sup> and younger age<sup>32</sup>.

The presence of SLE itself was found as an independent predictor for HPV infection<sup>30</sup> and a risk factor for high-risk HPV types<sup>7</sup>. The identification of Pap smear abnormalities and  $\geq 2$  sexual partners were found to be also independent risk factors for high risk HPV infection<sup>7</sup>. On the other hand, Lyrio *et al.* did not show statistically significant difference with relation to the age at first sexual intercourse, number of sexual partners, time of the diagnosis of SLE or the use of immunosuppressive drugs in SLE patients with or without cervical HPV infection<sup>30</sup>.

The study performed by Costa Pinto *et al.* aimed to determine the prevalence of *Chlamydia trachomatis* infection and if it was a risk factor for HPV-induced lesions. The prevalence of vulvar condyloma, low-grade lesion and cervical intraepithelial type 1 neoplasia were significantly higher among SLE patients, but there was no association between the presence of HPV lesions and *Chlamydia trachomatis* infections in this population<sup>29</sup>.

Tam *et al.* showed also that the use of baseline HPV testing had a higher sensitivity than abnormal cytology (defined as ASCUS) in predicting the development of SIL. Combining HPV testing and cytology at baseline only increased the sensitivity of HPV testing alone from 47.7% to 50.0%. However, repeat cytology in 6 months had the highest sensitivity and relatively high specificity (58.3% and 96.8%, respectively) in predicting the development of SIL<sup>28</sup>.

The only study in SSc that evaluated HPV status was performed by Martin *et al.*, who described multi-HPV infections near two times more frequent in the SSc group (50% vs. healthy controls 26.3%). The diffuse skin involvement, a shorter duration of the disease and a younger age at first intercourse were associated with HPV infection. Current smoking was 3 to 4 times more frequent in women seropositive for anti-HPV 16/18, compared to seronegative<sup>36</sup>.

#### FREQUENCY OF CERVICAL DYSPLASIA AND CERVICAL CANCER AND ASSOCIATED FACTORS

Four large cohort studies included different rheumatic diseases<sup>17-20</sup>. Kim *et al.* assessed the risk of high-grade cervical dysplasia in women with systemic inflammatory diseases (SID) compared with women without SID<sup>17</sup>. The incidence rate (IR) of high-grade squamous intraepithelial lesions (HGSIL) and cervical cancer was 94.2 per 100 000 person-years in the SID and 73.4 per 100.000 person-years in the non-SID cohort. In the multivariable analyses the hazard ratio (HR) adjusted for potential confounders were 1.49 in RA and 1.53 in SLE<sup>17</sup>. Chang *et al.* reported the incidence of cervical cancer increased only in patients with SLE (Standardized Incidence Ratio (SIR) =4.282) but not in RA or SSc<sup>19</sup> while other authors<sup>19,20</sup> found an increased IR in SSc (SIR=2.33 and 1.6; respectively) and slightly increased in SLE (SIR=1.39 and 1.1) and RA (SIR=1.1).

In one other case-control study including 118 patients, with different autoimmune diseases, the frequency of abnormal Papanicolaou (Pap) smear was significantly higher in the case group than controls (7.6% vs 1.7%;  $p=0.03$ ), but the frequencies of patients in SLE and RA were not significantly different from controls and no abnormal results were found in the few patients with SSc included<sup>21</sup>.

In a Mexican study of RA patients, the prevalence of abnormal Pap test and squamous intraepithelial lesions were higher than in controls (13.7% RA vs 7.0% controls; and 12.6% RA vs 1.6% controls respectively). There was no significant difference in the number of sexual partners between women with RA and controls but women with RA without abnormal Pap smear had less sexual partners than those with RA and abnormal cytology<sup>22</sup>. Gillet *et al.* in a population of 289 RA women reported a prevalence of abnormal Pap smear of 29.1%. In the multivariable logistic regression, they found ever using any birth control (OR= 2.31) and previous diagnosis of any sexual transmitted disease (OR= 3.38) to be associated with an increased risk of abnor-

mal Pap smear result<sup>23</sup>.

Relatively to SLE patients, Lee *et al.* found an abnormal Pap smear in 16.4% in comparison with 2.8% of the controls (OR 4.4, 95% CI 2.5-7.8;  $P<0.001$ )<sup>7</sup>. Also increased prevalence of HGSIL in SLE comparing with controls in the study of Klumb *et al.*<sup>4</sup>, but not in other studies<sup>27,29,30</sup>. Tam *et al.* performed a prospective cohort study, with a mean follow-up of 30.7 months, and found abnormal cervical cytology in 19% of the SLE patients and a risk of developing ASCUS and low-grade SIL of 5.8 and 3.4 per 1,000 patient-months, respectively. The presence of cervical intraepithelial neoplasia (CIN) 2 or 3 was identified at colposcopy only in 3 (2.2%) of 137 patients<sup>28</sup>. In a multivariate analysis Klumb *et al.* showed that SLE women had a 7-fold higher prevalence of cervical dysplasia and an 11-fold higher prevalence of premalignant cervical dysplasia compared with controls, and found as independent risk factors for abnormal Pap smears history of 3 or more life-time sexual partners (OR 2.44) and the diagnosis of SLE (OR 7.08)<sup>4</sup>.

Three studies, with a follow-up between 8.8 and 14.7 years determined the occurrence of cancer in patients with SLE<sup>33-35</sup>. Dreyer *et al.*<sup>33</sup> found a SIR of epithelial dysplasia/ carcinoma in situ of uterine cervix of 1.8 while Dey *et al.* a SIR of cervical cancer of 4.0 and a statistically significant association between cancer and antithyroid globulin antibodies, haematological manifestations and damage scores<sup>34</sup>. Skare *et al.*, in a recent retrospective study of 395 SLE patients, with a median follow-up of 105 months, reported an increased incidence of cervical cancer than in general population ( $p<0.0001$ ), with an OR of 10,4 and an association with disease duration ( $p=0.006$ )<sup>35</sup>.

In a Canadian study that included 320 SSc patients, an abnormal Pap test was found in 25.4%. There was a significant positive association between self-reported abnormal Pap test and diffuse skin involvement (odds ratio [OR]=1.87) and an independent association between an abnormal Pap test with smoking (OR 2.43) and younger age at disease onset<sup>37</sup>.

#### ROLE OF IMMUNOSUPPRESSIVE TREATMENT

Some studies found an association between immunosuppressive treatments and higher risk of cervical dysplasia, cervical cancer or HPV infection.

In a large cohort study, including different autoimmune diseases, the risk of cervical cancer was higher in patients exposed to azathioprine, and a relationship with higher cumulative doses (HR=2.2) and duration

of treatment ( $\geq 5$  years after high-dose exposure (HR=3.3)). No statistically significant dose-response relationship was observed for other IM except in women treated with prednisone having SLE, SS and SSc (HR=3.0)<sup>20</sup>.

In RA patients under anti-TNF therapy no short-term risk of exacerbation and/or progression of HPV genital infection was observed<sup>24</sup>.

In a study performed to determine the prevalence of cervical HPV in Mexican women with SLE and RA, they could find that the group of HPV positive patients had a higher frequency for utilization of methotrexate ( $p=0.036$ ) and a longer duration of treatment with prednisone (3.2 years vs 1.3 years,  $p=0.05$ ) compared with HPV negative<sup>26</sup>.

A relationship between long-term use of immunosuppression and a higher prevalence of low and high-grade SIL was also reported in SLE<sup>4</sup>. Particularly the use of cyclophosphamide (CYC), as shown by Tam *et al.* in their study, was found as an independent risk factor for the incident SIL<sup>28</sup>. In other studies a significantly association with higher CYC and prednisone cumulative dose in HPV positive patients was also observed<sup>31,32</sup>.

On the other hand, other authors did not find any association between cervical dysplasia, cervical cancer<sup>17,35</sup> or as risk factor for HPV infection<sup>7,30</sup> with immunosuppressive treatment or doses and time of administration<sup>4</sup>.

#### HUMAN PAPILLOMAVIRUS VACCINE

Four studies evaluated the safety and immunogenicity of HPV vaccine in rheumatic patients. Two evaluated the quadrivalent HPV vaccine in female SLE patients<sup>11,38</sup>. The first enrolled 27 SLE patients, aged 12 to 26 years, and showed to be immunogenic with seropositivity rates greater than 94% for all four HPV types. The immune response occurred, despite the immunosuppressive treatment, in approximately 60% of the patients<sup>38</sup>. The seropositivity of this cohort was higher than in those SLE patients who received the quadrivalent HPV vaccine in the study by Mok *et al.*<sup>11</sup>. In the second study, 50 SLE women and 50 healthy controls, aged 18 to 35 years, were included. The seroconversion rates were superior to 74% in SLE patients and 93% in controls at month 7, being slightly increased after 12 months. No significant correlation between HPV antibody response and age at vaccination was found, but lower seroconversion rates were noted in those patients on both mycophenolate mofetil

and prednisolone, despite the low doses (mean dose  $1.1 \pm 0.33$  g/d and  $4.8 \pm 2.0$  mg/d respectively)<sup>11</sup>.

Two studies evaluated the bivalent vaccine and HPV16/18-specific IgG antibodies in patients with juvenile SLE and dermatomyositis<sup>39</sup>, and in female patients with juvenile idiopathic arthritis (JIA) comparing with healthy adolescents<sup>40</sup>. No significant differences were found between patients and controls in HPV-specific antibody concentrations, except in patients with juvenile dermatomyositis at 7 months; however, antibody concentrations were consistently lower. In JIA patients no effect of methotrexate treatment was found on HPV16 antibodies ( $p=0.79$ ) or HPV18 antibodies ( $p=0.37$ ) and all patients on anti-TNF treatment were seropositive after vaccination. The kinetics of HPV16/18 memory B cell responses was comparable between patients and controls, but the magnitude of these responses appeared lower in JIA patients<sup>40</sup>.

No relevant differences in adverse events or worsening of the diseases were found<sup>11,40</sup>.

#### DISCUSSION

Cervical precancerous lesions, particularly high-grade SIL, may lead to invasive cervical cancer after 10 to 15 years or in some cases spontaneously regress<sup>41</sup>. In rheumatic population the diseases themselves, impairing the normal clearance mechanisms, and the current treatments could play a role in the development of pre-malignant and malignant conditions.

As already shown in the systematic review by Santana *et al.*<sup>8</sup>, our analysis confirms that the prevalence of an abnormal Pap smear is significantly increased in patients with SLE<sup>4,26</sup>. Interestingly, also in RA patients we found an increased prevalence of Pap smear abnormalities compared with healthy controls<sup>22</sup>. In this systematic literature review, very few data were retrieved for SSc, but we noted a high prevalence of self-reported abnormal Pap tests in these patients<sup>36</sup>. No significant differences were observed between patients with Sjögren syndrome and the control group<sup>27</sup>.

In the previous systematic review<sup>8</sup> the frequency of cervical cancer in SLE was not different from the general population. On the contrary, we found different data; indeed, in recent studies on larger cohorts, with a long follow-up, an increased incidence of cervical cancer in SLE patients was reported<sup>17,33-35</sup> as in SSc patients<sup>19,20</sup>.

SLE patients have an increased susceptibility to HPV

infection, high-risk HPV types and multiple infections, which can develop precancerous lesions over time<sup>7,28,31-33</sup>. The presence of the disease itself was found as an independent predictor for HPV infection<sup>30</sup> and abnormal Pap smear<sup>4</sup>. The studies also provide evidence that the exposition to prednisone and long-term immunosuppression (in special cyclophosphamide) increase the risk of presenting more pre-malignant lesions than the general population<sup>4,20,26,28</sup>.

Pap smear screening is recommended in rheumatic patients according to national guidelines and screening programs for the general population. The American College of Obstetrics and Gynecologists guidelines recommend that any low-risk woman age 30 years or older who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no sooner than 3 years later<sup>40</sup>. A strict follow-up should be performed in HPV positive woman<sup>28</sup>.

There are two licensed HPV vaccines available; EU-LAR recommendation for vaccination in paediatric patients with rheumatic diseases is to adhere to national guidelines for vaccination against HPV<sup>41,42</sup>. Limited available data suggests that currently licensed HPV vaccines are likely to be immunogenic and well tolerated in SLE and JIA patients<sup>11,36-38</sup>. In adults, the vaccination should be considered in selected patients<sup>43</sup>.

In conclusion, the studies showed an increased prevalence of cervical dysplasia and cancer, with the HPV infection being an important associated factor, in particular in SLE patients. The data relatively to other rheumatic diseases are very scarce and more studies should be performed. A specific cervical cancer screening should be performed, regardless of the use or not of immunosuppressive therapies. The available vaccines seem to be generally safe and immunogenic in the short-period evaluation, but the follow-up should be continued and clinical studies performed to assess immunogenicity and safety during the time.

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**ANEXO**

**TABLE I: RESULTS OF THE INCLUDED STUDIES**

Author, year, (reference)	Study Type	Study objectives	Population Studied (nb)/Follow-up/ Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Kim, 2014, (17)	Cohort-study USA	Risk of high-grade cervical dysplasia in women with SID compared with the risk in women without SID.	133333 patients with SDI (IBD, psoriasis, RA, SLE) vs 533332 patients without SDI Mean follow-up- 2.1y 50.3±11.8 y	<b>Pap smear, colposcopy or HPV-DNA test:</b> considered the diagnosis of HGCD and cervical cancer in one of the screening test IR of HG SIL and cervical cancer: SID- 94.2/ 100000; non-SID- 73.4/ 100000 person-years; 1.41.1 in SLE, RA (HR = 1.49 in RA and 1.53 in SLE)	Multivariable HR were increased, but not statistically significant, in RA and SLE with baseline use of systemic immunosuppressive drugs or steroids.
Chang, 2014 (18)	Cohort-study Korea	Incidence of cancers.	3586 (2104 RA, 1052 SLE, 274 SSc, 107 DM, 49 PM) Mean follow-up 7.8±4.5 y (31064 persons/year)	<b>Cervical cancer:</b> SLE (SIR=4.282) RA (SIR=1.056) SSc, DM, PM (SIR=0)	
Hemminki, 2012, (19)	Cohort-study Sweden	Risk and survival of female cancers in patients diagnosed with 33 different AID.	199466	<b>Cervical cancer:</b> SLE (SIR= 1.39) RA (SIR=1.12) SSc (SIR=2.33) SS (SIR= 0.83)	
Dugué, 2015 (20)	Cohort-study Denmark	Risk of cervical cancer in AID and the effect of IM on this risk.	341758 AID Median follow-up 7.6 years 51.2 y	<b>Cervical cancer:</b> AID- N=720 (0.2%) (SIR=1.0) SSc (SIR=1.6); RA (SIR=1.1); SS (SIR=1.2); SLE (SIR=1.1)	The risks were very similar in the first five and the following years of follow-up (SIR=1.0) and not increased in women with multiple AID. Azathioprine: the risk increased with the cumulative dose (HR of 2.2) and when cervical cancer developed at least 5 years after high-dose exposure (HR=3.3). No significant dose-response relationship with other IM except in women treated with prednisone having SLE, SSc and SS (HR=3.0).

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**TABLE I. CONTINUATION**

Author, year, (reference)	Study Type	Study objectives	Population Studied (n)/Follow-up/ Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Esmaceli, 2011, (21)	Case-control study Iran	Frequency of abnormal Pap test between AID in comparison with healthy controls.	118 AID vs 118 controls (74 SLE, 32 RA, 7 SSC, 5 AS) 32-41 AID vs 34-40 y controls	<b>Abnormal Pap smear:</b> - 7.6% AID vs 1.7% controls (p=0.03) - (6 SLE, 3 RA and 2 controls patients)	
Mercado, 2010, (22)	Cross-sectional study Mexico	Evaluate the cervicovaginal cytology.	95 RA vs 1719 controls	<b>Abnormal Pap test:</b> 13.7% RA vs 7.0% controls SIL: 12.6% RA vs 1.6% controls	There was no significant difference in the number of sexual partners between women with RA and controls. Women with RA without abnormal. Pap smear had less sexual partners than those with RA and abnormal cytology.
Gillet, 2014, (23)	Cross-sectional study United States	Potential risk factors for the association between RA and HPV infection and abnormal Pap tests.	289 RA 61 y	<b>Abnormal Pap test:</b> 29.1% In the multivariable logistic regression ever using any birth control (OR=2.31) and previous diagnosis of any STD (OR 3.38) were significantly associated with an increased risk of abnormal Pap test.	
Waisberg, 2015, (24)	Prospective study Brazil	Evaluate HPV and Chlamydia trachomatis infections in RA patients pre- and post-TNF blocker treatment.	50 RA vs 50 age-matched healthy controls 49 y	<b>Abnormal Pap smear:</b> 12% RA vs 30% controls (P=0.048); ASCUS/LGSIL/HGSIL (3/2/1 RA vs 1/6/8 controls) P>0.05 <b>DNA – HPV of cervix cells (Hybrid Capture II assays):</b> Baseline- 14% RA vs 30 % controls, p = 0.054). <b>6 months after anti-TNF:</b> 12% RA (5 patients uncharged, 2 become negative, 1 new positive patient) (p = 1.0) 0% Chlamydia trachomatis infection in RA and controls pre and post-treatment.	A trend of lower frequency of HPV infection was observed in RA patients pre-anti-TNF compared with controls (14 vs. 30 %, p = 0.054). AR patients with HPV infection before anti-TNF therapy showed higher frequency of sexual intercourses (100 vs. 48 %, p = 0.014), higher median number of sexual partners [1 vs. 0 (p = 0.032)] and higher frequency of abnormal cervical cytology (43 vs. 7 %, p = 0.029) comparing with RA without HPV infection. Current age, disease duration, disease parameters and treatments were alike in both groups (p > 0.05).

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**TABLE I. CONTINUATION**

Author, year, (reference)	Study Type	Study objectives	Population Studied (nb)/Follow-up/ Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Rojo-Contreras, 2008, (25)	Cross-sectional study Mexico	Evaluate the prevalence of HPV and to analyze related factors in patients with RA.	61 RA vs 189 controls 40±8 RA vs 36±8 y controls	DNA – HPV of cervix cells (chain reaction polymerase): 30% RA vs 24% controls (OR= 0.8, p = 0.5). <b>High risk HPV:</b> 94% RA (mainly types 16, 18 and 58) vs 83% controls (mainly types 16, 18, 35 and 58); (p=0.2).	Factors associated with HPV infection adjusted to RA were: more than one sexual partner (OR = 5.8, p = 0.04), more than one sexual intercourse weekly (OR = 6.7, p = 0.06), circumcised sexual partner (OR = 9.0, p = 0.02).
Rojo-Contreras, 2012, (26)	Cross-sectional study Mexico	Evaluate the prevalence of cervical HPV in Mexican women with SLE and RA vs healthy controls.	34 SLE, 43 RA vs 146 controls 38.12±8.37 SLE/ /38.70±7.67 RA vs 36.79±7.09 y controls	<b>Pap smear:</b> HGSIL: 5.9% SLE, 0% RA (p=0.19), 0.7% controls (p=0.09). Cervical cancer stage I: 1 SLE patient. <b>Low-risk HPV types (6,11):</b> 2.9% SLE/ 0% RA vs 10.3% controls (p>0.05) <b>High-risk HPV types (16,18,33, 35,51,58):</b> 11.7% SLE/27.9% RA vs 26% controls (p>0.05)	In SLE patients was not found any difference between SLEDAI score and positive or negative HPV. The group of HPV (+) patients had a higher frequency of methotrexate use (p=0.036) and a longer duration of treatment with prednisone (3.2 years vs 1.3 years, p=0.05) compared with HPV (-).
Cirpan, 2007, (27)	Case-control Study Turkey	Evaluate women with SS using cervical cytology, colposcopic examination and HPV-DNA testing and to compare with controls.	33 SS vs 67 controls	<b>Suspicious cervical cytology:</b> 2 (6.1%) SS vs 62 (92.5%) controls. <b>Abnormal colposcopy:</b> 1 (3%) SS vs 4 (6%) controls <b>DNA – HPV of cervix cells (chain reaction polymerase):</b> HPV+: 1 SS vs 1 controls	No significant differences were observed between SS and the control group.
Tam, 2011, (28)	Prospective cohort study China	Risk factors for the development of squamous intraepithelial lesions.	137 SLE Median follow-up – 30.7 months 41±9 y	<b>Abnormal Pap smear:</b> 19.0%. - 16.1% developed at least one episode of ASCUS (15 patients with ASCUS only) 8.8% developed at least one episode of low-grade SIL during the follow-up. - None of the patients had high-grade SIL. - CIN 2 or 3 at colposcopy in 3 (2.2%) of 137 patients. - Cumulative prevalence: any HPV - 21.9%; high-risk HPV - 17.5%	Independent risk factors for the incident SIL: Use of CYC ever (OR 5.6, P= 0.041) Persistent high-risk HPV infection (OR 26.9, P=0.002). Other demographic, lifestyle, and clinical parameters and the use of other immunosuppressant were not associated with the development of SIL.

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**TABLE I. CONTINUATION**

Author, year, (reference)	Study Type	Study objectives	Population Studied (nb)/Follow-up-/Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Klumb, 2010, (4)	Cross-sectional study Brasil	Study the prevalence of cervical dysplasia among SLE patients submitted or not to IM and the association with classic risk factors.	171 SLE vs 222 controls Group1: 87 SLE receiving IM ≥12 months; Group2: 32 SLE receiving IM ≤5 months + 52 who had never received any IM 40.2±11.4 vs 37.7±10.3 y	<b>Pap smear:</b> - Abnormal: Group1- 26.4%; Group2- 20.2%; Controls- 4% - ASCUS: Group1- 12.6%; Group2- 13.1%; Controls- 3.1% - LGSIL: Group1- 5.7%; Group2- 5.9%; Controls- 0.9% - HGSIL- Group1- 6.9%; Group2- NA Controls- NA (p<0.05 between SLE groups vs controls)	Multivariate analysis showed in SLE women: - cervical dysplasia (OR 7.23) - premalignant cervical dysplasia (OR 11.36) Independent risk factors for abnormal Pap smears: - history of 3 or more life-time sexual partners (OR: 2.44, P =0.01) - diagnosis of SLE (OR 7.08, P<0.0001)
Costa Pinto, 2013, (29)	Cross-sectional study Brasil	<i>Chlamydia trachomatis</i> infection among SLE patients and evaluate whether or not is a risk factor for HPV-induced lesions.	105 SLE vs 104 controls 38±11 vs 36±11 y	<b>Pap smear:</b> ASCUS – 1% SLE vs 0% controls (p=1.0); LGSIL- 12% SLE vs 1% controls (p<0.001); HGSIL- 4% SLE vs 0% controls (p=0.12) <b>PCR test for CT:</b> 3.0 % SLE vs 5.0 % controls, p = 0.49	There was no association between the presence of HPV lesions and CT Infections in this population (all SLE patients with HPV-induced lesions tested negative for CT infection).
Lyrio, 2013, (30)	Cross-sectional study Brasil	Prevalence of cervical HPV infection and evaluate the presence of cervical lesions in women with SLE, in comparison with healthy women.	88 SLE vs 70 controls 41.4±11.6 vs 29.0±5.9 y	<b>Pap smear:</b> Normal: 1.4% SLE vs 20% controls (p=0.004) ASCUS: 4.2% SLE vs 0% controls (p=0.56) LGSIL: 15.5% SLE vs 8% controls (p=0.50) HGSIL: 4.2% SLE vs 0% controls (p=0.56) <b>DNA – HPV of cervix cells (chain reaction polymerase):</b> 80.7% SLE vs 35.7% controls (OR= 7.1; p=0.0001)	In a multivariate logistic regression, the presence of SLE was an independent predictor for HPV infection.
Lee, 2010, (7)	Cross-sectional study Korea	Prevalence and risk factors for high risk HPV infection and cervical cytological abnormalities.	134 SLE vs 4565 controls 39.5±9.4 SLE y	<b>Abnormal Pap smear:</b> 16.4% SLE vs 2.8%, (OR 4.4, P<0.001) <b>DNA – HPV of cervix cells (chain reaction polymerase):</b> High-risk HPV: 24.6% SLE vs. 7.9% controls (OR 3.8, P<0.001)	SLE itself was identified as independent risk factor for high risk HPV infection (OR 3.8) along with ≥2 sexual partners (OR 8.5) and Pap smear abnormalities (OR 97.3).

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**TABLE I. CONTINUATION**

Author, year, (reference)	Study Type	Study objectives	Population Studied (n)/Follow-up/ Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Klumb, 2010, (31)	Cross-sectional study Brasil	HPV prevalence among SLE patients and to evaluate associated risk factors, including the use of IM.	173 SLE vs 217 controls 39.7±11.2 vs 37.3±10.3 y	DNA – HPV of cervix cells (chain reaction polymerase): 20.2% SLE vs 7.3% controls (p<0.0001)	Variables associated with cervical HPV infection in SLE patients: ≥4 lifetime sexual partners, previous HPV infection, previous sexually transmitted disease, and use of IM> 12 months. HPV positive SLE patients had higher median CYC cumulative dose (10.1 versus 7.7 g, p=0.049) and higher median Pred cumulative dose (38.1 versus 20.2g, p=0.02) than HPV negative SLE patients.
Mendonza-Pinto, 2013, (32)	Cross-sectional study Mexico	Prevalence and factors associated with HPV infection.	148 SLE 42.5±11.8 y	DNA – HPV of cervix cells (chain reaction polymerase): - any HPV - 29% - high-risk HPV- 72% - ≥2 HPV infections- 13.5%	Cervical HPV positive patients were: younger (p = 0.05) and had higher Pred doses (p = 0.01) and cumulative doses (p = 0.005); mycophenolic acid therapy (9.3% vs. 0.9%, respectively, p=0.02; OR 10.6,95%); rituximab therapy (20.9% vs. 8.5%, respectively, p=0.03; OR 2.8); higher cumulative CYC dose (p = 0.05). In the logistic analysis, only the cumulative GC dose was associated with cervical HPV infection (OR 1.03).
Dreyer, 2011, (33)	Cohort study Denmark	Long-term occurrence of cancer, potentially caused by virus infections, from SLE diagnosis.	576 SLE Mean follow-up- 13.2 years 33 y at the time of diagnosis	Epithelial dysplasia/ carcinoma in situ of uterine cervix: SIR 1.8 (95% CI 1.2-2.7)  Cervical cancer: SIR 4.00	
Dey, 2013, (34)	Cohort study United Kingdom	Development of cancer after the diagnosis of SLE.	595 SLE Mean follow-up 14.7 years 33.5±12.7 y at diagnosis		
Skare, 2014, (35)	Retrospective study Brasil	Incidence of cancer in women with SLE.	395 SLE Median follow-up 105 months.	Cervical cancer: 2.5% SLE patients (comparison with the general population using data of Brazilian National Cancer Institute)	The cervical cancer in SLE patients was more common than in general population (p<0.0001), with an OR of 10.4). The presence of tumors was associated with disease (p=0.006) but not with IM treatment (p>0.05).

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**TABLE I. CONTINUATION**

Author, year, (reference)	Study Type	Study objectives	Population Studied (nb)/Follow-up/ Mean Age-years (y)	Outcome	Association with demographic/clinical characteristics
Martin, 2014, (36)	Case-control study France	Evaluation of Pap test and HPV status.	31 SSc vs 50 controls 59.8±11 vs 60.2±8.3 y	Pap smear: 1 HGSL in controls (normal colposcopy) Overall HPV: 32% SSc vs 38% controls HR or pHR HPV: 28% SSc vs 34% controls Most common genotype: HPV52 SSc vs HPV52, 53 controls ≥2 HPV: 50% SSc vs 26.3% controls Serological testing for antibodies: Ab anti HPV 16/18: 13%/ 6.5% SSc	Diffuse SSc, a shorter duration, and a younger age at first intercourse were most frequently observed among women HPV DNA+. Current smoking was 3 to 4 times more frequently in women seropositive for anti-HPV 16/18, compared to seronegative. A greater number of sexual partners, a diffuse SSc with a shorter duration were more frequent in seropositive women.
Bernatsky, 2009, (37)	Cross-sectional study Canada	Prevalence of abnormal Pap test reported by women with SSc onset <50 years.	320 SSc 34.5±10.4 y at first SSc symptom	Abnormal Pap smear: 25.4%	Diffuse SSc tended to have a higher prevalence of self-reported cervical dysplasia (31.7%) vs limited disease (20.7%). Significant positive association between self-reported abnormal Pap test and diffuse disease [OR=1.87; 95% CI 1.01, 3.47]. An independent association of an abnormal Pap test with smoking (OR 2.43; 95% CI 1.23, 4.78) and with younger age at disease onset.

nb: number; NA: not available; odds ratio; OR; IR: incidence rates; HR: hazard ratio ; SID: systemic inflammatory diseases; SSc: Systemic sclerosis; IBD: Inflammatory bowel disease; RA: rheumatoid arthritis, SLE: systemic lupus erythematosus; DM: dermatomyositis, PM: polymyositis, SS: Sjögren syndrome; AID: autoimmune diseases; HPV: *human papillomavirus*; CT: *Chlamydia trachomatis*; STD: sexually transmitted disease; IM: immunosuppressors; CYC: cyclophosphamide; Pred: prednisone; AZA: azathioprine; MTX: methotrexate; SLI: squamous intraepithelial lesions; CIN: cervical intraepithelial neoplasia; Pap: Papanicolaou, HR HPV: High risk *human papillomavirus*; pHR HPV: probably high risk *human papillomavirus*; HGSL: high-grade intraepithelial lesions; LSIL: low-grade intraepithelial lesions; ASCUS: atypical squamous cells of undetermined significance; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

**TABLE II. HUMAN PAPILLOMAVIRUS VACCINE IN RHEUMATIC PATIENTS**

Author, year, (reference)	Study Type	Objectives	Population Studied (nb)/ /Age – years (y)	Immunogenicity	Safety
Soybilgic, 2013, (38)	Prospective-study USA	Safety and immunogenicity of quadrivalent HPV vaccine in SLE patients.	27 SLE 12-26 y	Seroconversion rates anti-HPV types 6, 11, 16 and 18: After three doses of the vaccine - 94.4%, 100%, 100%, 94.4%. 1 patient who received rituximab during the vaccine protocol did not develop immunogenicity to HPV.	33.3% had a mild-moderate flare during the study period, with symptoms similar to previous flares.
Mok, 2013, (11)	Prospective case-control study China	Safety and immunogenicity of quadrivalent HPV vaccine in SLE patients.	50 SLE women vs 50 healthy controls 18-35 y	Seroconversion rates anti-HPV types 6, 11, 16 and 18: Month 7- SLE 74%, 76%, 92%, 76% and controls 96%, 95%, 98%, 93%. Month 12 - SLE 82%, 89%, 95%, 76% and controls 98%, 98%, 98%, 80%.	No significant difference in the frequency of adverse events was observed between patients and controls.
Heijstek, 2013, (39)	Prospective case-control study Netherlands	Immunogenicity of bivalent HPV vaccine in juvenile SLE and DM patients.	6 Juvenile SLE and 6 DM vs 49 healthy controls 12-18 y	HPV16/18-specific antibody concentrations were lower in patients compared to controls, reaching statistical significance in patients with juvenile DM at 7 months. At 12 months, no statistically significant differences were detected.	1 SLE patient experienced a mild/moderate flare at 7 months.
Heijstek, 2014, (40)	Prospective case-control study Netherlands USA	Immunogenicity of bivalent HPV vaccine in JIA patients.	68 JIA vs 55 healthy controls 12-18 y	All participants were seropositive for HPV16 and HPV18 at 7 months. 1 patient turned seronegative at 12 months for HPV16/18. No significant differences were found between patients and controls in HPV-specific antibody concentrations; but were lower in patients.	No relevant differences in adverse events were found. The occurrence of arthralgia was similar in both groups, but the mean duration was significantly longer in JIA patients (p<0.001).

SLE: Systemic lupus erythematosus; DM: dermatomyositis; JIA: juvenile idiopathic arthritis