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Prevalence of High Risk Human Papilloma Virus (Types 16 and 18) In Women with Rheumatoid Arthritis

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Abstract
Background: The past decade witnessed an interest in study of actual prevalence of HPV infection in patients of lupus, renal transplant recipients on immunosuppressant and HIV positive subjects. Since Rheumatoid arthritis (RA), like SLE, is an immunologically mediated disease, it is logical to suspect an association between RA and persistence of HPV infection.
Objective: To estimate the prevalence of high risk HPV infection (types 16 and 18) in cervical smears of women with rheumatoid arthritis.
Material and Method: Analytical, cross-sectional studies of 150 women with rheumatoid arthritis selected from the rheumatology clinic of PGIMER (Chandigarh). Endocervical brushings were taken. The sample was then processed and subjected to DNA extraction and PCR for HPV 16 and 18. Prevalence was calculated and subjected to analysis using p value.
Results: A total of 150 female patients with rheumatoid arthritis were enrolled in the study. Out of the 150 patients, in 28 patients (18.7%), DNA could not be extracted due to inadequatesampling.A total of 112 /122(91.8%) patients were negative for both strains of HPV. While 10 patients (8.2%) were positive for either HPV type 16 or 18, 9 were positive only for HPV type 16 (7.4%) while 1 was positive for HPV type 16 as well as type 18 (0.8%). None of the cases was positive for HPV type 18 only.
Conclusion: The prevalence of HPV (high-risk types) in patients of RA as seen in the index study was definitely higher than the regional data provided by Aggarwal *et al*37 for asymptomatic healthy women in the same center although the level of significance was not high.

Keywords: Independent Directors, Companies Act, Corporate Governance, Stakeholders

Introduction

Human papilloma viruses (HPV) especially the high- risk types have been implicated as causative agents in the dysplasia- cancer continuum. Detection of HPV is associated with a 250- fold increased risk of high – grade cervical intraepithelial neoplasia (CIN) [1]. Of the high – risk types, types 16 and 18 are responsible for majority of cases. Type 16 is the most common HPV found in invasive cancer and in CIN2 andCIN3, and it is found in 47 % of women with cancer in all stages [2]. It is also the most common single type found in cases of low grade intraepithelial lesions (around 16 %). HPV type 18 is found in 23 % of women with invasive cancer, 5 % women with CIN 2 and CIN3, 5 % with CIN1 and fewer than 2% with normal cervical cytology [3]. Thus while type 16 is more sensitive, type 18 is more specific at the cost of sensitivity. The incidence of infection also varies with use of barrier contraception. The incidence of genital HPV infection was 38 % in women whose partners used condoms for all instances of intercourse compared to 89 % infection rate in women whose partners used barrier method less than 5 % of the time [4]. One study of sexually active women showed that 70% cleared the infection within one year and 91% within two years [5]. Persistent high – risk HPV infection increases the risk of high – grade dysplasia three-hundred fold and is required for the development of CIN3 [6, 7] Cigarette smoking increases the risk of disease following infection by impaired clearance secondary to altered immune response [8]. It has thus been wisely concluded that any condition which plays with the immune system is likely to lead to persistent HPV infection. It is a well-accepted fact that prevalence of HPV infection is significantly higher in Human Immunodeficiency Virus (HIV) – positive individuals owing to impaired clearance [9]. Positive association was also noted in renal transplant recipients on immunosuppressant and the persistence of HPV infection [10]. Since Rheumatoid arthritis (RA), like SLE, is an immunologically mediated

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disease, it is logical to suspect an association between RA (with / without steroid treatment) and persistence of HPV infection and cervical dysplasia/neoplasia. RA is a chronic systemic inflammatory disease mainly involving synovial joints. Although the exact cause of RA is unknown, we know that autoimmunity plays a pivotal role in both its progression and chronicity. There has been limited work on the prevalence of HPV infection in rheumatoid patients but the lone study by Rojo [11] has indicated that despite a higher absolute prevalence of HPV infection in these patients compared to healthy controls, the difference is statistically insignificant. Therefore, this study was designed to explore the association between RA (disease characteristics and treatment) and prevalence of HPV infection and cervical smear abnormalities.

Aims and Objectives
To estimate the prevalence of high risk HPV infection (types 16 and 18) in cervical smears of women with rheumatoid arthritis.

Materials and Method
Study area
Rheumatology clinic run by the department of Internal Medicine, PGIMER, Chandigarh and department of Obstetrics and Gynaecology of the same. A total of 150 women diagnosed with RA were enrolled after an informed consent. Cervical smears (with Ayer's spatula) and endocervical brushings were obtained from each patient.

Sampling technique
Patient' s thorough history was taken with special emphasis on number of sexual partners, age at marriage, age at first childbirth, number of pregnancies and inter – pregnancy intervals. Also noted was any use of contraception. The details of RA were enquired into by asking about the duration of illness (indirectly indicated by appearance of early morning stiffness, small and large joint swelling or pain), duration of treatment, compliance with the treatment and finally the drugs being used were noted down along with the dose. The patient's Erythrocyte sedimentation rate and positivity / negativity of C - reactive protein were noted. A general physical examination was done including tender and swollen joint examination followed by a per speculum examination. An Endocervical brushing was taken (rotating the Endocervical brush clockwise around four to five times) and dipped in a vial containing PBS (phosphate buffer saline) for transportation. The slide was prepared and stained in the conventional manner and then examined under the microscope for any abnormality.

The vial containing the endocervical brushing dipped in PBS solution was transported to the pathology laboratory for processing within 1- 2 hours of sampling. Phosphate buffer solution is a transporting buffer commonly y used in biological research. It is a water – based salt solution containing sodiumchloride, potassium chloride, disodiumhydrogen phosphate, potassium dihydrogen phosphate. The phosphate ions in the solution help to maintain the pH of the solution at around 7.4. The solution is isotonic and non- toxic to cells. It is sterilized by autoclaving (20minutes, 121^0 C, liquid cycle). The sample was then processed and subject to DNA extraction using commercially available Qiagen kit (catalogue number 50134, onekit for every fifty samples). The technique used was as per user

manual. After DNA extraction, PCR technique was used to identify HPV -16 and HPV -18 separately

Reporting
The results of HPV DNA were expressed as positive or negative for HPV 16 or HPV 18.

Observations and Results
The present study was carried out at the Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh in collaboration with Rheumatology clinic of the Department of Internal Medicine of the same institute with an objective to determine the prevalence of high risk human papilloma virus infection (types 16 and 18) and cervicalcytological abnormalities in cervical smears of patients of rheumatoid arthritis. A total of 150 female patients with rheumatoid arthritis were enrolled in the study. Out of the 150 patients, in 28 patients (18.7%), DNA could not be extracted due to inadequate sampling. The cervical cytology of these 28 patients was atrophic. Hence further comparative assessment shall be limited to 122 cases only. Distribution of subjects according to prevalence of high risk human papilloma virus (types 16 and 18) has been shown in Table 1 below:

Table 1: Distribution of cases according to prevalence of high risk human papilloma virus (types 16 and 18) (n=122)

Status	No. of cases	Percentage
Negative for HPV types 16 or 18	112	91.8
Positive for either HPV 16 or 18	10	8.2
Positive for HPV type 16 only	9	7.4
Positive for HPV type 16 and 18	1	0.8
Positive for HPV type 18 only	0	0

A total of 112 /122(91.8%) patients were negative for both strains of HPV. While 10 patients (8.2%) were positive for either HPV type 16 or 18, 9 were positive only for HPV type 16 (7.4%) while 1 was positive for HPV type 16 as well as type 18 (0.8%). None of the cases was positive for HPV type 18 only.

Table 2: Demographic Characteristics of Patients Enrolled in the study

SN	Characteristic	HPV Negative (n=112)N (%)	HPV Positive (n=10)N (%)	Significance of difference
1.	Mean Age ± SD (years)	41.84±10.39	41.50±8.61	t=0.100; p=0.900
2.	Education			
	Illiterate	22 (19.6%)	0 (0%)	χ^2=5.000; p=0.172
	Up to 10thstandard	18 (16.1%)	4 (40.0%)	
	10-12thstandard	56 (50.0%)	5 (50.0%)	
	Graduate or Above	16 (14.3%)	1 (10.0%)	
3.	Working women	7 (6.3%)	0 (0%)	χ^2=0.663; p=0.415

Age of patients ranged from 22 to 68 years. Age of patients negative for HPV ranged from 22 to 68 years with a mean age of 41.50±8.61 years whereas the same for HPV positive patients ranged from 30 to 54 years with a mean age of 41.50±8.61 years. Statistically, the difference between two groups was not significant (p=0.920). Majority of patients

were educated beyond class 10th. Statistically, there was no significant difference in educational status of the two groups (p=0.172). Except for 7 (6.3%) patients in HPV negative group, all the patients were housewives. Statistically, there was no significant difference between the two groups with regard to working status (p=0.415).

Table 3: Reproductive and Contraceptive history of Patients Enrolled in the study

SN	Characteristic	HPV Negative (n=112) N (%)	HPV Positive (n=10) N (%)	Significance of difference
1.	Duration of marriage			
	a) <10 yrs	24 (21.4%)	2 (20.0%)	χ^2=0.015; p=0.992
	b) 10-20 yrs	34 (30.4%)	3 (30.0%)	
	c) >20 yrs	54 (48.2%)	5 (50.0%)	
2.	Para 3 or above	38 (33.9%)	3 (30.0%)	χ^2=0.054; p=0.801
3.	Age at first childbirth$\leq$18 yrs	8 (7.1%)	2 (20.0%)	χ^2=2.017; p=0.156
4.	Gap between any two pregnancies <3 yrs	46 (41.1%)	4 (40.0%)	χ^2=0.004; p=0.947
5.	Contraceptive use			
	None	86 (76.8%)	7 (70.0%)	χ^2=1.546; p=0.462
	Barrier	7 (6.3%)	0 (0.0%)	
	IUCD/Tubal Ligation	19 (17.0%)	3 (30.0%)	
	Any contraceptive	26(23.3)	3(30%)	
6.	Multiple sexual partners	0	0	–

Almost half (48.2%) of HPV negative and exactly half (50%) of HPV positive patients were married for >20 years. 38 (33.9%) of HPV negative and 3 (30%) of HPV positive patients had parity of 3 or more. Age at first childbirth was reported to be $\leq$18 years by 8 (7.1%) in the HPV negativegroup and 2 (20%) in the HPV positive group. A total of 46 (41.1%) patients in the HPV negative and 4 (40%) patients in the HPV positive group had <3 years gap between two pregnancies. Contraceptive use was reported in 26 (23.3%) of negative and 3 (30%) of positive patients. While 7 patients (6.3%) in the HPV negative group reported use of barrier contraception (male condom), none in the HPV positive group had used barrier method. None of the patients was reported to be having multiple sexual partners. Majority of the patients reported infrequent intercourse. Statistically, there was no significant difference between the two groups for any of the reproductive and contraceptive variables (p>0.05).

Table 4: Medical, treatment and drug history of Rheumatoid Arthritis patients enrolled in the study

SN	Characteristic	HPV Negative (n=112)		HPV Positive (n=10)		Significance of Difference	
		No.	%	No.	%	χ^2	P
1.	History of RA$\geq$10 years	28	25	4	40.0	1.068	0.302
2.	Duration of treatment						
	$\leq$1 Yr	41	36.6	0	0.0	5.514	**0.019**
	> 1 Yr	71	63.4	10	100.0		
3.	Irregular treatment	12	10.7	2	20.0	0.779	0.377
4.	Drug history						
	Paracetamol	20	17.9	1	10.0	0.396	0.528
	Methotrexate	64	57.1	6	60.0	0.031	0.861
	Hydroxychloroquine	66	58.9	9	90.0	3.742	0.053
	Prednisolone	71	63.4	6	60.0	0.045	0.831

History of rheumatoid arthritis for $\geq$10 years was present in 25% of the HPV negative and 40% of the HPV positive patients yet the difference was not significant statistically (p=0.302).
All (100%, n=10) patients in the HPV positive group and 71 (63.4%) in the HPV negative group had a history of treatment for more than one year (>1yr), showing a significant difference between the two groups (p=0.019).
A total of 12 (10.7%) patients in the HPV negative group and 2 (20%) in the HPV positive group hada history of irregular treatment but the difference was not associated significantly with HPV positivity (p=0.377).

Paracetamol was the least commonly used drug in both the groups. In HPV negative patients the most commonly used drug was Prednisolone (63.4%) followed by HCQS (58.9%) and Methotrexate (57.1%). In the HPV positive group HCQS (Hydroxychloroquine) was the most commonly used drug (90%) followed by Prednisolone and Methotrexate (n=6; 60% each). Paracetamol use was observed in 1 HPV positive patient (10%). However, no significant association between HPV positivity and drug history could be seen (p>0.05). There was overlap in the usage of drugs as most patients were on more than one drug treatment.

Table 5: ESR and specific laboratory test findings of patients enrolled in the study

SN	Characteristic	HPV Negative (n=112)		HPV Positive (n=10)		Significance of Difference	
1.	Mean ESR±SD (mm/1st hour)	43.41±17.78		43.00±20.04		t=0.069; p=0.945	
		N	%	N	%	χ^2	P
2.	CRP (C Reactive Protein) positive	103	92.0	10	100	0.868	0.352
3.	Rheumatoid factor positive	110	98.2	10	100	0.182	0.670

Mean ESR value in the HPV negative patients was 43.41±17.78 mm/1st hour whereas the same in the HPV positive patients was 43.00±20.04 and the difference was not significant statistically (p=0.945).

All the patients in the HPV positive group (n=10, 100%) were CRP positive compared to 103 patients (92%) in the HPV negative group. All patients (n =10, 100%) in the HPV positive group were also positive for Rheumatoid factor as compared to 110 (98.2%) patients in the HPV negative group. Statistically, no significant association was found between ESR and specific laboratory test findings with HPV positivity (p>0.05).

Discussion
The primary objective of this study was to determine the prevalence of high-risk HPV types 16 and 18 in cervical smears of patients with Rheumatoid Arthritis. The prevalence of high-risk HPV DNA types 16 and 18 determined from cervical smears of 122 patients of RA (after excluding 28 smears from which DNA could not be retrieved) was found to be 8.2%, 7.4% and 0.8% respectively for HPV 16 or 18, type 16 only and HPV 16 and18 in the same patient. None of the patients tested positive for type 18 alone. The study by Aggarwal et al [13] is especially important for comparison as it was conducted in the same institute as the index study (Post Graduate Institute of Medical Education and Research, Chandigarh) and therefore cultural and regional differences would be minimum between the subjects studied. This study quoted a prevalence of 3.2 % for HPV 16, 4% for HPV 18 and 0.4% for both of these high – risk types (from cervical smears of four hundred and seventy two asymptomatic healthy women with benign cervical cytology). Thus, compared to healthy controls the prevalence of HPV DNA types 16 and 18 is higher in patients with rheumatoid arthritis but the level of significance cannot be calculated as these are two separate studies.

Bhatla et al [12] summarised the results of nine prevalence studies from across the country and concluded that in healthy women the overall prevalence of HPV (any type) was 9.9% with the 16/18 fraction being 3.9%. Comparing our results with these studies, the absolute prevalence of HPV types 16 and 18 is higher in RA although statistical significance could not be extracted.

The index study shows a higher prevalence of HPV 16 compared to HPV 18 (7.4% and 0.8% respectively), a pattern reaffirmed by Bhatla et al [12] in the normal population.

The lone study on the prevalence of HPV in cervical smears of women with RA was conducted in Mexican women by Rojo et al. [11] and was a case control study (sixty- one women with RA and one hundred and eighty nine healthy controls). This study reported a prevalence of 24 % for all types of HPV together in asymptomatic healthy women (much higher than the Indian national average of 9.9%) and the prevalence of HPV (again all types) in cervical smears of women with RA as 30%. The difference however, was not found to be significant (odds ratio of 0.8 and p value 0.5). All types of HPV were studied in Rojo's study while the prevalence of types 16 /18 alone was not mentioned separately although it was reported that 94% of positive cases were 16, 18 and 58.

The prevalence of HPV infection characteristically peaks soon after initiation of sexual activity, usually among women in their early 20s, and it is associated with the number of sexual partners and frequency of intercourse. One of the plausible causes of the lack of significantly higher prevalence of HPV infection in our study group of RA patients, could be the sexual practices in India wherein sexual activity markedly falls beyond the 30 s (the mean age of our study group was 41). Also, because of disease related disability and pain and poor self-care these women had infrequent intercourse. The prevalence of HPV (high-risk types) in patients of RA as seen in the index study was definitely higher than the regional data provided by Aggarwal et al [13] for asymptomatic healthy women although the level of significance would not be high. These findings are very much similar to the findings of the study by Rojo et al [11] wherein there is a definitely higher prevalence of HPV infection in patients with RA as compared to asymptomatic healthy controls although the difference was not statistically significant.

The mean age of patients in both HPV negative and HPV positive groups was around 41.5 +/- 8.61 years and therefore no significant difference was observed for this demographic variable (p value 0.9).

There was no significant difference in HPV positivity or negativity with respect to duration of marriage (which would be a measure of duration of sexually active life in years), p value being 0.99. Rojo et al [11] did not report any significant difference in HPV positivity or negativity with respect to duration of marriage.

While only 7.1% of HPV negative patients were found to have age of less than 18 at the time of first child birth, around 20 % of those with HPV positivity had age less than 18 at first child birth. This difference, however, was not found to be stati the prevalence of HPV in the asymptomatic controls in the study by Rojo et al [11] was 24% which was much higher than the Indian average of 9.9% for all types of HPV as reported by Bhatla et al [12]. In the former, when adjusted for RA, the factors which were associated with a higher prevalence of HPV were: more than one sexual partner, frequency of sexual intercourse and circumcised partner (p value 0.02). Cultural differences, sexual practice and number of sexual partners would obviously differ in the two populations in question (in Rojo et al's study and this present study) and can explain the difference in prevalence of HPV in the two especially as monogamous relationships are still the norm in most parts of India (none of the subjects in the index study reported more than one sexual partner).

There was no difference noted in HPV status with respect to parity. 33.9 % of those with HPV negative and 30% of those with HPV positive status had parity more than 3 (p value 0.801). stically significant (p value of 0.156). The disease characteristics which were studied were:
1. Duration of rheumatoi Duration of treatment
2. Drugs used for treatment.
3. Disease activity as assessed by ESR and Q-CRP.

A higher proportion of patients with HPV positivity had duration of disease of more than 10 years (25 % vs. 40 %, p value 0.3). This value does implicate RA in persistence of infection or higher susceptibility to infection. d arthritis (since onset of symptoms)

There was statistically significant difference in duration of treatment taken in the two groups. While 63.4% of HPV negative patients had undergone treatment for more than 1 year, 100% of HPV positive patients reported more than 1 year of treatment. (p value 0.019).

There are three general classes of drugs commonly used in

the treatment of rheumatoid arthritis: non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). Corticosteroids have both anti-inflammatory and immunoregulatory activity. There is thus a theoretical possibility of increased risk of infections in patients on steroids. The immunomodulatory action of methotrexate also implies an increased risk of infections or failure to clear infections.

Logically the use of steroids should have made the difference in HPV positivity but our study did not show any significant difference in steroid usage in the two groups. There was no difference in HPV positivity with Methotrexate usage (57% in HPV negative and 60% of HPV positive patients). There was, however, a significant difference in the use of HCQS in the two groups. While 58.9% of patients in the HPV group were found to be taking HCQS, nearly 90% of the HPV positive patients were on HCQS (p value 0.05). No significant differences were found in the HPV status with the use of immunosuppressive agents by Lee et al [4] in lupus patients, a finding similar to the index study.

ESR is used to monitor response to treatment and a falling ESR is considered favourable. Thus ESR is an indicator of disease activity. This study showed no statistically significant difference in the mean ESR in the two groups (mean ESR was found to be 43.4 mm/1st hour in the negative and 43.0 mm / 1st hour in the positive group).

In a nutshell, the prevalence of HPV infection with the high-risk types 16 and 18 was definitely higher than the asymptomatic healthy population, even if not statistically significant. The demographic variables like age and education and reproductive and sexual variables like duration of marriage, parity and inter-pregnancy interval did not show any bearing on the HPV status. Contraceptive use and the type of contraceptive also did not influence HPV status.

Summary and Conclusion
The present study was undertaken with the objective of determining the prevalence of human papilloma virus infection and cervical cytological abnormalities in women with Rheumatoid Arthritis. A total of 150 diagnosed cases of RA in the age group between 28 to 68 years were enrolled in this study. The Pap smears and endocervical brushings from these patients were examined for cervical cytological abnormalities and HPV DNA (types 16 and 18) respectively. 28 patients were excluded due to inability to extract DNA from their samples (most of these had atrophic smears). The observations were:
1. HPV prevalence in patients of RA was 7.4 % for HPV 16 alone and 0.8% for both HPV 16 and 18. This was higher than the national average of 3.2 and 0.4% shown by published data from the same region a few years back
2. The overall prevalence of HPV infection with any of the two genotypes was 8.2%.
3. There was a higher prevalence of HPV infection in patients who had been suffering from RA for more than a decade. This was, however, not statistically significant.
4. There was statistically significant higher prevalence in patients who had been taking treatment for more than a year. This higher prevalence was, however, not attributable to steroids or methotrexate.
5. There was a significantly higher prevalence of HPV infection in patients on hydroxychloroquine (HCQS). Probably the higher prevalence of infection in patients on treatment for more than a year could be attributed to HCQS.
6. Epidemiological, reproductive and contraceptive factors like age, parity and use of contraception did not show any positive correlation.

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