JOURNAL OF WOMEN'S HEALTH
Volume 23, Number 9, 2014

DOI: 10.1089/jwh.2013.4658

Behavioral and Clinical Factors Associated with Self-Reported Abnormal Papanicolaou Tests in Rheumatoid Arthritis

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Abstract

Background: Some evidence suggests that women with rheumatoid arthritis (RA) are at increased risk for the development of cervical cancer; however, it is unclear how this increase risk is conferred. We aimed to assess the factors related to abnormal Papanicolaou (Pap) tests in women with RA to determine whether they are similar to those reported for the general population.

Methods: A structured questionnaire was mailed to 503 female patients from a longitudinal RA cohort. The survey included items on sociodemographic, behavioral, and gynecological factors. Univariate and multivariable logistic regression models examined the association of self-reported abnormal Pap results with a number of potential behavioral risk factors.

Results: The questionnaire response rate was 57.5% ($n = 289$). Median age was 61 years and 97% had ≥ 1 Pap test previously. Twenty-nine percent of respondents reported a previous abnormal Pap result. In the multivariable logistic model adjusted for age, number of lifetime sexual partners, age at menarche, birth control use, and history of sexually transmitted disease (STD), ever using birth control (odds ratio [OR] 2.31, 95% confidence interval [CI] 1.18–4.52) and previous STD (OR 3.38, 95% CI 1.70–6.70) were associated with an increased risk of abnormal Pap result. Compared with either the state or national population, a greater proportion of the respondents was older, married, and previous smokers, and completed postsecondary education and obtained a Pap test.

Conclusions: In this cross-sectional study, self-reported abnormal Pap results were associated with use of birth control and history of STD in RA patients.

Introduction

The incidence of cervical cancer is decreasing, but it is still the third most common gynecologic cancer with the estimated incidence of 7.9 per 100,000 women per year in the United States.[1,2] Human papillomavirus (HPV), the most commonly diagnosed sexually transmitted disease (STD) in the United States, has been established as a necessary cause of cervical cancer.[3] However, in most patients, the HPV infections, even high-risk HPV strains, clear before leading to invasive cancer. The known risk factors for cervical cancer fall into two categories: those that increase the possibility of HPV infection—such as number of sexual partners, high-risk sexual partners, age at first intercourse, and diagnosis of other STDs—and those that induce HPV-mediated carcinogenesis, such as smoking, use of oral contraceptives and immunosuppressives, and multiparity.[4,5]

Autoimmune systemic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may predispose to the development of cervical cancer. Several observational studies reported increased risks of HPV infection and abnormal Papanicolaou (Pap) tests in these immunocompromised patients.[6–8] In one recent large population-based cohort study, women with RA and SLE had a 1.5 times greater risk of high-grade cervical dysplasia and cervical cancer than women without systemic inflammatory disease (SID). However, the study could not ascertain whether immunodeficiency, its treatment, or another factor

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entirely caused the increased risk.[9] Multiple studies show that having a chronic medical condition is associated with an increased risk for engaging in health risk behavior such as smoking, alcohol misuse, illegal drug use, and early sexual debut, as compared with healthy peers.[10–12] In the aforementioned cohort study, women with RA appeared to be more sexually active but potentially less likely to use oral contraceptive or cigarettes than those without SID.[9] If the increased risk of cervical cancer conferred by these behaviors is altered by rheumatoid arthritis or its treatment the fact that they engage in such behaviors at different rates from the general population could lead to a significant misunderstanding of how risk for HPV infection and cervical cancer is affected by RA or its treatment. To date, limited data is available on whether RA treatments such as disease-modifying antirheumatic drugs (DMARD) are associated with an increased risk for HPV infection and cervical cancer.

In this study, we explored potential risk factors for the association between RA and HPV infection and abnormal Pap tests, such as behavioral risk factors, disease severity, and use of immunosuppressive drugs in women with RA, and examined whether these factors occurred more frequently in women with a history of abnormal Pap tests. Additionally, we assessed whether there were differences in sociobehavioral risk factors and gynecological history between the study cohort and the general population.

Methods

Study population

The study population was recruited from female RA patients enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS).[13] The BRASS cohort, established in 2003, consists of over 1,300 patients diagnosed with RA at Brigham & Women's Hospital, who are followed in the Brigham Arthritis Center and sent questionnaires at six month intervals.

Patient survey

Study data were collected and managed using both paper surveys and REDCap electronic data capture tools. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.[14] We mailed a paper survey to all 503 female BRASS participants and emailed a link to the REDCap survey to the 416 women with email addresses on file. In order to optimize the response rate, two successive reminder letters with surveys enclosed were sent out to nonresponders at 1 and 4 months after the initial mailing. The questionnaire asked about behavioral risk factors for cervical dysplasia and HPV infection and included questions on participants' demographics, social history, and gynecological history. To determine Pap test utilization and results we asked a series of four questions: (1) Have you ever had a Papanicolaou (Pap) test?; (2) If yes, when was your last test?; (3) Have you ever had an abnormal Pap test?; and (4) If yes, how many times have you had an abnormal Pap test? We linked respondents' data with their clinical information about sociodemographics, RA disease severity, medication use, and gynecological history in the BRASS.

We obtained general population estimates of cervical cancer risk factors from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System (BRFSS) 2010 results for Massachusetts (MA) and the United States as a whole.[15] BRFSS is a state-based system of health surveys that collects information on health risk behaviors, preventive health practices, and health care access primarily related to chronic disease and injury.

Data analysis

Student t-tests, chi squares, and univariate and multivariable logistic regression models were used to determine which variables were significantly associated with abnormal Pap results within our cohort. The final multivariable logistic model included *a priori* defined variables—age, any history of STD, number of sexual partners, and age at menarche—and a variable that had a p-value < 0.05 from univariate analyses (ever use of any birth control). Descriptive analyses were performed to compare those who responded to our survey versus the general female population of MA in terms of demographics and behavioral risk factors for cervical cancer. A p-value < 0.05 was considered statistically significant. All data analyses were carried out using SAS, version 9.2.

Ethics statement

This work was approved by the Institutional Review Board of the Brigham and Women's Hospital. The informed consent of each participant was obtained as a part of the survey.

Results

Of 503 BRASS participants contacted with the mean age 59.9 (standard deviation 12.8) years, 289 (57.5%) completed the survey, 120 (23.9%) opted out of the study, and 94 (18.7%) sent back no response of any kind. Two hundred forty six (48.9%) returned the paper survey, 58 (11.5%) filled out the online survey, and one participant provided questionnaire answers to a researcher over the phone. Sixteen (3.2%) participants returned both electronic and paper surveys; for these participants we used only the first survey returned.

The majority of respondents were white (93.7%), non-Hispanic (97.9%) and married (59.4%). The median (interquartile range) age was 61 (51–69) years. About half (53.0%) reported having smoked at least 100 cigarettes in their lifetime, though the vast majority were not smokers at the time of the survey (89.2%). Post-secondary education was reported by 76.5%. About one-fourth had more than six lifetime sexual partners and 81.7% had at least one pregnancy. Of those who had ever been pregnant, 45% had three or more pregnancies. The majority reported having ever used birth control (84.0%), having ever received a Pap test (96.5%) and having received a Pap test within the past 3 years (76.4%), which is consistent with the current recommendations for screening frequency for women under 65 years of age.[16] Of those ever diagnosed with a STD ($n = 54$, 18.7%), HPV ($n = 18$) was the most common followed by herpes ($n = 14$) and genital warts ($n = 11$). Eighty-four (29.1%) patients reported having 1 or more previous abnormal Pap test results. Of those with abnormal Pap tests, 32 women (39.5%) had two or more abnormal Pap tests.

The characteristics of study participants by Pap test results are included in Table 1. Three respondents did not answer the

Table 1. Characteristics of the Survey Participants

	Abnormal Pap (N = *84*)	*Normal Pap* (N = *202*)	p-*Value*
Demographic			
Age, mean (SD)	55.2 (12.5)	61.7 (12.3)	< 0.0001
White race, *n* (%)	80 (95.2)	186 (92.1)	0.28
Social			
Education level completed, *n* (%)			
HS or less	20 (23.8)	45 (22.3)	0.78
College	35 (41.7)	106 (52.5)	0.10
Graduate school	29 (34.5)	50 (24.8)	0.09
Marital status, *n* (%)			
Married	51 (60.7)	118 (58.4)	0.72
Single	11 (13.1)	29 (14.4)	0.78
Other	22 (26.2)	55 (27.2)	0.86
Household income, *n* (%)			
Under $30,000	13 (15.5)	48 (23.8)	0.12
$30,000–$69,999	25 (29.8)	50 (24.8)	0.38
$70,000 or more	46 (54.8)	104 (51.5)	0.61
Smoked at least 100 cigarettes in lifetime, *n* (%)	42 (50.0)	93 (46.0)	0.64
Consumption of any alcohol in past year, *n* (%)	61 (72.6)	128 (63.4)	0.15
Gynecological			
Ever used birth control, *n* (%)	53 (63.1)	99 (49.0)	0.001
Methods of birth control used, *n* (%)			
IUD	17 (20.2)	36 (17.8)	0.67
Condoms	46 (54.8)	73 (36.1)	0.005
Oral contraceptives	58 (69.0)	113 (55.9)	0.05
Currently using birth control, *n* (%)	5 (6.0)	7 (3.5)	0.61
Age began using birth control (years), mean (SD)	22.5 (5.9)	23.4 (5.6)	0.34
Age stopped using birth control (years), mean (SD)	31.4 (7.9)	31.3 (7.5)	0.92
Age at first menstruation (years), *n* (%)			
9–11	13 (15.5)	21 (10.4)	0.23
12–13	34 (40.5)	85 (42.1)	0.80
14+	13 (15.5)	43 (21.3)	0.26
Age menstruation ceased (years), mean (SD)	48.5 (6.1)	47.4 (6.9)	0.43
Ever had a Pap test, *n* (%)	82 (97.6)	195 (96.5)	0.63
Of yes, when was the last test?			
Within 1 year, *n* (%)	61 (72.6)	100 (49.5)	0.0003
2–3 years ago, *n* (%)	10 (11.9)	50 (24.8)	0.02
More than 3 years ago, *n* (%)	7 (8.3)	40 (19.8)	0.02
Number of sexual partners, *n* (%)			
<3, (%)	24 (28.6)	113 (55.9)	< 0.0001
3–6, (%)	28 (33.3)	52 (25.7)	0.19
>6, (%)	31 (36.9)	36 (17.8)	0.0005
Ever been pregnant, *n* (%)	68 (81.0)	166 (82.2)	0.81
Of yes, how many times?, mean (SD)	2.2 (1.7)	2.5 (1.8)	0.27
Ever had an STD, *n* (%)	32 (38.1)	22 (10.9)	< .0001
Of yes, which one(s), *n* (%)			
HPV	18 (21.4)	0 (0)	< 0.0001
Chlamydia	3 (3.6)	3 (1.5)	0.26
Gonorrhea	1 (1.2)	3 (1.5)	0.85
Herpes	6 (7.1)	8 (4)	0.26
Trichomonas	3 (3.6)	3 (1.5)	0.26
Genital warts	6 (7.1)	5 (2.5)	0.06
RA severity			
Age of RA symptom onset (years), mean (SD)	34.1 (14.4)	40.1 (13.4)	0.001
Duration of RA symptoms (years), mean (SD)	15.1 (11.8)	15.3 (12)	0.86
MDHAQ overall score, mean (SD)	0.6 (0.5)	0.6 (0.5)	0.35
MDHAQ depression subscore, mean (SD)	0.5 (0.6)	0.5 (0.7)	0.83
MDHAQ fatigue scale, mean (SD)	44.8 (26.2)	44 (30.3)	0.83
Medication usage			
Medicines previously taken, *n* (%)			
Steroid	66 (78.6)	161 (79.7)	0.77
Any DMARD	61 (72.6)	140 (69.3)	0.62
Biologic DMARD	24 (28.6)	44 (21.8)	0.23
Nonbiologic DMARD	57 (67.9)	134 (66.3)	0.85
NSAID	9 (10.7)	13 (6.4)	0.22

Three respondents did not report data on previous Papanicolaou (Pap) tests, and are not included in this analysis.

DMARD, disease modifying antirheumatic drug; HPV, human papillomavirus; HS, high school; MDHAQ, Multi-Dimensional Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; SD, standard deviation; STD, sexually transmitted disease.

questions pertaining to previous Pap results, and their results are not included in Table 1. Women who had ever received an abnormal Pap test were younger and were more likely to report obtaining a Pap test within the last year, ever using birth control, specifically using condoms or oral contraceptives, having more than six sexual partners in their lifetime, ever having an STD, and younger age of RA symptom onset. No differences in RA severity and use of DMARDs were noted between women with abnormal and normal Pap tests.

Univariate analysis showed a significant association between abnormal Pap tests and age, age at RA onset, use of any birth control, history of STD, and number of lifetime sexual partners (Table 2). In the multivariable logistic regression simultaneously adjusted for age, number of lifetime sexual partners, age at menarche, birth control use, and history of STD, ever using any birth control (odds ratio [OR] 2.31, 95% confidence interval [CI] 1.18–4.52) and previous diagnosis of any STD (OR 3.38, 95% CI 1.70–6.70) remained significantly associated with an increased risk of abnormal Pap result (Table 2).

Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/jwh) shows the characteristics of study participants and the general female population of MA and the United States. The respondents were older, more likely to be married, more likely to be previous smokers, more likely to have completed postsecondary education, and more likely to have obtained a Pap test than either the state or national population.

Discussion

Although increased risks of abnormal Pap tests and HPV infection have been repeatedly reported in women with SLE,[8] little data was available regarding the risk associated with RA. Recently, a recent large population-based cohort study showed a 1.5-times greater risk of high-grade cervical dysplasia and cervical cancer in 58,979 women with RA compared with 533,332 women with no RA or other systemic inflammatory disease.[9] To fully understand the increased risk of cervical dysplasia (i.e., abnormal Pap tests) and cervical cancer associated with RA, it is important to assess the risk factor profiles of women with RA. In this cross-sectional study of RA patients, a number of known risk factors for abnormal Pap tests and HPV infection such as smoking (47%), multiparity (45%), having >6 lifetime sexual partners (23%), and history of STD (19%) were prevalent. Furthermore, about a third of women with RA reported having at least one abnormal Pap test and some had several abnormal Pap results. Univariate analysis showed that younger age, ever use of birth control, history of STD, and a greater number of sexual partners were associated with an increased risk of abnormal Pap tests.

Compared to the general population, the study respondents were more likely to be older, married, and former smokers and more likely to have a higher education and a Pap test. While higher proportions of lifetime smokers and those who had at least one Pap test in the past might be associated with an increased risk of abnormal Pap results, older age and lower proportion of current smoking might be associated with a decreased risk of abnormal Pap results. Thus, it does not appear that the risk profile of our RA patients as compared with the general population would change the risk of abnormal Pap test in a particular direction. With a better understanding of potential sociodemographic and clinical risk factors for HPV infection and cervical cancer specific to RA patients, cervical cancer screening and cervical dysplasia management strategy could be tailored for women with RA.

This study has several limitations. First, abnormal Pap tests and results were self-reported and no specific information on the pathology was obtained. Although we had access to rich clinical data about the patients' rheumatologic history, many women in the BRASS did not receive primary medical or gynecological care at the institution where the BRASS data was collected. Therefore, actual review of the Pap results was not feasible. While self-reported Pap test results may not completely reflect actual Pap results, self-report may be more accurate in this study cohort, as the BRASS patients are more likely to see a doctor on a regular basis and have a higher than average level of education. A previous study validating self-report of cancers to cancer registry records calculated high sensitivity (between 0.59 and 0.86) and specificity (0.99) between of self-report cancer diagnosis in women with SLE.[17]

Second, our study may be subject to information bias. One can certainly imagine that there was underreporting of history of STDs and number of lifetime sexual partners as a result of either recall error or reluctance to disclose. The question therefore is whether imperfect self-report might occur differentially in women with a history of abnormal Pap tests. Whether women with abnormal Pap results are more likely to accurately recall number of previous sexual partners or symptomatic STDs is unknown. However, diagnosis of both asymptomatic STDs and cervical dysplasia may both be more likely in women who are in regular contact with a gynecologist and the association we found between these two factors may be partially explained by such bias. Third, we did not obtain full survey participation. If nonresponders were more likely to have normal test results, then we will have overestimated the incidence of abnormal pap results in RA patients. Fourth, although we did not observe an association between abnormal Pap tests and RA severity or use of DMARDs, it might be related to the relatively small size and cross-sectional nature of the study (e.g., no information about the temporal relationship of between Pap results and DMARD therapy or RA disease progression). Lastly, as the BRASS cohort consists of well-established RA patients from a single academic institution, our results may not be generalizable in other populations.

Conclusions

In this cross-sectional study of established RA patients, abnormal Pap tests were common in patients with RA and use of birth control and history of STD were significantly associated with abnormal Pap tests. These risk factors are similar to those reported in studies of the general population.[5] Our results do not suggest evidence that the increased risk of HPV infection and cervical cancer seen for RA patients in a previous study[9] is due to significant deviations in how behavioral factors confer risk in these patients. Since our study was confined to patients with RA, we are unable to determine that the risks conferred by these behaviors are equal in RA patients and the general population. Although we did not find an association between use of immunosuppressants and risk for

Table 2. Univariate and Multivariate Analyses on Factors Associated with Abnormal Papanicolaou Tests in Women with Rheumatoid Arthritis

	Abnormal Pap (N = 84)	*Normal Pap (N = 202)*	*Total*	p-*Value*	*Univariate OR (95% CI)*	*Multivariate OR (95% CI)*
Continuous variables	Mean (SD)	Mean (SD)				
Age (years)	55.2 (12.5)	61.7 (12.3)		<.0001	**0.96 (0.94–0.98)**	0.98 (0.95–1.00)
Age at RA symptom onset (years)	34.1 (14.4)	40.1 (13.4)		0.001	**0.97 (0.95–0.99)**	
Number of pregnancies	2.2 (1.7)	2.5 (1.8)		0.27	0.92 (0.79–1.07)	
Categorical variables	*n* (%)	*n* (%)	*n* (%)			
Race						
Non-white race	4 (20.0)	16 (80.0)	20 (100)	0.34	1	
White race	80 (30.1)	186 (69.9)	266 (100)	0.28	2.01 (0.56–7.18)	
Marital status						
Not currently married	33 (28.2)	84 (71.8)	117 (100)	0.72	1	
Married	51 (30.2)	118 (69.8)	169 (100)	0.72	1.10 (0.64–2.04)	
Highest level of education						
<College	20 (30.8)	45 (69.2)	65 (100)	0.78	1	
College	35 (24.8)	106 (75.2)	141 (100)	0.10	0.76 (0.40–1.45)	
Graduate school	29 (36.7)	50 (63.3)	79 (100)	0.09	1.33 (0.67–2.68)	
Household income						
<$30,00	13 (21.3)	48 (78.7)	61 (100)	0.12	1	
$30,000–69,999	25 (33.3)	50 (66.7)	75 (100)	0.38	1.85 (0.85–4.02)	
$70,000+	46 (30.7)	104 (69.3)	150 (100)	0.61	1.63 (0.81–3.30)	
Cigarettes smoked						
<100 in lifetime	42 (27.8)	109 (72.2)	151 (100)		1	
100+ in lifetime	42 (31.1)	93 (68.9)	135 (100)	0.64	1.13 (0.68–1.88)	
History of DMARD use						
Never	23 (27.1)	62 (72.9)	85 (100)		1	
Ever previous	61 (30.3)	140 (69.7)	201 (100)	0.62	1.15 (0.66–2.04)	
History of steroid use						
Never	18 (30.5)	41 (69.5)	59 (100)		1	
Ever previous	66 (29.1)	161 (70.9)	227 (100)	0.77	0.91 (0.49–1.70)	
Number of pregnancies						
0	16 (30.8)	36 (69.2)	52 (100)		1	
1+	68 (29.1)	166 (70.9)	234 (100)	0.81	0.92 (0.48–1.77)	
Use of any birth control						
Never	31 (23.1)	103 (76.9)	134 (100)		1	
Ever previous	53 (34.9)	99 (65.1)	152 (100)	**0.001**	**1.78 (1.06–3.00)**	**2.31 (1.18–4.52)**
Use of OC pills						
Never	26 (22.6)	89 (77.4)	115 (100)		1	
Ever previous	58 (33.9)	113 (66.1)	171 (100)	**0.04**	1.70 (0.99–2.92)	
Use of non-OC contraceptives						
Never	21 (18.4)	93 (81.6)	114 (100)		1	
Ever previous	63 (36.6)	109 (63.4)	172 (100)	**0.0009**	1.39 (0.81–2.41)	
Any STD diagnosis						
Never	52 (22.4)	180 (77.6)	232 (100)	**<0.0001**	1	1
Ever previous	32 (59.3)	22 (40.7)	54 (100)		**5.04 (2.67–9.40)**	**3.38 (1.70–6.70)**
Number of lifetime sexual partners						
<3	24 (17.5)	113 (82.5)	137 (100)	**<0.0001**	1	1
3–5	28 (35.0)	52 (260.0)	20 (100)	0.19	**2.46 (1.31–4.62)**	1.68 (0.85–3.33)
6+	31 (46.3)	36 (13.5)	266 (100)	**0.0005**	**3.93 (2.06–7.50)**	1.93 (0.93–3.99)
Age at first menses						
<12	13 (38.2)	21 (61.8)	34 (100)	0.23	1	1
12 or 13	34 (28.6)	85 (71.4)	119 (100)	0.8	0.80 (0.46–1.40)	0.50 (0.25–1.01)
14+	13 (23.2)	43 (76.8)	56 (100)	0.26	0.61 (0.29–1.26)	0.50 (0.21–1.19)

CI, confidence interval; OC, oral contraceptive; OR, odds ratio; STD, sexually transmitted disease.

abnormal Pap tests, future research should evaluate whether the increased risk of cervical dysplasia and cervical cancer in RA patients is related to RA treatment or the degree of immunosupression based on the potential association between HPV infection and immunosuppressants.[18]

Acknowledgments

We acknowledge Michelle Frits and Raisa Levine for programming support. VG Gillet participated in the study design, patient recruitment, patient survey, data collection, data management, statistical analysis, and manuscript preparation. DH Solomon participated in the study design, patient recruitment, patient survey, data interpretation, and manuscript preparation. NA Shadick and ME Weinblatt participated in the study design, patient recruitment, data interpretation, and manuscript preparation. CK Iannaccone participated in patient recruitment, data collection and management, and manuscript preparation. S Feldman participated in the study design, data interpretation, and manuscript preparation. SC Kim received research funding for this study and participated in the study design, patient survey, data collection, statistical analysis, data interpretation, and manuscript preparation. All authors read and approved the final manuscript.

Disclosure Statement

VG Gillet, S Feldman, and CK Iannaccone have no conflicts of interest to disclose. This study is funded by Dr. SC Kim's NIH grant K23 AR059677. Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) is funded by Bristol Myers Squibb, Crescendo Biosciences, and Medimmune. DH Solomon is supported by the NIH grants K24 AR055989, P60 AR047782, and R01 AR056215 and received research support from Amgen and Lilly. He serves in unpaid roles on studies sponsored by Pfizer, Novartis, Lilly, and Bristol Myers Squibb. NA Shadick received research support from Abbott, Amgen, and Genentech. ME Weinblatt received research support and served as a consultant to Bristol Myers Squibb, Crescendo Biosciences, and Medimmune. CS Kim is supported by the NIH grant K23 AR059677. She received research support from Pfizer and tuition support for the Pharmacoepidemiology program at the Harvard School of Public Health funded by Pfizer, Millennium, Pharma, and Asisa.

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