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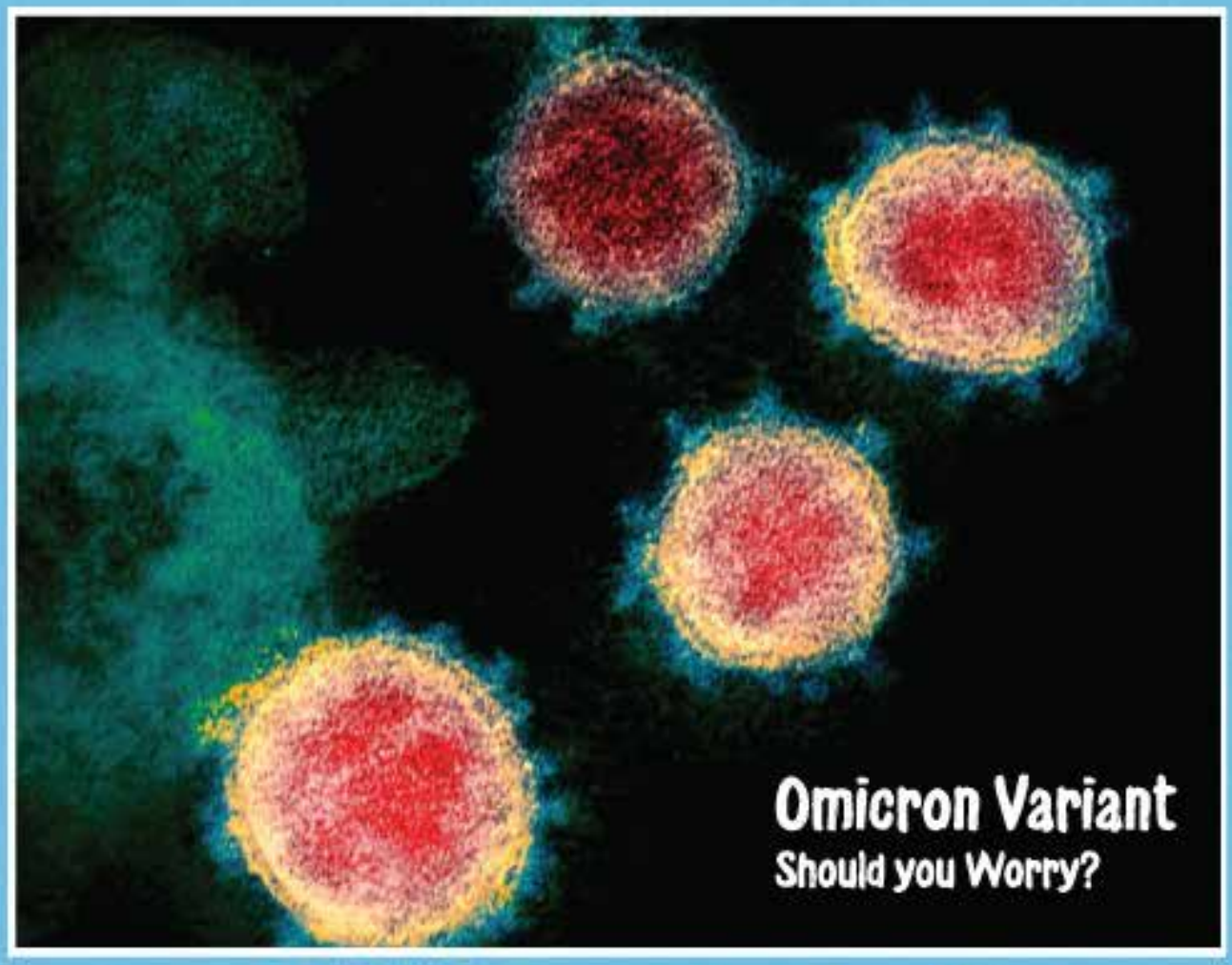

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Original Article

Post–Menopausal Status and Risk for Cervical Dysplasia

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Abstract

Introduction: The study aim is to determine the association of post–menopausal status with abnormal Pap smear cytology and cervical dysplasia detected by colposcopically–directed biopsy. We also study the association of biopsy–confirmed dysplasia with Pap smear results.

Patients and Methods: This retrospective study included 480 women with abnormal Pap smear results who were referred for colposcopy. Covariates considered included demographic (age, race/ethnicity, smoking status), sexual activity (age first sexual intercourse, number lifetime partners, duration current partner), and disease (HIV, high–risk HPV, immunosuppression).

Results: Post–menopausal status was not significantly associated with abnormal Pap smear cytology or cervical dysplasia. We found a statistically significant association of high–grade dysplasia with high–grade Pap smear results: ASC–H (B=3.43, SE=0.84, p<0.001); HSIL (B=3.50, SE=0.84, p<0.001) and AGC (B=3.47, SE=1.02, p<0.01).

Discussion and Conclusion: Although clinicians may want to consider not requiring colposcopically–directed biopsy for certain post–menopausal patients, we recommend continuing with current cervical cancer guidelines of screening for all women regardless of menopausal status.

Keywords: uterine cervical dysplasia, cervical intraepithelial neoplasia, postmenopause, menopause, papanicolaou test

Introduction

Human papilloma virus (HPV) is the most common sexually transmitted infection diagnosed in the United States, where approximately 80% of the population will contract HPV during their lifetime.[1,2] Although HPV infections may be self–limited and asymptomatic, persistent infection with high–risk HPV (HrHPV) serotypes is associated with a higher predisposition to develop cervical intraepithelial neoplasia (CIN) and if untreated, a higher predisposition to develop cervical cancer.[1,3,4] The Centers for Disease Control and Prevention (CDC) estimates that approximately 12,000 new cases of HPV–induced cervical cancer are diagnosed annually with the highest rates among black and Hispanic women.[5]

Current guidelines recommend investigation of abnormal Pap smear results, including persistent HrHPV, atypical squamous cells of undetermined significance (ASC–US), low–grade squamous intraepithelial lesion (LSIL), high–grade squamous intraepithelial lesion (HSIL), atypical squamous cells–cannot exclude HSIL (ASC–H), and atypical glandular cells (AGC) that are associated with high–risk HPV serotypes by an invasive procedure called colposcopy and tissue biopsy [6]. Risk factors for developing cervical dysplasia include 1) demographics including age[7] and history of smoking;[8,9] 2) sexual activity variables including number of lifetime partners,[8,10,11] age of first sexual intercourse,[10,12] persistent HPV infection,[3] and duration with current partner;[13] and 3) disease variables including HIV status,[14,15] and other immunocompromised conditions.[16]

Post–menopausal status is positively associated with abnormal Pap smears, since postmenopausal squamous atypia mimics squamous intraepithelial neoplasia.[17,18] The association of cervical dysplasia confirmed by colposcopically–directed biopsy and post–menopausal status is unclear. While no differences have been reported between final histopathologic diagnosis in pre–menopausal versus post–menopausal women with abnormal Pap smear cytology,[19] others have reported decreased rates of CIN3 among post–menopausal women,[20,21,22] or alternatively significantly more CIN3 among post–menopausal patient with abnormal Pap

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smear cytology.[23] To our knowledge, none of the studies comparing post–menopausal status with cervical dysplasia from colposcopically–directed biopsy include a comparison of the aforementioned clinical risk factors for cervical cancer.

This study has four objectives. First, we study the association of post–menopausal status with cervical dysplasia confirmed by colposcopically–directed biopsy relative to other risk factors for cervical cancer. Second, we study the association of post–menopausal status with abnormal Pap smear cytology. Third, we study the association of cervical dysplasia on colposcopically–directed biopsy with Pap smear results. Fourth, we study the association of post–menopausal status in the subset of those with high–grade dysplasia confirmed by colposcopically–directed biopsy with Pap smear results of high–grade dysplasia.

Methods

Setting

This is a retrospective study of 480 consecutive patients seen in a dysplasia clinic at a suburban New York City hospital that serves mostly low–income patients. Data were obtained from visits that occurred from May 2017 through January 2019. Eligibility criteria included: age >21 and an abnormal Pap smear requiring subsequent patient evaluation by colposcopy. For this time period, 623 of the 5,570 pap smears performed were abnormal (11.2%). We excluded the 143 patients that were not evaluated in our subspecialty clinic. Exclusion criteria for evaluated patients included those currently pregnant at time of colposcopy, gross cervical lesions suspicious for malignancy at time of colposcopy, previous history of cervical or endometrial cancer, previous history of total hysterectomy, or seen in the dysplasia clinic for other conditions such as condyloma treatment, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia surveillance. The study was ethically conducted and was approved by the hospital Institutional Review Board.

Variables

Demographic variables were age (years), race/ethnicity (white, black, Hispanic, other), and smoking history (no/yes). Sexual activity variables were age of first sexual intercourse (< 20 years versus > 20) years,[24] lifetime sexual partners (≤ 5 versus > 5),[13,24] and duration with current partner (months). Disease variables were HIV status (negative versus positive), HrHPV (no/yes), and immunosuppression (no/yes). Immunosuppression was defined as a documented history of diabetes, history of lupus, chronic steroid use >6 months, or current treatment with immunosuppressive or chemotherapeutics. Pap smear results had categories of negative for malignancy (NFM) and abnormal cytology (ASC–US, LSIL, ASC–H, HSIL, and AGC). Post–menopausal status was classified as last menstrual period greater or equal to one year and pre–menopausal status was classified as last menstrual period less than one year prior to the clinic visit. Colposcopically–directed biopsy had categories of negative, CIN1, and CIN2/3. The two patients diagnosed with squamous cervical cancer and one patient diagnosed with endometrial cancer were included in the CIN2/3 group.

Statistical Analyses

Descriptive statistics of mean and standard deviation were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Analysis of variance compared the continuous variables. As appropriate, either the Pearson chi square test or the Fisher's exact test compared the categorical variables. Multivariate binary logistic regression compared the predictor variables that significantly differed between the menopause groups. Multinomial logistic regression compared the predictor variable that significantly differed between the colposcopy biopsy histology groups. All p–values were two–tailed. IBM SPSS Statistics Version 25 (Armonk, NY, 2017) and Stata/SE Version 15 (College Station, TX, 2017) were used for the analyses.

Results

The sample included 371 pre–menopausal and 109 post–menopausal women. Table 1 shows the sample characteristics for each group by menopausal status. For demographic variables, there was a significantly greater mean age ($p<0.001$) for post–menopausal (M=57.3 years) as compared to pre–menopausal (M=36.3 years), significantly greater percentage of black race/ethnicity ($p=0.001$) for post–menopausal (34.9%) as compared to pre–menopausal (16.7%), and significantly greater percentage with a smoking history ($p=0.01$) for post–menopausal (20.2%) as compared to pre–menopausal (10.2%). For sexual activity variables, there was a significantly greater mean duration with current partner ($p<0.001$) for post–menopausal (M=119.1 months) as compared to pre–menopausal (M=72.3 months). For disease variables, there was a significantly greater percentage of HIV ($p=0.01$) for post–menopausal (9.3%) as compared to pre–menopausal (3.0%), and a greater percentage of immunosuppression ($p<0.001$) in post–menopausal (12.8%) as compared to pre–menopausal (3.5%). When analyzing Pap smear results, at the significance level of $p=0.05$, there was a greater percentage of NFM for post–menopausal (34.9%) as

Variable	Pre–menopause M (SD) or # (%) (n=371)	Post–menopause M (SD) or # (%) (n=109)	p–value
Age (years) [mean]	36.3 (7.39)	57.3 (7.86)	<0.001
Race/ethnicity			0.001
White	8 (2.2)	3 (2.8)	
Black	62 (16.7)	38 (34.9)	
Hispanic	286 (77.1)	64 (58.7)	
Other	15 (4.0)	4 (3.7)	
Smoking history (yes)	38 (10.2)	22 (20.2)	0.01
Age first sexual intercourse (years)			0.66
< 20 years	83 (22.8)	22 (20.8)	
≥ 20 years	281 (77.2)	84 (79.2)	
Lifetime sexual partners (number)			0.18
< 5	295 (80.6)	79 (74.5)	
≥ 5	71 (19.4)	27 (25.5)	
Duration with current partner (months) [mean]	72.3 (80.39)	119.1 (152.25)	<0.001
HIV (positive)	11 (3.0)	10 (9.3)	0.01
HrHPV (yes)	340 (94.2)	99 (94.3)	0.97
Immunosuppression (yes)	13 (3.5)	14 (12.8)	<0.001
Pap smear results			0.05
NFM	85 (22.9)	38 (34.9)	
ASC–US	134 (36.1)	26 (23.9)	
LSIL	114 (30.7)	30 (27.5)	
ASC–H	17 (4.6)	5 (4.6)	
HSIL	14 (3.8)	7 (6.4)	
AGC	7 (1.9)	3 (2.8)	
Colposcopically–directed biopsy			0.90
Negative	285 (76.8)	86 (78.9)	
CIN1	55 (14.8)	15 (13.8)	
CIN2/3	31 (8.4)	8 (7.3)	

Table 1. Sample Characteristics Compared by Menopause Status

Note: M=mean, SD=standard deviation, HIV=human immunodeficiency virus, HrHPV=high–risk human papillomavirus, CIN=cervical intraepithelial lesion, NFM=normal, ASC–US=atypical squamous cells of undetermined significance, LSIL=low–grade squamous intraepithelial lesion, ASC–H=atypical squamous cells, cannot exclude HSIL, HSIL=high–grade squamous intraepithelial lesion, AGC=atypical glandular cells. The CIN2/3 group included 2 people with squamous cervical cancer and 1 person with endometrial cancer. Sample size for the following variables were less than 480: age first sexual intercourse (n=470), lifetime sexual partners (n=472), duration with current partner (n=452), HIV (n=474), HPV (n=466).

compared to pre–menopausal (22.9%), and a lesser percentage of ASC–US for post–menopausal (23.9%) as compared to pre–menopausal (36.1%).

Table 2 shows multivariate binary logistic regression by menopausal status. Increasing age was significantly associated with increased odds for being post–menopausal ($p<0.001$). Other race/ethnicity was significantly associated with decreased odds for being post–menopausal ($p<0.05$). None of the other demographic, sexual activity, disease, or Pap smear results variables were significantly associated with post–menopausal status.

In Table 3, sample characteristics were compared among the colposcopically–directed biopsy groups. No clinical variables, including menopausal status, were significantly different ($p=0.90$) between negative histology (23.2%), CIN1 (21.4%), and CIN2/3 (20.5%). Only Pap smear results were significantly associated with histologic results ($p<0.001$). Among patients with NFM cytology, the two patients with confirmed CIN2/3 were both pre–menopausal. There were no post–menopausal patients with CIN2/3 among those with NFM cytology.

Multinomial logistic regression analysis by cervical cytology compared the colposcopically–directed biopsy groups. In analyses comparing CIN1 to negative, only the low–grade Pap smear result of LSIL (beta=0.81 (SE=0.36), $p<0.05$) was significantly positively associated with a CIN1 classification. None of the high–grade Pap

Variable	OR (95% CI)
Age (years) [mean]	1.54 (1.38, 1.73)***
Race/ethnicity	
White	1.00
Black	0.51 (0.04, 5.83)
Hispanic	0.72 (0.66, 6.82)
Other	0.01 (<0.001, 0.48)*
Smoking history (yes)	0.86 (0.24, 3.04)
Duration with current partner (months) [mean]	0.999 (0.995, 1.003)
HIV (positive)	1.01 (0.18, 5.78)
Immunosuppression (yes)	0.67 (0.14, 3.30)
Pap test results	
NFM	1.00
ASC–US	1.35 (0.39, 4.69)
LSIL	1.93 (0.63, 7.66)
ASC–H	0.42 (0.02, 5.93)
HSIL	2.07 (0.19, 23.16)
AGC	0.54 (0.04, 8.19)

Table 2. Logistic Regression Analysis for those with Post–menopause

Note: OR=odds ratio, CI=confidence interval, HIV=human immunodeficiency virus, NFM=normal, ASC–US=atypical squamous cells of undetermined significance, LSIL=low–grade squamous intraepithelial lesion, ASC–H=atypical squamous cells, cannot exclude HSIL, HSIL=high–grade squamous intraepithelial lesion, AGC=atypical glandular cells. *p<0.05, ***p<0.001

smear results (ASC–H, HSIL, and AGC) were significantly associated with CIN1 classification. In analyses comparing CIN2/3 to negative, all high–grade Pap smear results of ASC–H (beta=3.43 (SE=0.84), p<0.001), HSIL (beta=3.50 (SE=0.84), p<0.001), and AGC (beta=3.47 (SE=1.02), p<0.01) were each significantly positively associated with a CIN2/3 classification. None of the low–grade Pap smear results were significantly associated with CIN2/3 classification.

An exploratory analysis compared menopause status with Pap smear results among the subset of patients with colposcopy biopsy histology of CIN2/3/cancer. No significant difference (p=0.45) occurred in percentage of low–risk (NFM, ASC–US, LSIL) versus high–risk (ASC–H, HSIL, AGC) Pap smear results between pre–menopause [low risk: n=17 (54.8%), high risk: n=14 (45.2%)] and post–menopause [low risk: n=3 (37.5%), high risk: n=5 (62.5%)] for those with histologically confirmed high–grade dysplasia.

Discussion

Our study found an association of cervical dysplasia by colposcopically–directed biopsy results with Pap smear cytology results. We did not find any association of post–menopausal status with biopsy–confirmed cervical dysplasia nor with abnormal Pap smear cytology. We did not find a difference between pre–menopausal and post–menopausal status in the subset of those with high–grade dysplasia according to colposcopically–directed biopsy with high–grade abnormal Pap smear results.

Cervical dysplasia on colposcopically–directed biopsy was positively associated with Pap smear cytology results. All high–grade abnormal Pap smear results (ASC–H, HSIL, and AGC) were each significantly positively associated with CIN2/3 while none of the low–grade Pap smear were associated with CIN2/3. Similarly, we found that LSIL was positively associated with CIN1. These findings are consistent with other published studies.[19,21] The likely reason for this pattern is that HrHPV strains have oncogenic proteins which lead to neoplastic changes in the squamous epithelium that can be identified histologically on biopsy.[25]

We did not find any association of post–menopausal status with cervical dysplasia on colposcopically–directed histologic results. A number of studies report that post–menopausal status is associated with lower risk for high–grade dysplasia on colposcopically–directed biopsy histology.[20,21,22,26] Also, it is well–supported that HrHPV is associated with increased risk for cervical dysplasia.[3,4,27] In addition to a lower risk for high–grade dysplasia on colposcopically–directed biopsy histology, post–menopausal women have also exhibited a lower detection of HrHPV as compared to pre–menopausal women.[22,28,29] Our study differs from the patterns reported in these studies. In our study, the rates of HrHPV were similar in both the pre–menopausal and post–menopausal groups, as was the incidence of cervical dysplasia. These findings may be explained by a difference in selection criteria for our study group. In contrast to most studies, we only included those patients for whom colposcopy was recommended based on accepted referral guidelines that include co–testing for cervical cytology and HrHPV as part of routine cervical screening. Similar findings are reported by others using comparable screening in China.[30]

We did not find any association of post–menopausal status with abnormal Pap smear cytology results. This differs from a number of studies that report that post–menopausal status is associated with abnormal Pap smear cytology.[17,18] A novel aspect of our study is that we adjusted using multivariate analysis for other demographic, sexual activity, and disease variables that are associated with increased risk of cervical cancer. Furthermore, the univariate differences by menopausal status for these variables were expected. Postmenopausal women

Variable	Negative M (SD) or # (%) (n=371)	CIN1 M (SD) or # (%) (n=70)	CIN2/3 M (SD) or # (%) (n=39)	p–value
Age (years) [mean]	41.4 (11.78)	39.7 (10.33)	40.1 (11.78)	0.44
Race/ethnicity				0.89
White	10 (2.7)	1 (1.4)	0 (0.0)	
Black	80 (80.0)	11 (15.7)	9 (23.1)	
Hispanic	265 (71.4)	56 (80.0)	29 (74.4)	
Other	16 (4.3)	2 (2.9)	1 (2.6)	
Smoking history (yes)	47 (12.7)	5 (7.1)	8 (20.5)	0.13
Age first sexual intercourse (years)				0.36
< 20 years	85 (23.3)	15 (22.4)	5 (13.2)	
≥ 20 years	280 (76.7)	52 (77.6)	33 (86.8)	
Lifetime sexual partners (number)				0.59
< 5	291 (79.3)	55 (82.1)	28 (73.7)	
≥ 5	76 (20.7)	12 (17.9)	10 (26.3)	
Duration with current partner (months) [mean]	81.5 (101.74)	82.6 (110.39)	92.8 (93.85)	0.82
HIV (positive)	18 (4.9)	2 (2.9)	1 (2.6)	0.85
HrHPV (yes)	335 (93.6)	67 (95.7)	37 (97.4)	0.73
Immunosuppression (yes)	21 (5.7)	3 (4.3)	3 (7.7)	0.68
Post–menopause (yes)	86 (23.2)	15 (21.4)	8 (20.5)	0.90
Pap smear results				<0.001
NFM	108 (29.1)	13 (18.6)	2 (5.1)	
ASC–US	124 (33.4)	26 (37.1)	10 (25.6)	
LSIL	107 (28.8)	29 (41.4)	8 (20.5)	
ASC–H	14 (3.8)	0 (0.0)	8 (20.5)	
HSIL	13 (3.5)	0 (0.0)	8 (20.5)	
AGC	5 (1.3)	2 (2.9)	3 (7.7)	

Table 3. Sample Characteristics Compared by Colposcopy–directed Biopsy Histology

Note: M=mean, SD=standard deviation, HIV=human immunodeficiency virus, HrHPV=high–risk human papillomavirus, CIN=cervical intraepithelial lesion, NFM=normal, ASC–US=atypical squamous cells of undetermined significance, LSIL=low–grade squamous intraepithelial lesion, ASC–H=atypical squamous cells, cannot exclude HSIL, HSIL=high–grade squamous intraepithelial lesion, AGC=atypical glandular cells. The CIN2/3 group included 2 people with squamous cervical cancer and 1 person with endometrial cancer. Sample size for the following variables were less than 480: age first sexual intercourse (n=470), lifetime sexual partners (n=472), duration with current partner (n=452), HIV (n=474), HPV (n=466). Pearson chi square test performed for Pap test results due to too many cells exceeding the memory limit requirements for conducting the Fisher's exact test.

were older, more likely to smoke, and more likely to be immunosuppressed. However, these variables were not significant by multivariate analysis when simultaneously adjusting for other variables. It is reported that the reason for post–menopausal differences in cytologic abnormalities are due to hypoestrogenic changes and atrophy related to post–menopausal status.[17,18] Our study does not support this explanation and suggests that this pathway may not clinically impact current screening for cervical cancer.

We did not find a difference between pre–menopausal and post–menopausal status in those with high–grade dysplasia according to colposcopically–directed biopsy with Pap smear results of high–grade dysplasia. Clinically, treatment of biopsy–confirmed high–grade cervical dysplasia is recommended to prevent progression to invasive cancer. If detection of CIN2/3 varies by menopausal status, screening guidelines could safely be modified to minimize invasive evaluation of those patients at low risk. We are not aware of any related research to determine risk of cervical dysplasia by menopausal status. Also, the incidence of persistent HrHPV is bimodal with an increased risk between ages 26–30 years and ages 46–50 years.(7) We found 8.13% (n=39) of our sample exhibited potentially treatable disease of CIN2/3/cancer. A much larger sample size would potentially be needed to determine any difference in high–grade dysplasia by menopausal status among this patient population. We

recognize that colposcopy is invasive and uncomfortable, especially in postmenopausal women, many of whom already experience dyspareunia or are no longer sexually active. Future research is warranted to study this topic and better define the cervical cancer screening process of post–menopausal women.

This study has several limitations. First, many post–menopausal women were excluded from the study because older women were more likely to have undergone a total hysterectomy and as there was no remaining cervix, no cervical cancer screen was performed. Second, of the postmenopausal women who were seen at the dysplasia clinic, many were likely to have first time NFM HrHPV, and thus colposcopy was not indicated. These patients were not included in the study. Third, the cytologic interpretation at our hospital may differ from reports used in other studies. Future research should consider demographic, sexual activity, and disease variables as potential covariates.

Conclusion

In conclusion, we did not find an increased independent association of post–menopausal status with abnormal Pap smear cytology or cervical dysplasia on colposcopically–directed biopsy. Although clinicians may consider not requiring colposcopically–directed biopsy for certain post–menopausal patients, we do not advocate this approach. Clinicians should continue to follow the accepted guidelines for cervical cancer screening regardless of menopausal status.

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The authors did not receive any funding to conduct this work and have no conflict of interest for disclosure.

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