



Factors Associated with Cyto-Histological Misinterpretation of Cervical Smear according to Menopausal Status

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Objectives: This study aimed to compare histological outcomes between pre-menopausal and post-menopausal women with cervical cytological abnormalities and to investigate the clinical factors affecting the misinterpretation of cytology and histology.

Methods: We conducted a retrospective analysis of 599 patients with abnormal cervical cytology who underwent loop electrosurgical excision procedure (LEEP) between January 2010 and May 2019. Baseline characteristics were collected, including age, height, weight, body mass index, gravity, parity, and menopausal status. In total, 477 pre-menopausal women and 122 post-menopausal women were recruited.

Results: Atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions were cytologically observed in 73.4% (135/184) of the pre-menopausal women, which were high-grade lesions confirmed by LEEP. In post-menopausal patients with cytology results that cannot exclude high-grade squamous intraepithelial lesions (ASC-H) or high-grade squamous intraepithelial lesions (HSIL), 27.0% (24/89) were confirmed to have histologically low-grade lesions. High-risk HPV (hrHPV) prevalence in abnormal cervical smears was 92.2%. Moreover, other hrHPVs had a higher risk of unexpected histological outcomes unrelated to cytologic results.

Conclusions: Menopausal status and HPV infection are associated with misinterpretation of cervical cytology and histology. Therefore, the menopausal status of patients should be considered for the management of cervical cytology, and primary co-testing is recommended to identify women at risk of cervical abnormalities.

Key Words: Cervical cancer, Cytology, Histology, Menopause, Pap smear

INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths in women [1]. According to the Korea Central Cancer Registry in 2019, around one-third of the 3,200 patients diagnosed each year died from the disease [2]. Survival rates depend on the stage of cervical cancer. The 5-year survival rate is 92% when detected at an early stage. If cervical cancer has spread to surrounding tissues or organs and/or regional lymph nodes, the 5-year survival rate is 58% [3].

Cervical cancer can be diagnosed at the pre-cancerous

stage using cervical smear testing. The results of cervical smear tests were classified using the Bethesda System, a standardized cytology report introduced in Bethesda, Maryland, in 1998. It was recently reviewed and updated in 2014 with improvement in Bethesda atlas of cervical cytology (Supplementary Table 1, available online) [4]. The decisions regarding patient management are based on this system of classification.

The assessment of cervical smears from post-menopausal women presents specific diagnostic challenges. Many studies have demonstrated a low detection rate of dysplasia in the histologic follow-up of post-menopausal women with cytological reports of atypia or atypical

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squamous cells of undetermined significance (ASC-US). The factors that cause misinterpretation include hormonal changes, inflammation, reactive metaplasia, air drying, and sampling problems [5-8]. However, the extent of misinterpretation of histological outcomes from menopausal status is not well-documented, and there are no specific guidelines for menopausal status-dependent management. This challenge may lead to unnecessary follow-up and clinical interventions, such as loop electrosurgical excision procedures (LEEP) conization.

Therefore, we compared the histological outcomes between pre- and post-menopausal women with cervical cytological abnormalities and investigated significant clinical factors affecting the misinterpretation of the cytology and histology.

MATERIALS AND METHODS

Study population

The retrospective study was performed at Inje University Haeundae Paik Hospital. We retrieved data from patients with cervical cytology who underwent LEEP between January 2010 and May 2019. All the patients included in the study underwent liquid-based Pap smear tests. Only patients with known results of Pap smear, LEEP biopsy, menopausal status, and those who met the indication for conization were enrolled in our study. Menopause was defined in the study as women aged 40 or older who had not menstruated for more than a year. Women with premature menopause (menopause < 40 years), a history of cervical intraepithelial neoplasia (CIN), cervical cancer or other gynecological malignancy were excluded. Five hundred ninety-nine subjects were divided into pre-menopausal and post-menopausal group.

Clinical variables

Baseline characteristics, including age, height, weight, body mass index (BMI), gravity/parity, and menopausal status were obtained from the patients. Obesity was defined as BMI ≥ 25 kg/m² or greater. The cytological and histological results were collected. In addition, HPV status was identified using an HPV DNA chip and HPV real-time polymerase chain reaction (PCR), and the data were classified as positive for HPV 16 or 18, other high risk HPV (hrHPV), and negative for HPV.

Classification of cytology and histology

Cytological classification was based on the 2014 Bethesda system. Cytological results were defined as ASC-US, cannot exclude high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL). In this study, we classified cytology results into low-risk (ASC-US and LSIL) and high-risk groups (ASC-H and HSIL). Histological terminology was based on the 2012 Lower Anogenital Squamous Terminology [9]. Biopsy results included LSIL, HSIL, carcinoma in situ, and carcinoma. In addition, LEEP biopsy results were classified as low-grade lesions, such as LSIL or non-malignant lesions, and high-grade lesions, such as HSIL or other malignant lesions. We classified the misinterpretations as underrated or overrated. Underrating was defined as the detection high-grade lesions using LEEP in patients with results of low-risk cervical cytology results. Overrating was defined as the detection low-grade lesions using LEEP in patients with high-risk cervical cytology results.

Statistical analysis

All data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA). Baseline characteristics were compared using the Student's *t* test and chi-square test. The correlation between cytological and histological tests was analyzed using chi-square test and confusion matrix. We performed logistic regression analysis to evaluate the association between clinical variables (menopausal status, obesity, gravity, and HPV type) and misinterpretation. The results were described using crude and adjusted odds ratios (OR) and 95% confidence interval (CI). Statistical significance was set at $P < 0.05$.

Ethical consideration

The study design and a waiver of informed consent from participants were approved by the Institutional Review Board of Inje University Haeundae Paik Hospital (IRB no. 201907014) and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki (2013). In accordance with the journal's guidelines, we will make our data available for the reproducibility, if requested.

RESULTS

Baseline characteristics of the study population

The baseline patient characteristics are presented in [Table 1](#). Of these, 477 and 122 were pre-menopausal and post-menopausal women, respectively. Significant differences were observed between pre-menopausal and post-menopausal groups. The mean age was 38.6 years in pre-menopausal women and 58.8 years in post-menopausal women. BMI was 21.9 kg/m² in pre-menopausal women and 24.2 kg/m² in post-menopausal women, respectively. For the patients included in the study, the HPV DNA chip or HPV real-time PCR was performed for 325 pre-menopausal and 70 post-menopausal women. In the pre-menopausal group, the hrHPV 16/18 positivity rate was 41.5% and the other hrHPV positivity rate was 50.5%, while in post-menopausal women, 22.9% were positive for hrHPV 16/18, and 70.0% were positive for other hrHPV ($P < 0.01$).

Cytological and histological results according to menopause

Cytological and histological reports in pre-menopausal and post-menopausal women are shown in [Supplementary Table 2](#) (available online). Overall, the distribution of cervical cytology results was as follows: ASC-US (18.4%), LSIL (17.9%), ASC-H (17.4%), and HSIL (46.4%). In [Supplementary Table 3](#) (available online), based on the corresponding histology, the cytology results are divided into true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN). The proportion of FP cases was higher in the post-menopausal group and the proportion of FN cases was higher in the pre-menopausal group ([Tables 2 and 3](#)).

Cyto-Histological misinterpretations according to menopause

We analyzed FN and FP, implying a cyto-histological discrepancy. FN was defined as underrated detection

Table 1. Comparison of baseline characteristics between the two study groups

Variable	Total (n = 599)	Pre-menopausal group (n = 477)	Post-menopausal group (n = 122)	P value
Age (y)	42.7 ± 11.7	38.6 ± 8.5	58.8 ± 7.6	< 0.01
Height (cm)	159.6 ± 5.5	160.5 ± 5.1	155.9 ± 5.5	< 0.01
Weight (kg)	57.0 ± 8.1	56.5 ± 8.2	58.7 ± 7.9	< 0.01
Body mass index (kg/m ²)	22.4 ± 3.2	21.9 ± 3.1	24.2 ± 3.0	< 0.01
Gravity				< 0.01
0	101 (16.9)	99 (20.8)	2 (1.6)	
1	83 (13.9)	78 (16.4)	5 (4.1)	
2	141 (23.5)	121 (25.4)	20 (16.4)	
≥ 3	274 (45.7)	179 (37.5)	95 (77.9)	
Parity				< 0.01
0	174 (29.0)	171 (35.8)	3 (2.5)	
1	111 (18.5)	95 (19.9)	16 (13.1)	
2	240 (40.1)	172 (36.1)	68 (55.7)	
≥ 3	74 (12.4)	39 (8.2)	35 (28.7)	
HPV tested	395	325	70	< 0.01
hrHPV 16, 18	151 (38.2)	135 (41.5)	16 (22.9)	
Other hrHPV	213 (53.9)	164 (50.5)	49 (70.0)	
HPV negative	31 (7.8)	26 (8.0)	5 (7.1)	
HPV not tested	204	152	52	

Data are presented as mean ± SD or number (%).

P values are calculated by Student's *t* test for continuous variables and chi-square test was performed for categorical variables between pre-menopausal group and post-menopausal group.

HPV: human papillomavirus, hrHPV: high-risk human papillomavirus.

Table 2. Outcome of underrating cases in pre-menopausal and post-menopausal women

	Underrate (false negative case)		P value ^a
	Pre-menopausal group	Post-menopausal group	
Cytology	Low-risk (ASC-US/LSIL)		
Histology			
Low-grade lesion (n = 70)	49 (26.6)	21 (63.6)	< 0.01
High-grade lesion (n = 147)	135 (73.4)	12 (36.4)	
Total (n = 217)	184 (100)	33 (100)	

Data are presented as number (%).

^aChi-square test was performed for comparing between pre-menopausal group and post-menopausal group.

ASC-US: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion.

Table 3. Outcome of overrating cases in pre-menopausal and post-menopausal women

	Overrate (false positive case)		P value ^a
	Pre-menopausal group	Post-menopausal group	
Cytology	High-risk (ASC-H/HSIL)		
Histology			
Low-grade lesion (n = 58)	34 (11.6)	24 (27.0)	< 0.01
High-grade lesion (n = 324)	259 (88.4)	65 (73.0)	
Total (n = 382)	293 (100)	89 (100)	

Data are presented as number (%).

^aChi-square test was performed for comparing between pre-menopausal group and post-menopausal group.

ASC-H: cannot exclude high-grade squamous intraepithelial lesions, HSIL: high-grade squamous intraepithelial lesion.

Table 4. Logistic regression results for overrating

Overrating	Crude	P value	Adjusted ^a	P value
Menopause				
No	1.00 (reference)		1.00 (reference)	
Yes	3.19 (1.81–5.62)	< 0.01	2.77 (1.30–5.91)	< 0.01
Obesity				
BMI < 25 kg/m ²	1.00 (reference)		1.00 (reference)	
BMI ≥ 25 kg/m ²	2.02 (1.10–3.72)	0.02	3.74 (1.73–8.08)	< 0.01
Gravity				
Nullgravida	1.00 (reference)		1.00 (reference)	
Multigravida	0.54 (0.29–1.02)	0.06	0.30 (0.13–0.69)	< 0.01
HPV				
hrHPV 16, 18	1.00 (reference)		1.00 (reference)	
Other hrHPV	3.16 (1.41–7.07)	< 0.01	3.25 (1.40–14.9)	< 0.01
HPV negative	3.44 (1.04–11.33)	0.04	4.25 (1.21–14.9)	0.02

Data are presented as odds ratio (95% confidence interval).

^aThis model was adjusted for menopause, obesity, gravity, and HPV status.

BMI: body mass index, HPV: human papillomavirus, hrHPV: high-risk human papillomavirus.

of high-grade lesions by LEEP when cytology results were classified as low-risk group. In Table 2, of the 147 FN women, 135 (73.4%) were pre-menopausal and 12 (36.4%) were post-menopausal. FP was defined as an overrate of detecting low-grade lesions by LEEP when cytology results were classified as high-risk group. Of the 58 FP patients, 34 (11.6%) were pre-menopausal and 24 (27.0%) were post-menopausal women (Table 3).

Supplementary Table 4 (available online) shows the calculations using a confusion matrix. In pre-menopausal and post-menopausal women, the FN rate was 0.34 and 0.16, respectively, and the FP rate was 0.41 and 0.53, respectively. Sensitivity and accuracy for pre-menopausal women were 0.66 and 0.65, respectively. In post-menopausal women, the sensitivity and accuracy were 0.84 and 0.70, respectively.

Table 5. Logistic regression results for underrating

Underrating	Crude	<i>P</i> value	Adjusted ^a	<i>P</i> value
Menopause				
No	1.00 (reference)		1.00 (reference)	
Yes	0.28 (0.15–0.52)	< 0.01	0.37 (0.17–0.81)	0.01
Obesity				
BMI < 25 kg/m ²	1.00 (reference)		1.00 (reference)	
BMI ≥ 25 kg/m ²	0.74 (0.44–1.23)	0.24	0.65 (0.32–1.33)	0.24
Gravity				
Nullgravida	1.00 (reference)		1.00 (reference)	
Multigravida	0.77 (0.48–1.24)	0.29	1.26 (0.70–2.27)	0.44
HPV				
hrHPV 16, 18	1.00 (reference)		1.00 (reference)	
Other hrHPV	0.51 (0.32–0.82)	< 0.01	0.55 (0.34–0.90)	0.02
HPV negative	0.70 (0.29–1.68)	0.43	0.70 (0.29–1.69)	0.43

Data are presented as odds ratio (95% confidence interval).

^aThis model was adjusted for menopause, obesity, gravity, and HPV status.

BMI: body mass index, HPV: human papillomavirus, hrHPV: high-risk human papillomavirus.

Association between clinical variables and misinterpretations

We performed logistic regression analysis of the clinical variables associated with discrepancies between cytology and histology. In [Table 4](#), the factors associated with overrating were post-menopausal status (adjusted OR, 2.77; 95% CI, 1.30–5.91; $P < 0.01$), obesity (adjusted OR, 3.74; 95% CI, 1.73–8.08; $P < 0.01$), multigravida (adjusted OR, 0.30; 95% CI, 0.13–0.69; $P < 0.01$), and other hrHPVs (adjusted OR, 3.25; 95% CI, 1.40–14.9; $P < 0.01$). On the contrary, post-menopausal status (adjusted OR, 0.37; 95% CI, 0.17–0.81; $P = 0.01$) and other hrHPV types (adjusted OR, 0.55; 95% CI, 0.34–0.90; $P = 0.02$) were significantly associated with underrating ([Table 5](#)).

DISCUSSION

In this study, we reviewed the outcomes of cervical cytology and histology according to menopausal status and analyzed the factors associated with cyto-histological misinterpretations. Among pre-menopausal women with cytological diagnoses of ASC-US or LSIL (i.e., low-risk cytology group), 73.4% (135/184) were confirmed to having high-grade lesions through LEEP biopsy, compared to only 36.4% (12/33) of post-menopausal women. In contrast, in post-menopausal patients of high-risk cytology group (ASC-H or HSIL),

27.0% (24/89) were confirmed to having low-grade lesions, compared to 11.6% (34/293) in pre-menopausal patients. Our study showed that menopausal status and HPV type were associated with the correlation between cytology and histology. Post-menopausal status and other hrHPV were at a higher risk of overrating.

Cervical smear assessment can be affected by air drying, inflammatory changes, and immature squamous metaplasia. Immature metaplasia and reactive changes can be falsely interpreted as squamous atypia or more severe lesions [8]. Post-menopausal hormonal changes, such as lack of estrogen, may increase the likelihood of atrophic changes. Atrophic changes of the genital tract are relevant to the migration of the transformation zone, making adequate sampling difficult, by morphologically mimicking high-grade cervical dysplasia causing misinterpretation. Gilani and Mazzara [10] reported increased propensity of sampling or biopsy errors in post-menopausal women due to the difficulty in visualizing the involved area in older women. This supported the finding that FP rate of the post-menopausal group (0.53) was higher than that of pre-menopausal group (0.41) in our study. However, the sensitivity and accuracy were higher in post-menopausal women than pre-menopausal women (sensitivity 0.84 vs. 0.66, accuracy 0.70 vs. 0.65). One possible reason for this result is the use of a local estrogen cream for atrophy. Richards and Dalrymple [11] observed that the use of vaginal

estrogen cream in patients with smear abnormalities improved the accuracy of the prediction of true high-grade pre-invasive disease. In this study, some post-menopausal women who used exogenous estrogen cream were included, and they had fewer atrophic changes allowing adequate sampling. However, the use of estrogen cream was not identified in our data.

In total, 395 patients underwent HPV testing. The prevalence of hrHPV in abnormal cervical smear was 92.2% (364/395), and hrHPV 16/18 (38.2%, 151/395) and others hrHPV (53.9%, 213/395) were detected. Previous studies have reported varying rates of hrHPV infection in women with abnormal Pap smears, ranging from 48.2% to 84.3%. Samaha et al. [12] conducted a retrospective study of Egyptian women of ages 25–65 years, where the prevalence of hrHPV in abnormal Pap smears was 48.2%. Ouh et al. [13] reported HPV positivity in 79.2% of ages 19–88 years with an abnormal Pap smear. Chinese study showed that the overall HPV infection rate was 84.37% in patients with CIN 1 and CIN 2-3 [14].

Our results showed that the HPV type was significantly associated with the correlation between cytology and histology. Positivity for other hrHPVs had a higher risk of overrating, but not for underrating. In this study, the overall prevalence of other hrHPV type was higher than that of hrHPV 16/18, particularly in post-menopausal women. The proportion of other hrHPV type in post-menopausal women may have affected our results. We did not distinguish the association between HPV type and cervical cyto-histological misinterpretation since the HPV results of all patients were not included in the data. We recommend further research to assess whether HPV genotype affects the correlation between cytology and histology results.

Clearance of HPV infections by the immune system and spontaneous regression of lower-grade dysplasia occurred frequently in younger women [15,16]. Kiff et al. [17] showed hrHPV testing was significantly more specific in the post-menopausal women than in the pre-menopausal women, suggesting the importance of primary hrHPV screening in post-menopausal women. Other studies have suggested that HPV testing could assist in distinguishing patients with significant disease from those whose smears showed cytological features that mimic the features of squamous intraepithelial lesions [18,19]. As the incidence of squamous intraepithelial lesions and HPV positivity in post-menopausal women diagnosed with atypical squamous cells is

considerably lower than in pre-menopausal women, we suggest that HPV testing may assist in identifying a small number of post-menopausal women with high-grade disease.

The strength of our study is that it was a single-institution study, and we compared cervical cytology and histology by menopausal status rather than by age, including final histological outcome through LEEP biopsy. Additionally, our study supports the assumption that menopausal status affects the interpretation of cervical cytology and histology, and the need to establish the management of post-menopausal patients with abnormal cytology. The limitations of this study include its retrospective nature and insufficient results to assess Pap smear and HPV genotype. In addition, data on factors that could affect the atrophic changes of cervix after menopause, such as the use of topical estrogen creams or the length of time since menopause commencement, were not evaluated. Therefore, further prospective studies are needed to further examine these aspects.

In conclusion, we found that interpreting smears from older women is challenging, probably due to the presence of inflammation, air drying, degeneration, and age-related epithelial aberrations. Menopausal status and HPV infection are associated with misinterpretation of cervical cytology and histology. We recommend primary HPV co-testing to identify women at risk of cervical abnormalities. Further studies should be conducted to standardize the management of abnormal cytology according to menopausal status.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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