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Immediate colposcopic evaluation in postmenopausal women with low-grade squamous intraepithelial lesion cytology

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Key words
Low-grade squamous intraepithelial lesion, postmenopausal woman, premenopausal woman, colposcopy, human papilloma virus

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Conflict of interest
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Abstract

Objective. To compare the final diagnosis among pre- and postmenopausal women with low-grade squamous intraepithelial lesion (LGSIL) cervical smear results. *Design.* Retrospective, comparative study. *Setting.* Departments of obstetrics and gynecology in two teaching and research hospitals. *Population.* Data were evaluated on 712 women with LGSIL between April 2005 and April 2011. *Methods.* Results from 129 postmenopausal women with LGSIL were compared with 583 premenopausal women with a similar LGSIL result with respect to sociodemographic data and histopathology. *Main outcome measures.* Final clinicopathological diagnosis. *Results.* The mean age of the pre- and postmenopausal women was 37.2 and 52.5 years, respectively, and lesions of cervical intraepithelial neoplasia grade 2 or worse were detected by biopsy and/or endocervical curettage in 13.6 and 9.3%, respectively. There was no significant difference between the final diagnosis among pre- and postmenopausal women with LGSIL cytology (relative risk 1.43; 95% confidence interval 0.82–2.48; $p = 0.19$). Invasive cervical cancer was detected in three premenopausal (0.5%) and two postmenopausal women (1.6%). *Conclusions.* Cervical pre-invasive and invasive disease rates were similar in pre- and postmenopausal women with LGSIL cytology. For this reason, LGSIL in postmenopausal women should be considered more seriously, and colposcopic evaluation may be as acceptable an option in the management of LGSIL in this group of patients as it is with premenopausal women.

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; LGSIL, low-grade squamous intraepithelial lesion.

Introduction

Precancerous lesions and invasive cancer of the uterine cervix are associated with high-risk human papilloma virus (HPV) infection in 95% of cases. Human papilloma virus is a highly infectious virus, which causes latent infections that regress spontaneously without intervention. Although HPV infection is very common, it rarely results in neoplasia. According

Key Message

Management of women with low-grade squamous intraepithelial lesion cytology should not be based on their menopausal status.

to the 2001 Bethesda system, low-grade squamous intraepithelial lesions (LGSIL) are characterized by the presence of koilocytosis caused by HPV infection and/or mild dysplasia (1). The pooled estimate of high-risk oncogenic HPV DNA positivity among women with LGSIL is reported as 76.6% (2). The percentage of LGSIL in cervical cytological screening is 1–3%, and LGSIL cervical smears resolve spontaneously at the next screening instance in almost half of the cases, especially in young women. The prevalence of cervical intraepithelial neoplasia (CIN) grade 2 or higher, identified at initial colposcopy among women with LGSIL, is 12–16% (3). Low-grade squamous intraepithelial lesions progress slowly to high-grade squamous intraepithelial lesions in 20% of cases. (4). Currently, the recommended management for women with LGSIL is colposcopy, except for special populations like postmenopausal women and adolescents (5).

The few studies that have included women of older age suggest that they have a lower prevalence of HPV compared with younger women. However, among those who test positive, the proportion of high-risk cancer-related HPV types is high, regardless of age (6,7). Also, it has been observed that in older women with marked atrophy, benign degenerative changes in squamous cells occasionally mimic LGSIL and invasive cancer and, in contrast with younger women, bland nuclear enlargement is relatively common, but rarely associated with a significant histological abnormality in postmenopausal women (8). Based on these findings, previous guidelines have suggested that postmenopausal women with LGSIL can be managed less aggressively than premenopausal women, and triage using HPV testing might be preferred (5). In spite of previous guidelines recommending triage for management of postmenopausal women with LGSIL, there are no strong data supporting this. A previous study conducted to compare pre- and postmenopausal women with abnormal cervical cytology showed no significant difference for CIN 2 or worse lesions between pre- and postmenopausal women with LGSIL (9). No study has indicated that there may be a lower incidence of CIN 2 or that more serious lesions may develop in postmenopausal women with LGSIL.

With the aim of investigating whether postmenopausal women with LGSIL can be managed less aggressively than premenopausal women, we conducted a retrospective case–control series on women with a diagnosis of LGSIL to assess the histological outcome with respect to the menopausal status.

Material and methods

This is an institutional review board approved, retrospective chart review study, which was carried out at the Unit of Colposcopy of the Bakirkoy Women's and Children's Teaching and Research Hospital and Haseki Teaching and Research Hospital between April 2005 and April 2011.

The histopathological results of 129 postmenopausal women with LGSIL cervical smears were compared with those of 583 premenopausal women with LGSIL cervical smears. The postmenopausal women had not been using hormone therapy for at least six months and had been postmenopausal for at least one yearv. The details of sociodemographic data, reproductive history, the number of lifetime sexual partners, age at first intercourse, concomitant genital warts and current smoking status were obtained from the database in the colposcopy unit. Conventional cervical smears with a Plastimed® smear brush (Plastik Medikal Urunler San. Ltd, Istanbul, Turkey) were used as the cervical screening method in both centers.

Colposcopic examination was performed after irrigation of the cervix with saline solution and the application of 5% acetic acid solution. The examination was considered 'satisfactory' when the entire squamocolumnar junction could be visualized. Colposcopy was considered 'positive' when a flat or slightly elevated, mostly well-demarcated aceto-white lesion or punctuation pattern or mosaic pattern was seen after acetic acid application. Colposcopy was defined as 'unsatisfactory' if the squamocolumnar junction was not visible. All patients with a positive colposcopy, with or without a visible squamocolumnar junction, had one or more punch-targeted biopsies from the lesions, while patients with a non-visible squamocolumnar junction, regardless of the positivity of colposcopy, also had endocervical curettage. All procedures were done by gynecologic oncologists (O.A., B.P.C.G. or C.N.). Both biopsies and endocervical specimens were fixed in formalin, submitted to the pathology laboratory and reviewed by experienced gynecologic pathologists.

All patients with positive histological findings following punch biopsy or endocervical curettage had surgical treatment tailored to the definitive histological findings. Histopathology results were classified in three categories: normal (including atrophy, metaplasia, cervicitis and cervical polyp), CIN 1 and CIN 2 or higher grades.

All data were analysed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Differences between post- and premenopausal women were assessed using the chi-squared and Mann–Whitney *U*-tests for categorical variables and Student's *t*-test for continuous variables. Relative risk (RR) and 95% confidence interval (CI) for RR were calculated in premenopausal women with LGSIL for CIN 2 or higher lesions. A p-value <0.05 was considered significant.

Results

Information from a total of 712 patients was analysed, of whom 129 (18.1%) were postmenopausal. Demographic characteristics are summarized in Table 1. The rate of satisfactory colposcopic examination was significantly higher in pre- compared with postmenopausal women (70.1 vs. 57.4%,

Table 1. Demographic characteristics of the pre- and postmenopausal women with low-grade squamous intraepithelial lesions.

Characteristic	Premenopausal ($n = 583$; 81.9%)	Postmenopausal ($n = 129$; 18.1%)	p-Value*
Age (years; mean ± SD)	37.2 ± 7.3	52.5 ± 5.7	0.0001
Parity [median (range)]	2 (0–15)	3 (0–9)	0.0001
Curettage [median (range)]	0 (0–8)	1 (0–8)	0.001
Number of partners [median (range)]	1 (1–10)	1 (1–3)	0.65
Age at the first coitus (years; mean ± SD)	20.1 ± 3.6	19.6 ± 2.5	0.12
Concomitant genital wart [*n* (%)]	9 (1.5)	1 (0.8)	0.50
Smoking [*n* (%)]	148 (25.4)	16 (13.1)	0.003

* A value of $p < 0.05$ was considered significant.

Table 2. Colposcopic features of the pre- and postmenopausal women with low-grade squamous intraepithelial lesions.

Colposcopic features	Premenopausal		Postmenopausal		p-Value*
	n	Percentage	*n*	Percentage	
Satisfactory	407	70.1	74	57.4	0.005
Abnormal findings	372	63.8	69	53.5	0.02

* The significance of the differences was determined using chi-squared tests.

$\chi^2 = 7.776$, df = 1, $p = 0.005$). The rate of abnormal findings during colposcopic examination was also significantly higher in the premenopausal compared with the postmenopausal women (63.8 vs. 53.5%, $\chi^2 = 24.771$, df = 1, $p = 0.02$; Table 2). Cervical biopsy was performed in 494 (84.7%) of the premenopausal and 106 (82.2%) of the postmenopausal women. Endocervical canal curettage was needed in 56.2% of the premenopausal and 61.3% of the postmenopausal women.

Cervical intraepithelial neoplasia grade 2 or higher lesions were detected in 13.4% of pre- and 9.2% of postmenopausal women on biopsy (RR 1.39; 95% CI 0.79–2.47; $p = 0.24$). On endocervical canal curettage, CIN 2 or higher lesions were found at a rate of 1.5 and 3.9% in pre- and postmenopausal women, respectively (RR 0.43; 95% CI 0.14–1.25; $p = 0.11$; Table 3). At the final diagnosis, CIN 2 or higher lesions were detected in 13.6% of the pre- and 9.3% of the postmenopausal women. There was no significant difference between the final diagnosis for pre- and postmenopausal women with LGSIL cytology (RR 1.43; 95% CI 0.82–2.48; $p = 0.19$). Invasive cervical cancer was detected in three of the premenopausal (0.5%) and two postmenopausal women (1.6%).

Discussion

The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study showed that LGSIL was associated with a 27.6% risk of histological CIN grade 2 or 3 within two years, and that further testing with colposcopy and cervical biopsy should almost always be recommended for premenopausal women with an LGSIL smear (10). High-risk HPV infection is very prevalent in women with LGSIL, ultimately devaluing the potential benefits of HPV testing. In the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study trial, 84% of women with LGSIL tested positive for high-risk HPV, resulting in a high rate of referral for colposcopy (10). Testing for high-risk HPV strains was found to have lower specificity for detecting severe CIN in this population in comparison to those with atypical squamous cells of undetermined significance (ASCUS; 10). Repeat cytology is also unacceptable for the follow-up of women with LGSIL owing to the high rate of subsequent abnormal repeat cytology (53–76%) and the associated risk of delaying identification of serious disease (10). Follow-up with repeat cytology or HPV testing is recommended only if colposcopic findings support the absence of CIN (5).

According to the 2006 ASCCP (American Society for Colposcopy and Cervical Pathology) guideline, women with LGSIL should be referred for colposcopy, with the exception of adolescent and low-risk postmenopausal women. The management of LGSIL in postmenopausal women is different from premenopausal LGSIL, because atrophy of the postmenopausal cervical tissues can cause the appearance of abnormal cells that mimic positive cytology. When compared with younger women, older women are thus more likely to have false-positive cytology results. In addition, cytology findings often resolve with time and usually are not related to the changes caused by HPV.

Another reason for the different approach towards postmenopausal LGSIL is that these women are believed to be positive for high-risk HPV less often (6,7). In many studies,

Table 3. Comparison of the histopathological results of pre- and postmenopausal women with low-grade squamous intraepithelial lesions.

	Premenopausal		Postmenopausal		*p*-Value
	n	Percentage	*n*	Percentage	
Biopsy					
No biopsy performed	89	15.3	23	17.8	
Number of patients who needed biopsy	494	84.7	106	82.2	
Normal/CIN 1	415	71.3	94	72.9	0.24
CIN 2 or worse	78	13.4	12	9.3	
Endocervical canal curettage					
Not performed	255	43.8	50	38.7	
Number of patients who needed curettage	328	56.2	79	61.3	
Normal/CIN 1	319	54.7	74	57.4	0.11
CIN 2 or worse	9	1.5	5	3.9	
Final diagnosis					
Normal/CIN 1	504	86.4	117	90.7	0.19
CIN 2 or worse	79	13.6	12	9.3	

Abbreviation: CIN, cervical intraepithelial neoplasia.

the prevalence of HPV is 15–20% in premenopausal women (11,12). The prevalence generally reaches a peak of about 20–30% (maybe as high as 40% in some populations) among women aged 20–24 years and gradually declines through life, becoming 3–10% among women aged over 30 years (4). Only a few studies have evaluated healthy women over the age of 40 years to detect the prevalence of HPV infections, and it has been reported to vary widely. In contrast, recent studies reported that the prevalence of HPV DNA in the cervix of postmenopausal women was 14–18%, which was higher than expected and comparable with the premenopausal HPV prevalence (11–14). Furthermore, a comparison of women of all ages in different countries showed that HPV frequency varied widely among countries (1–22%; 15).

Despite cervical smear test screening being one of the greatest public health successes with regard to women's health services, the lack of adherence to follow-up recommendations limits its effectiveness. A review of USA-based quantitative studies that addressed compliance with abnormal cervical smear follow-up concluded that attendance rates ranged from 19.8 to 90% (16,17). The majority of studies concur that women with less severe lesions are less likely to attend for follow-up (16–18). Reasons for this may include the belief among both women and clinicians that follow-up is less important for less severe findings. While this may be a true argument in general, it paves the way for undesirable consequences when the lesions are disregarded. Although there are few data that support the deferral of colposcopy in the postmenopausal age group, this approach is recommended in new guidelines based on clinical experience and advice from an expert consensus committee (5). For this reason, the outcome of this approach needs to be investigated, because less aggressive management of LGSIL may result in a delay in the identification of serious disease.

In the present study, we compared the biopsy and endocervical curettage results of pre- and postmenopausal women with LGSIL cytology. The prevalence of CIN 2 or higher lesions was similar in pre- and postmenopausal women with LGSIL. According to our findings, proportionally more premenopausal women with LGSIL had CIN 2 or higher lesions compared with postmenopausal women; however, in order to make this difference significant with an α error of 0.05 and a β error of 0.20, the study must contain at least 667 women in each group. Invasive cervical cancer rates were also similar in pre- and postmenopausal women with LGSIL. For this reason, LGSIL in postmenopausal women should be considered more seriously, and immediate colposcopic evaluation might be an acceptable option in the management of these women, as with the premenopausal women.

Although this study is limited by its retrospective nature and by the lack of HPV DNA status of the patients with or without CIN 2 or worse lesions, we would like to highlight the significance of LGSIL in postmenopausal women. In conclusion, further studies with a larger number of patients are needed in order to compare the histopathology and HPV results for the management and follow-up of postmenopausal women with LGSIL and to determine the optimal management of LGSIL in the older aged population.

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