



## Atypical squamous cells of undetermined significance in postmenopausal women: a comparative retrospective analysis

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### ABSTRACT

**Objectives:** To determine the outcomes of women with a diagnosis of atypical squamous cells of undetermined significance (ASCUS) with respect to menopausal status.

**Study design:** Between October 2006 and March 2010, the data of 214 postmenopausal women with ASCUS results on Pap smear were evaluated. Sociodemographic data and histopathological results were compared with those of 1018 premenopausal women with ASCUS cytology.

**Results:** At the final diagnosis, most histological findings were normal in pre- and postmenopausal women with ASCUS cytology (70% and 70.1%, respectively). In the premenopausal group, 23.1% of the women had cervical intra-epithelial neoplasia (CIN) 1 lesions and 6.7% had CIN 2/3 lesions. Similarly, CIN 1 and CIN 2/3 lesions were detected in 23.4% and 6.1% of postmenopausal women, respectively. No significant difference in the final diagnosis was found between the two groups ( $p = 0.88$ ). Two premenopausal women (0.2%) and one postmenopausal woman (0.5%) had micro-invasive cervical carcinoma. There were no cases of invasive carcinoma in either group.

**Conclusions:** According to this study, the rates of pre-invasive and micro-invasive cervical carcinoma were similar in pre- and postmenopausal women with ASCUS cytology.

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### 1. Introduction

The term 'atypical squamous cells of undetermined significance' (ASCUS) was introduced by the 1988 Bethesda System to report cervical cytologies with more marked cellular abnormalities than those attributable to reactive/inflammatory cellular changes, but which are quantitatively or qualitatively inadequate for definitive diagnosis of a squamous intra-epithelial lesion [1,2]. The percentage of ASCUS diagnoses in cervical cytological screening is 3–10%, and this diagnosis may indicate the presence of histological lesions ranging from cervical intra-epithelial neoplasia 1 (CIN 1; 5–17% of cases) to cancer (0.2% of cases) [3,4]. Cervical cytology has been the mainstay of screening for cervical cancer, and is widely acknowledged as a highly effective screening tool for this disease.

Due to the nature of cervical cancer, the majority of women participating in Papanicolaou (Pap) smear screening are under 50 years of age. There is no consensus about screening postmenopausal women for cervical neoplasia. As reported in the Consensus

Guidelines for the Management of Women with Cervical Cytological Abnormalities, postmenopausal women represent a 'special circumstance' because abnormal cervical cytology may not necessarily be predictive of a precancerous lesion [5,6]. Current recommendations by professional groups include discontinuing screening at 65 years of age in previously screened women with a history of normal cervical smears [7]. Studies evaluating cytological abnormalities have concentrated on younger women and the management of postmenopausal low-grade cytological abnormalities, and the number of studies with older women with abnormal cytology seen at any one site is relatively small [8–11]. In postmenopausal women with marked atrophy, benign, degenerative changes in immature squamous cells occasionally mimic squamous intra-epithelial lesions and even invasive cancer. In contrast with younger women, bland nuclear enlargement is relatively common and is rarely associated with a significant histological abnormality in peri- and postmenopausal women. The importance of management of postmenopausal low-grade cytological abnormality is still not clear, and these studies promote close clinical follow-up of these patients as the frequency of precancerous lesions was between 10% and 20%. Previous observational [12] and prospective [13] studies, focused on the fact that treatment may ameliorate atrophy that could be mistaken for cytological atypia, reported conflicting data on the

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effect of hormone replacement therapy (HRT) on cytological abnormalities. The 1992 National Cancer Institute Workshop advocated the therapeutic use of topical oestrogen creams in postmenopausal women with ASCUS [14] on the basis of supporting evidence [15]. However, according to current guidelines, postmenopausal women with ASCUS should be managed in the same way as women in the general population.

The fact that low-grade cytological abnormalities appear to have a different cause and histological findings in postmenopausal women compared with younger women raises the possibility that they could be managed differently. As such, the authors conducted a retrospective case–control series of patients with a diagnosis of ASCUS to specifically quantitate the prognostic value of outcome with respect to menopausal status.

## 2. Material and methods

This retrospective chart review study was approved by the institutional review board, and carried out at the colposcopy units of Haseki Teaching and Research Hospital and Bakirkoy Women's and Children's Teaching and Research Hospital. Between October 2006 and March 2010, the data of 214 postmenopausal women with ASCUS cytology on Pap smear were evaluated. All women were at least 1 year post menopause. In addition, 1018 premenopausal women with ASCUS cytology were selected for comparison of sociodemographic data and histopathological results.

Details of the sociodemographic data and reproductive history, current smoking status, use of contraceptives and HRT, lifetime number of sexual partners and age at first intercourse were obtained from the colposcopy database. Women on HRT and/or with a history of CIN or cervical cancer were excluded from the study.

Cervical screening was performed by conventional Pap smear using a cytobrush at two centres. Adequacy was assessed according to the criteria of the Bethesda System. An adequate smear was defined as adequate squamous cells and evidence of transformation sampling.

Human papillomavirus (HPV) infection was assessed using polymerase chain reaction to amplify the viral DNA, followed by dot blot hybridization to detect the presence and types of HPV.

Colposcopic examination was performed after application of a 5% acetic acid solution to the cervix. The examination was considered to be satisfactory when the entire squamocolumnar junction (SCJ) and the margin of any visible lesion could be visualized with the colposcope. A colposcopy was considered positive when a flat or slightly elevated, mostly well-demarcated, aceto-white lesion, a punctuation pattern or a mosaic pattern could be found after acetic acid application. Colposcopy was defined as non-satisfactory if the SCJ was not visible during the examination. All patients showing an aceto-white lesion with a visible SCJ underwent a punch-targeted biopsy, while patients with an aceto-white lesion and a non-visible SCJ underwent endocervical curettage. All patients with positive histological findings (punch biopsy and/or endocervical curettage) underwent surgical treatment tailored to the definitive colposcopic and histological findings.

The total number of previous cervical screens, interval between last two cervical screens, adequacy of Pap smear, satisfactory/unsatisfactory colposcopic examination, rates of cervical biopsy and endocervical curettage, histopathological diagnosis, conization rates and histopathological results were obtained from patients' data. Histopathological data were classified into three categories: normal (including cervicitis, atrophy, cervical polyp, metaplasia), CIN 1 and CIN 2/3.

All data were analysed using Statistical Package for the Social Sciences Version 15.0 (SPSS, Chicago, IL, USA). Differences between the two groups of women were assessed using

Chi-squared test and Mann–Whitney *U*-test for categorized variables, and Student's *t*-test for continuous variables. All *p*-value calculations were two-tailed.

## 3. Results

Two hundred and fourteen postmenopausal women [mean age 52.6 (standard deviation, SD 5.0) years, mean time since menopause 5.9 (SD 5.2) years] and 1018 premenopausal women [mean age 37.2 (SD 7.3) years] were compared in this study. Thirty percent of premenopausal women and 11% of postmenopausal women were current smokers ( $p = 0.001$ ). Mean age at first coitus was 20.08 (SD 3.8) years and 20.08 (SD 6.09) years in the pre- and postmenopausal women, respectively, and the median number of sexual partners was one in both groups. Adequate smears were obtained in 95.3% and 94.2% of pre- and postmenopausal women, respectively ( $p = 0.79$ ). Four hundred and six (39.9%) premenopausal women and 77 (36%) postmenopausal women were analysed for HPV–DNA. High-risk HPV infection was detected in 18.7% and 12.9% of the pre- and postmenopausal women who were tested for HPV, respectively ( $p = 0.28$ ). Sociodemographic characteristics are summarized in Table 1.

Non-satisfactory colposcopic examination was significantly higher in postmenopausal women compared with premenopausal women (35% vs 13.9%, respectively;  $p = 0.001$ ). Cervical biopsy was more common among premenopausal women than postmenopausal women (76.2% vs 69.6%;  $p < 0.04$ ), whereas endocervical curettage was more common among postmenopausal women (50.5% vs 33.2%;  $p < 0.001$ ). Most premenopausal women had normal biopsy and endocervical curettage results (44.6% and 47.5%, respectively). CIN 2/3 lesions were detected by biopsy and endocervical curettage in 6.3% and 1.4% of premenopausal women, respectively. For postmenopausal women, normal biopsy and endocervical curettage results were achieved in 38.3% and 64.5% of cases, respectively. CIN 2/3 lesions were detected by biopsy and endocervical curettage in 4.2% and 3.3% of postmenopausal women, respectively. There was no significant difference in the number of the patients who underwent conization between the pre- and postmenopausal women (11.9% and 10.7%, respectively;  $p = 0.08$ ) (Table 2).

At final diagnosis, most findings were normal in pre- and postmenopausal women with ASCUS cytology (70% and 70.1%, respectively). In total, 23.1% and 6.7% of premenopausal women

**Table 1**  
Sociodemographic characteristics of pre- and postmenopausal women.

	Premenopausal <i>n</i> = 1018	Postmenopausal <i>n</i> = 214	<i>p</i>
Age in years, mean (SD)	37.2 (7.3)	52.6 (5.0)	
Age at first coitus in years, mean (SD)	20.08 (3.8)	20.08 (6.09)	0.02
Gravida, median	3	3	0.11
Parity, median	2	3	0.08
Endocervical curettage, median	0	0	0.18
Smoking, <i>n</i> (%)	315 (31.6%)	35 (16.3%)	0.003
Previous Pap screen, <i>n</i> (%)	342 (33.6%)	78 (36.6%)	0.57
Time since last Pap screen, <i>n</i> (%)			0.85
Never	676 (66.4%)	136 (63.4%)	
≤24 months	253 (24.9%)	57 (26.9%)	
>24 months	89 (8.7%)	21 (9.7%)	
HPV–DNA test, <i>n</i> (%)			
Available	406 (39.9%)	77 (36%)	
Positive	76 (18.7%)	10 (12.9%)	0.28
Negative	330 (81.3%)	67 (87.1%)	
Not available	612 (60.1%)	137 (64%)	
Adequate smear, <i>n</i> (%)	970 (95.3%)	201 (94.2%)	0.79

**Table 2**  
Colposcopic and histopathological features of the patients.

	Premenopausal n (%)	Postmenopausal n (%)	p
Satisfactory colposcopy	876 (86.1%)	139 (65%)	<0.001
Biopsy	776 (76.2%)	149 (69.6%)	<0.04
ECC	338 (33.2%)	108 (50.5%)	<0.001
Biopsy results			0.075
Normal	454 (44.6%)	82 (38.3%)	
CIN 1	219 (21.5%)	44 (20.6%)	
CIN 2/3	64 (6.3%)	9 (4.2%)	
Micro-invasive cancer	2 (0.2%)	1 (0.5%)	
No biopsy	279 (27.4%)	78 (36.4%)	
ECC results			<0.001
Normal	484 (47.5%)	138 (64.5%)	
CIN 1	33 (3.2%)	12 (5.6%)	
CIN 2/3	14 (1.4%)	7 (3.3%)	
Micro-invasive cancer	2 (0.2%)	1 (0.5%)	
No biopsy	485 (47.6%)	56 (26.2%)	
Conization	121 (11.9%)	23 (10.7%)	0.08

ECC, endocervical curettage; CIN, cervical intra-epithelial neoplasia.

**Table 3**  
Final diagnoses of pre- and postmenopausal women.

	Premenopausal n (%)	Postmenopausal n (%)	p
Final diagnosis			0.88
Normal	713 (70%)	150 (70.1%)	
CIN 1	215 (23.1%)	50 (23.4%)	
CIN 2/3	68 (6.7%)	13 (6.1%)	
Micro-invasive cancer	2 (0.2%)	1 (0.5%)	

CIN, cervical intra-epithelial neoplasia.

had CIN 1 and CIN 2/3 lesions, respectively. Similarly, CIN 1 and CIN 2/3 lesions were detected in 23.4% and 6.1% of the postmenopausal women, respectively. No significant difference in final diagnosis was found between the two groups ( $p = 0.88$ ) (Table 3). Two premenopausal women (0.2%) and one postmenopausal woman (0.5%) had micro-invasive cervical carcinoma. No cases of invasive carcinoma were found in either group.

#### 4. Comments

Postmenopausal hormonal changes such as hypo-oestrogenism, which results in atrophic changes of the genital tract, may increase the likelihood of inadequate or atypical findings on cervical cytology. In colposcopic examinations, the SCJ is often not visualized, making the colposcopic examination unsatisfactory [16]. A recent study, conducted to determine the clinical factors affecting the incidence of unsatisfactory conventional cervical Pap smears, showed that menopausal status did not change the incidence of unsatisfactory smears in univariate and multivariate analyses [17]. In the present study, the rate of inadequate cervical cytology was similar in pre- and postmenopausal women with ASCUS cytology. Among postmenopausal women, 35% had an unsatisfactory colposcopic examination and 50.5% needed to have endocervical canal curettage to evaluate the endocervical lesions. These rates were significantly higher than those for premenopausal women.

A previous study evaluated whether the use of oestrogen therapy affects the adequacy of colposcopic examination. HRT and, especially, local oestrogen replacement were found to improve the adequacy of colposcopic examination, and may reduce the number of endocervical curettage, loop excision or cone procedures needed for women with inadequate colposcopic examinations [18]. On the other hand, studies have shown that HRT is associated with Pap

smears mimicking low-grade squamous intra-epithelial lesions caused by cellular glycogenization [19], and current HRT use may affect the initial change in squamous cervical cytological abnormalities, such as ASCUS [20]. Menezes et al. identified HPV-like changes in ThinPrep screening of postmenopausal women who were on HRT [21]. In addition to artefactual HPV-like changes, HRT may upregulate viral expression with subsequent higher risk of genital cancer [22,23]. The postmenopausal women in the present study were not current HRT users, and 36% were tested for HPV. High-risk HPV was found in 12.7% of postmenopausal women who underwent HPV testing. Previous studies demonstrated that a diagnosis of ASCUS in postmenopausal women results in a negative HPV–DNA test in a significant proportion of patients [4,24,25]. It is not clear whether it is the hypo-oestrogenic status or HRT which causes or mimics ASCUS in postmenopausal women.

Sawaya et al. evaluated the predictive value of an abnormal cervical smear in postmenopausal women with recent normal smears using data from a randomized, controlled trial of oral oestrogen plus progestin [13]. The incidence of new cytological abnormalities in the 2 years following a normal smear was 110 per 4895 person-years, and most cases were reported as ASCUS (67%). Most of the women who were diagnosed with ASCUS cytology had normal histology; only 1.4% had high-grade histological conditions. At final diagnosis, most pre- and postmenopausal women in the present study had normal colposcopic and/or histopathological findings. The CIN 1 rate was 23.1% and 23.4% for the pre- and postmenopausal women, respectively. High-grade dysplastic histological findings were detected in 6.1% of postmenopausal women, and no significant difference in high-grade dysplastic lesions was found between pre- and postmenopausal women with ASCUS cytology. A previous study with a large number of cases of abnormal cytology, which aimed to determine the rate of cervical neoplasia after abnormal cytology among women aged  $\geq 50$  years of age, reported CIN 2/3 in 9% of cases. Older women with ASCUS cytology had significantly higher rates for negative histology (52%), CIN 3 (8%) and cancer (3%) than younger women with ASCUS. The authors suggested that immediate colposcopy was appropriate in older patients with ASCUS cytology, especially for those in whom compliance could be problematic [26].

Several limitations of this study include its retrospective design, the lack of further follow-up, and the use of traditional cervical sampling techniques. The use of liquid-based techniques may alter outcomes. However, to the authors' knowledge, this is the largest study among postmenopausal women with ASCUS cytology.

In conclusion, the effect of long-term use of HRT on cervical cytology is still not clear, but a hypo-oestrogenic status will probably induce unsatisfactory colposcopic examinations and may increase the number of cases of endocervical curettage. This study found no difference between the histological findings of pre- and postmenopausal women with ASCUS cytology. Most postmenopausal women with ASCUS cytology have benign histological changes; however, it should be kept in mind that high-grade or micro-invasive histology following ASCUS cytology in postmenopausal women would occur in the same percentage of premenopausal women at the time of first evaluation. It is suggested that ASCUS cytology should be evaluated in the same manner in pre- and postmenopausal women.

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