The Positive Predictive Value of Annual Cervical Smears in Postmenopausal Women

POSTMENOPOZAL KADINLARDA YILLIK SERVİKAL SMEAR ALMANIN POZİTİF PREDİKTİF DEĞERİ

Dr. Koray ELTER,[a] Dr. Fatih DURMUŞOĞLU,[a] Dr. Devrim SEZEN,[a] Dr. Meltem UYGUR[a]

[a]Department of Obstetrics and Gynecology, Medical School of Marmara University, İSTANBUL

Abstract

Objective: To evaluate the positive predictive value of annual cervical smears in postmenopausal women, and to determine the effect of estrogen + progestogen therapy (EPT) on Pap smear findings.

Material and Methods: Women, who had spontaneous menopause and who had up to 4 annual smears following presentation to our outpatient clinic between 1995 and 2002, were retrospectively analyzed. Women were either on no hormonal treatment or on EPT during the follow-up. Cervical smears, which reported ASCUS, AGCUS, LGSIL or HGSIL were accepted as abnormal. Extra smear results, and any additional diagnostic tests were evaluated, and pathology reports confirming histological diagnoses were analyzed.

Results: 3198 women had a smear at the initial presentation. 37%, 19% and 11% of these women had one, two, and three repeated annual smears, respectively. The rates of abnormal smear were 1.25%, 0.93%, 0.34% and 0.89% in the 4 consecutive annual smears, respectively (P>0.05). Ninety-one percent (51/56) of abnormal smears were ASCUS. Final diagnosis of only one woman was pre-cancerous. The rate of abnormal smears was comparable between women, who were on EPT and those, who were not on any treatment.

Conclusion: The rates of abnormal smear were comparable in the 4 consecutive annual smears in postmenopausal women. The incidence and positive predictive value of abnormal smears seem low in these women. This may increase the cost for detecting one pre-cancerous lesion of the cervix. Use of EPT does not increase the rate of abnormal smears in postmenopausal women.

Key Words: Menopause, cervical smear, hormone replacement therapy, screening, predictive value

Özet

Amaç: Postmenopozal kadınlardan arka arkaya alınan yıllık servikal smear sonuçlarının pozitif prediktif değerini incelemek ve östrojen - progestojen tedavisinin (ÖPT) anormal sonuçlara etkisini belirlemek.

Gereç ve Yöntemler: Spontan menopoza giren ve 1995 - 2002 yılları arasında kliniğimize başvuran ve takipte olduğu süre boyunca bir ile 4 adet arasında yıllık servikal smearı olan kadınlar bu retrospektif çalışmada incelenmiştir. Takipte oldukları sürece hormonal tedavi almayan kadınlar ile ÖPT alan kadınlar çalışmaya dahil edilmiştir. Sonucu ASCUS, AGCUS, LGSIL veya HGSIL olan smearlar anormal kabul edilmiştir. Bu anormal smearların takibi ve tedavisi amacıyla alınan ekstra smearlar ve yapılan işlemlerin sonuçları incelenmiştir.

Bulgular: 3198 kadından ilk başvuruda smear alınmıştır. Bu kadınlardan birinci yılda %37'sinden, 2. yılda %19'undan ve 3. yılda %11'inden servikal smear alınmıştır. İlk başvuruda ve takip eden yıllarda anormal smear oranları benzerdi ve sırasıyla %1.25, %0.93, %0.34 ve %0.89 idi. Anormal smearların %91'i (51/56) ASCUS idi. Sadece bir kadının kesin tanısının prekanseröz olduğu saptandı. ÖPT kullanan kadınlarla hormon kullanmayan kadınlar arasında anormal smear oranları benzerdi.

Sonuç: Postmenopozal kadınlarda ardışık olarak alınan 4 adet yıllık servikal smearlarda anormal sonuç oranları yıllar arasında benzerdir. Anormal smearın bu kadınlardaki insidansı ve pozitif prediktif değeri düşük olabilir. Bu düşük oran serviksin bir prekanseröz lezyonunu saptama maliyetinin artmasına sebep olacaktır. Östrojen - progestojen tedavisi anormal smear oranını arttırmamaktadır.

Anahtar Kelimeler: Menopoz, servikal smear, hormon replasman tedavisi, tarama, prediktif değer

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Cervical cancer is the third most common cancer worldwide, with at least 400,000 new cases identified throughout the world each year.[1] Primary strategies to prevent the development of cervical cancer focus on reducing the known risk factors by encouraging a healthy lifestyle, smoking cessation and the adoption of 'safer' sexual behaviours aimed at reducing the risk of human papillomavirus (HPV) infection.[2] However, many countries rely on secondary prevention methods to control incidences of cervical cancer, through

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Yazışma Adresi/*Correspodence:* Dr. Koray ELTER
Kuyubaşı Sok. Fenik Apt. No: 20 / 17 Feneryolu
34724, Kadıköy, İSTANBUL
korayelter@marmara.edu.tr

screening for the detection of abnormal or pre-cancerous cell changes (i.e. any changes which 'may' proceed, be associated with or carry a significant risk of developing cancer).

The Papanicolaou, or Pap smear, screening test is used worldwide, and is primarily aimed at detecting pre-cancerous changes within the cervix before they have an opportunity to progress to invasive carcinoma. Disease progression from dysplasia to invasive cancer is usually slow, therefore providing the opportunity to detect and treat pre-cancerous disease. Pre-cancerous lesions of the cervix are most common in young women, becoming less common with age.[3] The more frequently the target lesion is identified, the more the balance lies with benefit. Since women spend one third of their lives in the postmenopausal period, the issue of cervical screening has great public health importance.

The World Health Organization has calculated the level of protection, which women gain by regular screening, and the number of tests they will need in a lifetime.[4] Annual screening smears provide a 93.5% reduction in the incidence of cervical cancer and will mean a woman has approximately 50 smear tests in her lifetime. Two-, three- and five-yearly smears provide 92.5%, 90.8% and 83.6% reductions in the incidence of cervical cancer; respectively.[4] Even a smear every 10 years has a benefit with a 64.1% reduction in incidence.[4]

Until recently, the main focus of attention has been solely to increase the application of cervical screening. However, in many countries, the issue of informed consent has arisen through the recognition that screening might have associated harms as well as benefits for participants. Individuals may experience such detrimental side effects as anxiety, false alarms, false reassurance, unnecessary colposcopies and biopsies, over-diagnosis, and over-treatment.[5] In particular, important issues for Pap smear screening include the rate of false positives and the possibility that lower grade cervical abnormalities will never progress to invasive cancer. In many cases, the lower grades of cervical dysplasia will spontaneously regress or never develop into cancer.[6] However, those women may suffer adversely through receiving an abnormal smear test result and perhaps undergoing unnecessary treatment.

The effects of estrogen + progestogen therapy (EPT) on cervical smear findings remain unclear.[7,8] Initial studies suggested that short-term estrogen treatment eliminated overestimation in cytologic diagnosis in women with an atrophic cellular pattern.[9] However, recent studies are conflicting. [7,8]

Therefore, in the present retrospective analysis, we aimed to evaluate the positive predictive value of annual cervical smears in postmenopausal women. Our secondary aim was to determine the effect of EPT on Pap smear findings in these women.

Methods

Women, who had spontaneous menopause and who applied to our menopause outpatient clinic between 1995 and 2002 were analyzed in this retrospective analysis. Postmenopausal status was defined as the absence of natural menses for at least one year and a serum FSH level of more than 40 IU/L. Women, who were current-users of EPT on presentation, and those, who had no hormone therapy, were included in the present analysis. EPT regimens were either cyclic or continuous combined type.

At our clinic, women have been followed annually for a routine screening. Cervical smears were obtained at every visit by using the Cervex brush, an effective and economic technique in sampling both endocervical and ectocervical cells.[10] Women, who had up to 4 annual smears (Years 0, 1, 2, and 3) following presentation (Year 0), and whose treatments or the state of no treatment were continued during the follow-up duration, were analyzed in the present study. Smears, which reported atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGCUS), low-grade squamous intraepithelial lesion (LGSIL), or high-grade squamous intraepithelial lesion (HGSIL) were accepted as abnormal. All smears were analyzed in the Department of Pathology in our University. The study was approved by the Institutional Review Board at Marmara University.

Follow-up cares and final diagnosis for all women with abnormal smears were performed in our clinic. Smears were classified as "extra" if they were performed before an annual basis for the follow-up of an abnormal smear. If participants underwent any additional diagnostic tests, such as colposcopy, endocervical curettage, or endometrial biopsy (for the evaluation of AGCUS), results and pathology reports confirming histologic diagnoses were analyzed. Costs for the smear and procedures for the abnormal smears were obtained from the Marmara University Hospital.

Criteria for defining the final status as "Normal" were as follows; (i) The next two smears performed at 4- to 6-month intervals were normal, or (ii) colposcopy performed at any time within the subsequent year was normal. Colposcopy was accepted as normal when biopsy, endocervical curettage, or both were normal, or when no biopsy was performed due to the absence of any abnormal finding.

Incidence rates of cervical smear abnormalities for each year were calculated by dividing the number of women with abnormal smears by the number of women screened. The positive predictive value of each smear abnormality was calculated by dividing the number of women with the final diagnosis of cervical intraepithelial neoplasia (CIN) or worse by the number of women with any cervical abnormality (defined as ASCUS, AGCUS, LGSIL, or HGSIL).

Statistical analysis involved univariate comparisons between consecutive years (Years 0 - 3). Chi-square or Fisher's exact tests were used for categorical variables, where appropriate. ANOVA was used for comparisons between these groups for continuous variables. Since any significantly different variable between groups, except the abnormal smear rate, could be a confounder, the multivariate stepwise logistic regression analysis was performed, if necessary. The main outcome variable was the smear abnormality. Age at menopause, duration of menopause, BMI, nulliparity, multiparity (>4), EPT use and the number of years following presentation (which also indicate the number of normal annual smears following presentation) were included in the multivariate analysis.

Results

3198 postmenopausal women had a smear in their initial visit to our outpatient menopause clinic. Mean (± SD) age and BMI for these women were 51.6 ± 6.3 years and 26.4 ± 3.9 kg/m^2, respectively (Table 1). Mean (± SD) for the years since menopause was 3.9 ± 2.1 years (Table 1). Thirty-seven percent (1184/3198) of these women had two annual smears following their presentation. Nineteen percent and 11% of these 3198 women had three, and four annual smears, respectively. Mean BMI and rate of multiparous (Parity > 4) women decreased by each subsequent year (Ta-

Table 1. Demographic characteristics of the women, and incidences for abnormal smears in each year

	Year 0 (n = 3198)	Year 1 (n = 1184)	Year 2 (n = 593)	Year 3 (n = 336)	P
Age at menopause (years)	47.7±4.7	47.7±4.6	47.7±4.4	48±4.6	NS
Age (years)	51.6±6.3	52.3±5.9	53.0±5.4	54.1±5.2	NA
Years since menopause	3.9±2.1	4.6±1.9	5.4±2.5	6.1±3.3	NA
BMI (kg/m^2)	26.4±3.9	26.0±3.7	25.8±3.6	25.3±3.3	<0.001
Nulliparous women (%)	8.0	8.7	9.1	8.3	NS
Parity >4 (%)	5.7	4.4	3.0	2.1	0.002
EPT use (%)	62.9	77.7	81.5	83.0	<0.001
Abnormal smears (n)	40	11	2	3	NA
Abnormal smears (%)	1.25	0.93	0.34	0.89	NS
ASCUS (n)	36	11	2	2	
AGCUS (n)	2	0	0	0	
LGSIL (n)	2	0	0	1	
HGSIL (n)	0	0	0	0	

NA = Nonapplicable, NS = Not significant

Table 2. Incidences of abnormal smears in EPT users and women without any treatment

	EPT users			Women without any treatment			
	Smears (n)	Abnormal smears (n)	Rate (%)	Smears (n)	Abnormal smears (n)	Rate (%)	P
Year 0	2010	23	1.1	1188	17	1.4	NS
Year 1	920	10	1.1	264	1	0.4	NS
Year 2	483	1	0.2	110	1	0.9	NS
Year 3	279	3	1.1	57	0	0	NS
Total	3692	37	1.0	1619	19	1.2	NS

NS = Not significant

Table 3. Total interventions performed on 56 women for the final diagnosis

Type of intervention	n	Patient (n)	Indication	Cost (Euro*)
Extra smear	80	40	ASCUS	2500
Colposcopy				
+ ECC	6	6	ASCUS	414
+ Cervical biopsy	4	4	LGSIL / ASCUS	276
+ Endometrial biopsy + ECC	2	2	AGCUS	220
Four quadrant cervical biopsy + ECC	4	4	ASCUS	320
Hysterectomy	1	1	CIN 2 + patient approval	1500

ECC = Endocervical curettage
* 1.0 Euro = 1720000 Turkish Liras.

ble 1). The rates of abnormal smear were 1.25%, 0.93%, 0.34% and 0.89% in the 4 annual smears of these women, respectively ($P>0.05$, Table 1). Ninety-one percent (51/56) of the abnormal smears were ASCUS. Two of them were AGCUS, and three were LGSIL.

The rate of EPT users in these 4 consecutive years was 63%, 78%, 82%, and 83%, respectively ($P<0.001$, Table 1). On multivariate analysis, none of the variables were found to be an independent predictor of cytologic abnormality ($P>0.05$).

The rate of abnormal smears was comparable between women, who were on EPT and those, who were not on any treatment ($P>0.05$, Table 2). The rate of abnormal smears was also comparable between consecutive years in both EPT-users and women with no treatment ($P>0.05$, Table 2).

Types and numbers of interventions, which were performed on the 56 women with abnormal smears, are shown in Table 3. Final diagnosis of only one of the abnormal smears was CIN 2 following colposcopic-directed biopsy of the cervix. The result of the abnormal smear for this subject was LGSIL, and was obtained at the initial visit of that woman. After an appropriate discussion of the diagnosis and options for treatment, the woman wanted to have a hysterectomy. Final diagnoses for all other women were normal or nondysplastic. False positive rate and positive predictive value were 98.2% and 1.8%, respectively. Total cost for the smears and interventions for the abnormal smears was 171200 Euro (Conversion factor to Turkish Lira: × 1720000). This amount also corresponds to the cost for the detection of one cervical pre-cancerous or cancerous lesion in postmenopausal women, who were screened annually in the present study.

Discussion

Retrospective analysis of 3198 postmenopausal women, 336 of whom were followed for 4 years annually, revealed that 56 women had a cytological abnormality. The rate of abnormal smears was

1.25% at the initial visit. Rates for the following 3 years were between 0.34 – 0.93%. Of the 56 abnormal smears, all but one, were false positive. Thus, these women were many times more likely to have a false positive smear than a true positive smear.

Screening tests yielding high rates of false positive results is a major concern. Over-diagnosis and over-treatment due to false positive results are strongly associated with patient anxiety, depression and lowered self-esteem as previously reported.[11,12]

It has been previously suggested that there would appear to be little benefit in continuing cervical screening over the age of 50 in adequately screened women.[13,14] The rationale was the rarity of the pre-cancerous cervical lesions in these women. Cruickshank et al. have detected only one case of CIN 3 and one case of invasion among approximately 9000 women with adequate smear histories prior to age 50.[13] Van Wijngaarden et al. have analyzed women diagnosed as having CIN and microinvasive or invasive cancer of the cervix in 1989 and 1990 (798 cases), and observed that CIN has not been seen in women over 50 who had been screened every three years.[14] In that study, microinvasive or invasive cancer of the cervix has been diagnosed in 26 women over the age of 50 and none of these women had participated adequately in the cervical screening programme.[14]

The rate of abnormal smears among postmenopausal women in the HERS and WHI studies were between 1.9 and 8%.[7,8] However, lower rates have also been reported.[15,16] The rate of abnormal smears in the present study seems slightly lower than those in the HERS and WHI studies.[7,8] This may be due to differences between populations. The rate of abnormal smears in the present study seems lower than the 5 - 10% expected rate in the average population.[17]

The results in the present study also revealed that EPT use during postmenopausal period did not interfere with cytological abnormalities or affect the incidence of clinically evident cervical disease. However, in observational studies exogenous estrogen and progestin containing pills were found to be associated with cervical neoplasia.[18,19] This association is supposed to be the result of effects of estrogen and progestins on HPV.[20-22] Postmenopausal hormone therapy, however, does not appear to promote viral replication or related lesions in the lower genital tract.[23-27]

Recently, two prospective studies had conflicting results.[7,8] The cytological results of the HERS study showed that the rate of abnormal smears were comparable between the placebo and EPT groups in both the first and second years (3.4% versus 2.7% in the first year, and 1.7% and 1.0% in the second year for the treatment and placebo groups, respectively).[7] However, 5-year follow-up of women in the WHI study has shown that the EPT group yielded slightly more ASCUS, AGCUS or LGSIL than the placebo group (5.5% versus 7.8%).[8]

False-positive rate and positive predictive value were 98.2% and 1.8%, respectively, in the present study. In the HERS study, the positive predictive value of any smear abnormality was 0% in the first year and 0.9% in the second year.[7] In a retrospective analysis of approximately 78,000 women, 1.4% of those between the ages of 50 - 64 years had an abnormal smear in the first smear and 1.5% in the subsequent smear.[15] Final diagnosis revealed that 0.6% of these women had either a CIN or an invasive disease. This value also corresponds to the positive predictive value. These rates are lower than the incidence of CIN among the general population of women with abnormal cytological diagnosis (15 - 25%).[6]

The rate of EPT users increased by each subsequent year in the present study. Although WHI study was a prospectively randomized study, number of women with multiple Papanicolaou tests was slightly more in the EPT group than the placebo group.[8] The main reason for the increased rate of EPT users among women with annual smears in the present study was the noncompliance of the women without any treatment. On multivariate analysis, it has been shown that this was not a confounding variable that could account for the comparable cytological results between years in the present study.

The rate of multiparous and obese women decreased during follow-up in the present study. Previously, it has been reported that multiparity and

obesity were associated with a decreased rate of compliance.[28] This may be due to the low level of education among the non-compliant women, and health-oriented lifestyle among the compliant women. These variables also were not confounders in the present study.

In the present study, we did not compare annual screening with any alternative screening interval. Therefore, this study is limited to suggest an alternative interval. However, the present data suggest that the positive predictive value is low, and appears to be lower than that in the general population. Less frequent screening in postmenopausal women should be investigated in controlled studies.

In conclusion, the incidence of abnormal smears seems low in postmenopausal women. This is also associated with a low positive predictive value. This value seems lower than those in the general population. This may increase the cost of detecting one pre-cancerous lesion of cervix in these women. In the present study, this cost was 171200 Euro. Annual screening of postmenopausal women may not be cost-effective.

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