



Patients with Epithelial Cell Abnormality in PAP Smears: Correlation of Results with Follow-Up Smears and Cervical Biopsies

PAP Smearde Epitel Hücre Atipisi Saptanan Hastalar: Sonuçların Takip Smear ve Servikal Biyopsi ile Uyumları

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ABSTRACT

Objective: Cervical carcinoma has been included in the preventable diseases category ever since the use of cervical cytology in routine practice. The Pap test is an efficient screening test. We aimed to compare the cervical cytology diagnosis with biopsy and smear follow up results in our institution.

Material and Method: We aimed to compare the diagnosis of cytology material examined in our institution during the 2009-2012 period with their biopsy and smear follow ups. The diagnoses were compared with the follow up smears and/or cervical biopsies.

Results: 13610 Pap tests were examined during September 2009-July 2012. Among these cases, there were 370 atypical squamous cells of undetermined significance (ASCUS), 29 atypical squamous cells-high grade intraepithelial lesions cannot be excluded (ASC-H), 155 low grade squamous intraepithelial lesion (LSIL), 33 high grade squamous intraepithelial lesion (HSIL), and 5 atypical glandular cell (AGC) diagnoses. The ratio of atypical squamous cell (ASCUS and ASC-H) to squamous intraepithelial lesions was 2.12. Squamous intraepithelial lesion was verified in 47 of 91 ASCUS cases. Among patients who had a cervical biopsy, 52 of 64 LSIL cases and all of the 21 HSIL cases had biopsy-proven SIL.

Conclusion: Atypical squamous cell (ASC) is the most common diagnosis in abnormal cervical cytology. As it is indefinite, ASC is used as a quality assurance parameter and the aim is to decrease its use. As the ratio of epithelial cell abnormality is variable in different populations, the ASC/SIL is a more definite variable to be used for quality assurance. The efficiency in clinical use of the cervical cytology screening test is determined by biopsy verification. Our epithelial cell abnormality, ASC/SIL ratio and cytology-histology correlation values were parallel to the literature, proving that the methods are used reliably at our institution.

Key Words: Cervical smear, Cytology, Biopsy, Quality control

ÖZ

Amaç: Servikal sitolojinin rutin pratikte kullanılması ile birlikte serviks karsinomu önenebilir hastalıklar içine girmiştir. Pap smear etkin bir tarama testidir. Bölümümüzde incelenen servikal sitoloji materyallerinin tanıları ile biyopsi ve smear takip sonuçları karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada 2009-2012 yılları arasında bölümümüzde yapılan servikal sitoloji sonuçları gözden geçirilmiştir. Tanılar, kontrol smear tekrarı ve/veya biyopsi sonuçları ile karşılaştırılmıştır.

Bulgular: Bölümümüzde Ekim 2009-Temmuz 2012 tarihleri arasında 13.610 adet Pap smear raporu incelenmiştir. Bu olgular içinde 370 önemi belirlenemeyen atipik skuamöz hücre (ASCUS), 29 yüksek dereceli skuamöz intraepitelyal lezyonun ekarte edilemediği atipik skuamöz hücre (ASC-H), 155 düşük dereceli skuamöz intraepitelyal lezyon (LSIL), 33 yüksek dereceli skuamöz intraepitelyal lezyon (HSIL), 5 atipik glandüler hücre (AGH) saptanmıştır. Atipik skuamöz hücrenin (ASCUS ve ASC-H tanılarının toplamı) skuamöz intraepitelyal lezyona oranı (ASC/SIL) 2,12' dir. Biyopsi yapılan 91 adet ASCUS olgusunun 47'sinde SIL saptanmıştır. Biyopsi yapılan 64 adet olgusunun 52'sinde LSIL; 21 adet olgusunun tamamında HSIL tanısı doğrulanmıştır.

Sonuç: Atipik skuamöz hücre (ASH) anormal servikal sitolojideki en sık tanıdır. Belirsizlik ifade ettiği için fazla kullanımı önlenmeye çalışılmaktadır ve kalite kontrolünde kullanılmaktadır. Farklı toplumlarda, Epitel Hücre Anomalisi (EHA) oranı değişken olabildiği için, ASH/SIL oranı kalite yönetimi açısından daha net bir veri olarak değerlendirilmektedir. Bir tarama testi olan servikal sitolojinin klinik uygulamalarda güvenilir şekilde kullanımı ise biyopsi doğrulaması ile mümkündür. Serimizde EHA yüzdesi, ASC/SIL oranı ve smear ile biyopsi arasındaki uyum sonuçları literatür ilgilerine paralel olup, merkezimizde güvenilir bir yöntem olarak kullanılmaktadır.

Anahtar Sözcükler: Servikal yaymalar, Sitoloji, Biyopsi, Kalite kontrolü

INTRODUCTION

Cervical cytology has played a major role in reducing deaths due to cervical cancer in countries where screening programs have been used properly from the beginning. However, cervical cancer is still a major cause of death in countries where there are no regular screening programs. The incidence of cervical cancer is 6.6/100.000 in the United States and an estimated 12,200 new cases and 4,210 deaths due to the disorder are reported annually (1). It takes 8th place among women's cancers and the incidence is 4.2/100.000 in Turkey according to Globocan 2008 (2). There were 1,443 women diagnosed with cervical cancer and 556 women died of cervical cancer in Turkey in 2008. The five-year prevalence was 3998.

Although cervical cytology screening is the most effective method for preventing cervical carcinoma, it is not a diagnostic test (3). The specificity is reported to vary between 14 and 97%, with a mean value of 69%, and the sensitivity between 11 and 99% with a mean value of 58% (3-5). The compliance of cytological diagnosis with histology is an important method of quality control for pathology laboratories (4-7). The ratio of the atypical squamous cells (ASC), which is expressed as the total of ASCUS (Atypical Squamous Cells of Undetermined Significance) and ASC-H (Atypical Squamous Cells – cannot exclude HSIL) diagnoses to the squamous intraepithelial lesion (SIL) diagnosis is an important, easily calculated quality control data for pathology laboratories (4,8,9). The recommended ASC/SIL ratio is 2 to 3 in various articles (8,10,11), and between 0.87 and 4.49 in others (10-12). Ratios reported from Turkey vary between 3.28 and 12.6 in single-center studies (7,13-19). This ratio has been reported as 2.83 in a multi-center study of the Turkish Cervical Cancer and Cervical Cytology Research Group (20) reflecting most of Turkey.

Compliance with cervical cytology and biopsy diagnoses is an important finding showing the efficiency of the screening test, and can also be used as a measure of the performance of the pathology laboratory. While SIL was determined on biopsy in 90.8% of the patients with a positive cervical cytology result, the biopsy was found to be normal in 62.8% of the cases where no epithelial cell abnormality (ECA) was seen on cytology (21). The false positivity rate was 3.5%, and the false negativity rate 5.3% in the study of Mete et al. (4). The compliance of cervical cytology with biopsy increases in direct proportion with the increase of degree of atypia on cytology. While up to 100% compliance is reported for HSIL, this compliance rate decreases to 54% for ASCUS and to 20% for AGC (4,7,14,15,17,22).

MATERIAL and METHOD

Cervical cytology materials obtained from the patients that presented to the Gynecology and Obstetrics outpatient department between October 2009 and July 2012 for screening or any complaint and had been examined in our department and found to have ECA were included in our study. The follow-up of these patients was investigated. No cytotechnician works in our department so cervical smears are examined by specialist pathologists. Pathology reports were prepared according to the Bethesda 2001 criteria. The first abnormal smear, cervical biopsy and follow up smear results of the patients were compared. The results of the abnormal smears were examined from the documents, and the follow-up cervical smear or colposcopy cervical biopsy findings were obtained.

Numbers, percentages and means together with minimum and maximum values were used as descriptive statistics as well as sensitivity, specificity and positive predictive values.

RESULTS

The total number of smears in our department was 13,610 between the dates specified and made up 37% of the total number of material (36,626). The number of cases reported as ECA was 470 in cases where cervical cytological examination had been performed. However, there was more than one cervical smear diagnosed with ECA for the same patient due to smear repetition, so the number of reports diagnosed with ECA was 594. The ECA ratio was calculated as 4.3%. The mean age of the patients diagnosed with ECA was 32.9 with a range of 18 to 66 years.

The total number of reported ASCUS, ASC-H, and AGC diagnoses was 370, 29, and 5 respectively with 155 LSIL and 33 HSIL cases. The ASC/SIL ratio was 2.12. Biopsy was performed on 201 patients with colposcopy during the follow-up and conization was performed according to the biopsy results in 58 patients and directly in 8 patients without biopsy.

A total of 154 patients reported as ASCUS as a result of the Pap smear had no follow-up information. The result was reported as 'negative for ECA' in 44 and ECA in 12 (9 ASCUS, 2 LSIL, 1 HSIL) of the 56 patients who had a follow-up smear. Biopsy was performed in 91 ASCUS cases with SIL (37 LSIL, 10 HSIL) verified in 47 and SIL not found in the biopsy material in 44 patients. Follow-up biopsy was performed in 22 patients reported as ASC-H. The results were 1 LSIL and 12 HSIL cases with no SIL finding in the biopsy material in 9. Biopsy was performed in 3 of the 5 cases diagnosed with AGC and no ECA was found. The

results of the biopsy in 64 patients whose smear diagnosis had been LSIL were known and SIL (40 LSIL, 12 HSIL) was verified in 52 (81.3%). The SIL verification rate by biopsy in patients diagnosed with HSIL was 100% (1 LSIL, 20 HSIL) (Table I,II).

Cervical cytology materials of 21 patients with ECA or SIL on biopsy had been previously examined at our department and reported as ECA negative.

Our study data are presented in Table III; although the selectivity could not be calculated as patients with a negative smear and negative biopsy were not included in our study, the sensitivity was found to be 86.4%.

DISCUSSION

Cervical cytology is currently the most effective cancer screening system. Objective data are required in order to detect the efficiency of this screening test that is widely used. Various data such as the ASC ratio, abnormal smear ratio, and ASC/SIL ratio can be used for quality control in gynecological cytology. When the ECA rate that is the total of ASCUS, ASC-H, LSIL, HSIL, AGC, and carcinoma diagnoses was evaluated, it varied between 1.5 and 7.3% in countries with high-income (9,23,24). reported rates from Turkey ranged from 1.2 to 12.6% (7, 13-19) and was 1.8% in the study reflecting most of Turkey (20). The ECA rate of 4.3% in our study is above the mean value for Turkey. This difference was considered to be related to the patient population because our patient group consisted mostly of

Table I: The cytology and histology diagnoses of the patients who underwent biopsy

Pap smear	Histology diagnosis					Total
	PPV	SIL (-)	LSIL	HSIL	Carcinoma	
ASCUS	51.6	44	37	10	-	91
ASC-H	59	9	1	12	-	22
AGH	0	3	-	-	-	3
LSIL	81.3	12	40	12	-	64
HSIL	100	-	1	20	-	21
Total		68	79	54	-	201

PPV: Positive predictive value, SIL: Squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells-HSIL cannot be excluded

Table II: The results of patients who had follow-up smears

First smear diagnosis	Follow up smear results							Total
	Without follow up	ECA -	ASCUS	ASC-H	AGC	LSIL	HSIL	
ASCUS	154	44	9	-	-	2	1	210
ASC-H	3	-	-	1	-	-	-	4
AGC	2	-	-	-	-	-	-	2
LSIL	31	8	3	-	-	8	-	50
HSIL	3	-	-	-	-	-	-	3
Total	193	52	12	1	-	10	1	269

ECA: Epithelial cell abnormality, ASCUS: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells, HSIL cannot be ruled out AGC: Atypical glandular cell, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion.

Table III: Table of histology-cytology compliance in our department

Cytology Diagnosis		Histology Diagnosis	
		Positive	Negative
Cytology Diagnosis	Positive	133	68
	Negative	21

high-risk patients from the upper-middle socio-economic group. It is therefore similar to the data of countries with high income.

The ASC/SIL ratio is reported to be less variable when compared to the other parameters and creates mathematical data recommended for use for quality control (8, 10,12). This ratio is reported as 1.73 - 2.05 for cytopathologists and 0.87- 4.5 for cytotechnicians in the literature (10-12). An ASC/SIL ratio under 2-3 is recommended in various articles (8,10,11). Although quality control studies in Turkey are

limited, the ASC/SIL ratio in hospital-based studies varies between 2.25 and 12.6 (7, 13-19). When we exclude the figure of 12.6 found in the Coşkun et al study (18) where the results of screening performed in Kahramanmaraş were evaluated, the highest rate reported from Turkey is 5.3 (17). This value was 2.83 in a multi-center study of the Turkish Cervical Cancer and Cervical Cytology Research Group (20) which reflects most of Turkey. The ASC/SIL ratio was 2.12 in our study. It is reported that the ASC/SIL ratio may be lower in high-risk populations and higher in low-risk

Table IV: The results of cytology-histology compliance studies from Turkey

Histology Diagnosis						
PAP	STUDY	SIL (-)	LSIL	HSIL	CA	PPV
ASCUS	Kır 2003	10	3	6	3	54.5
	Mete 2007	5	9	9		78.3
	Keskin 2011	80	15	5		20
	Abalı 2011	179	68	9	-	30
	Boztosun 2012	25	5	3	2	28.5
	Current Study	44	37	10	-	51.6
ASC-H	Kaygusuz 2010	2	4	6		83.3
	Keskin 2011	3	3			50
	Abalı 2011	12	3	6	-	42
	Boztosun 2012	7	4	1	1	46.1
	Current Study	9	1	12	-	59
AGH	Kır 2003	1	-	-	1	50
	Keskin 2011	17	1		1	10.5
	Boztosun 2012	4	-	-	1	20
	Current Study	3	-	-	-	0
LSIL	Kır 2003	4	4	1	-	55.5
	Mete 2007	3	34	-	-	91.9
	Kaygusuz 2010	6	14	8	2	80
	Keskin 2011	30	12	6		37.5
	Abalı 2011	16	12	3		48
	Boztosun 2012	7	3	2		46.1
	Current Study	12	40	12	-	81.3
HSIL	Kır 2003	-	-	6	2	100
	Mete 2007	1	-	46		97.8
	Kaygusuz 2010	6	2	8	7	73.9
	Keskin 2011	2		6		75
	Abalı 2011	6	2	3	10	87
	Boztosun 2012	1	-	2	-	85.7
	Current Study	-	1	20	-	100
CA	Kır 2003	-	-	-	3	100
	Abalı 2011	-	-	-	18	100
	Boztosun 2012	-	-		6	100

SIL: Squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, CA: Carcinoma, ASCUS: Atypical squamous cells with undetermined significance, ASC-H: Atypical squamous cells where HSIL cannot be ruled out AGH: Atypical glandular cell, PPV: Positive predictive value.

populations (9). Our ratio complies with results from other countries and the suggested quality standards of the Turkish Cervical Cancer and Cervical Cytology Research Group. Our low rate when compared with other values reported from Turkey can be explained with our patient population consisting of high-risk patients.

One of the best parameters that can be used to measure the adequacy of cervical cytology as a screening test is ECA confirmed by cervical biopsy. The selectivity and sensitivity rates of cervical cytology are reported to be highly variable (5,23,24). The specificity ranging from 14 to 97% with a mean value of 69% and a sensitivity ranging from 11 to 99% with a mean value of 58% are reported in the literature (3-5,24). Although the selectivity could not be determined in our study, the sensitivity of 86.4% is in line with the literature data.

Studies from Turkey comparing cervical smear results with biopsy results are summarized in Table IV. The ECA rate histologically confirmed on smears diagnosed with ASCUS (positive predictive value, PPV) ranges between 20 and 78.3% in various studies (4,7,14,15,17,26). Similarly, it ranges between 42 and 83.3% for ASC-H (7,14,15,22), 10.5 and 50% for AGC (15,17,22) 48 and 91.9% for LSIL (4,7,14,15,22,26) and 75 and 100% for HSIL (4,7,14,15,17,22,26) cases and it is reported to be 100% in smears with a diagnosis of carcinoma (14,15,17). When the smear and biopsy results were compared in our study, the PPV was 51.6% for ASCUS, and 59%, 81.3%, and 100% respectively for ASC-H, LSIL and HSIL, consistent with the current literature. These rates increase from 51.6% for ASCUS up to 100% for HSIL and increase in direct proportion to the degree of atypia observed in the smear. There was no patient reported as carcinoma as a result of cervical cytology in the present study. Biopsy was performed on 3 patients with a diagnosis of AGC and no dysplasia was found in any of them. An AGC diagnosis in the smear is reported to be the diagnosis with the lowest rate of verification with biopsy (15,17,22). The lowest positive predictive value was found for the diagnosis of AGC in our study as well.

In conclusion, the ASC/SIL ratio remains important in terms of quality control. The cervical cytology results assessed by specialist doctors in our department were found to be reliable as the cervical smear diagnoses were verified with the cervical biopsy findings at a high rate. Planning new studies which will reflect Turkey in general is important in terms of quality control across the country. Similarly, because the comprehensive studies that also include HPV typing should be planned for the whole country to obtain country-specific data.

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