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Evaluation of colposcopy results for patients who are HPV DNA positive in KETEM

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ABSTRACT

We evaluated colposcopy and postoperative biopsy results in cases referred to our oncology center from the Cancer Early Diagnosis and Treatment Center (KETEM) due to Human Papilloma Virus (HPV) positivity and/or cervical premalignant lesion (CPL). A total of 1230 female patients who were admitted to Oncology outpatient clinic between January 2016 and December 2017 with positive HPV DNA screening tests from KETEM regardless of whether they had cervical premalignant lesion or not as a result of Papanicolaou smear (PAP smear) were included in the study. Colposcopy was performed in all cases and cervical biopsy was performed in patients who had suspicious lesions. No significant relationship was found between smoking status, educational status and financial status and HPV DNA screening test results ($p = 0.123$, $p = 0.201$, $p = 0.244$, respectively). The sensitivity of colposcopy to detect cervical premalignant lesions was 99.2% and positive predictive value (PPD) was 74.1%. In determining the cervical premalignant lesions, the sensitivity of smear was 41.3% and its specificity was 66.5%, PPV (positive predictive value) was 78.1% and NPV (negative predictive value) was 28.2%. In our study, the sensitivity of the HPV test to determine cervical premalignant lesions was 93.1%, PPV was 74%, specificity 86% and NPV was 30%. The accuracy of HPV types in determining CPLs was found to be (530 + 17)/776=71.4%. Positivity on the HPV DNA screening test is the leading risk factor for cervical cancer development. As a result, the first step in family medicine and KETEM activities is to reduce the frequency of these cancers and the complications related to the disease by increasing information and screening examination applications.

1. Introduction

Cervical cancer is the seventh among all cancers in the world, the second most common in cancer among women and third in cancer-induced deaths. According to research by Global Cancer Statistics 2012 published in 2015, 527,600 new cases of cervical cancer and 265,700 deaths were observed around the worldwide (Torre et al., 2015). Infections with oncogenic HPV types are thought to be involved in the etiopathogenesis of almost all cervical cancers and precancerous lesions, and HPV types 16 and 18 may be responsible for approximately 70% of all cervical cancers (Horry et

al., 2008). In addition, low education level, advanced age, obesity, active or passive smoking, early sexual intercourse, multiple sexual partners, multiparity, low socioeconomic status, and herpes simplex type 2 infection increase the frequency of cervical cancer (Munoz et al., 2002; Milutin et al., 2008).

Since the cervix is an easily accessible organ, early diagnosis and prognosis for cancers of this organ can be made with Pap smears. The Pap smear test was reported to reduce the incidence of cervical cancer by 79% and mortality by 70% since 1950. Especially in countries with organized screening programs, 60-70% decrease in the frequency and mortality of cervical cancer is reported (Türkiye Kanser İstatikleri, 2015). It can be used in screening of cervical cytology screening methods both in liquid based and conventional methods. In the past, colposcopy was mainly used to exclude asymptomatic early invasive cervical cancer, but is now used to diagnose preinvasive cervical disease (Cervical Cytology Screening, 2009). As a result, cytological, colposcopic and histological data are examined together to determine the right approach for the patient (Frank, 2008). Cytology and colposcopy do not compete with each other; on the contrary, they are complementary methods. Through colposcopy and subsequent biopsy, unnecessary conization and invasive surgical procedures have decreased. On the other hand, it is a personal procedure, highly dependent on the observer's assessment. Nowadays, because of the low sensitivity of cervical cytology, the approach in detecting the presence and type of HPV infection with cytology has come to the agenda. Today, it is emphasized that HPV should definitely exist for cervical cancer development and other risk factors increase the rate of virus exposure or viral persistence so it is important because it accelerates the carcinogenic process (Eroğlu et al., 2011). HPV is considered to be the etiologic agent in many cancers, especially anogenital and head and neck cancers. Nowadays, more than one HPV type has been detected and approximately 40 of them infect the anogenital area. Of these, 15 types (6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are in the oncogenic high-risk group, 3 types (26, 53, 66) are in the low risk group, and 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89) are in the low risk group (Horry et al., 2008).

In the family medicine discipline, preventive medicine has an important place in addition to therapeutic health services. In terms of preventive medicine, cervical cancer screening methods are one of the few screening methods that reduce the incidence and mortality of invasive cancer and have proven effective in this respect. In order to identify women at risk, regular screening should be done between the ages of 30-65 at recommended intervals. The national standards for screening cervical cancer were determined by the Department of Cancer Control Center in the Ministry of Health and are implemented in Cancer Early Diagnosis and Treatment Centers (KETEM). Because of the high incidence of HPV DNA in all cervical cancers and precancerous lesions, detection of HPV DNA in addition to cervical smear screening programs for preinvasive lesions and HPV DNA typing are important (Munoz et al., 2002). The community-level cervical cancer screening program in Turkey (Pap smear and HPV DNA) began in 2014. In our study, we aimed to evaluate HPV DNA positive patients referred to our oncology center by family medicine and KETEM.

2. Material and method

In this study, we evaluated the colposcopic diagnosis and colposcopic biopsy results of 1230 cases who applied to the Oncology Outpatient Clinic of Tepecik Training and Research Hospital between January 2016 and December 2017 who were diagnosed with oncogenic HPV positive and/or had Pap smear results in KETEM and whose results were found to be pathological (ASCUS, ASC-H, LSIL, HSIL and AGC). The Local Ethics Committee approved the study. The universal principles of the Helsinki Declaration were implemented. Age, socioeconomic status, learning status, and smoking habits of the cases were recorded. Epidemiological data, cervical smear and HPV samples were taken and colposcopic examination and biopsies were performed in our oncology center. Epidemiological data, cervical smear and HPV samples were taken and colposcopic examination and biopsies were performed in our oncology center. In the etiopathogenesis of cervical cancer, HPV types 16, 18, 31, 33, 45, 51, 58, 59, and 68 are considered to be high risk, 53 and 66 are possibly high risk and 6, 11, 40, 54 and 70 are considered low risk (Milutin et al., 2008). The cases were divided into two groups as high and low risk groups. Those who were pregnant, had conization and hysterectomy operation, who had vaginal bleeding, bad obstetric history and suspected medical conditions were not included in the study. None of the patients had HPV vaccination.

All patients had colposcopic observations. None of the patients had HPV vaccination. All patients underwent colposcopic observations. Biopsy was performed for the patients whose colposcopic observation was evaluated to be problematic. Colposcopic examinations were performed with colloquial colposcopy device (colposcope 1D-21100, Leisegang GmbH, 2014-03, Germany) capable of 4.5 to 30 magnification with a green filter. The cervix was first screened at small magnification after washing with saline, and the green filter and vascularization pathologies were investigated. Then 3% acetic acid was applied and left for at least 60 seconds and then the cervix was re-scanned in small

and large magnifications. Lugol solution was applied afterwards to the location of the acetowhite areas and vascular pathologies were determined. After staining the cervix with Lugol solution, iodine-free areas were determined.

After staining the cervix with Lugol solution, iodine-free areas were determined. Acetowhite, mosaic, punctation, leukoplakia, and atypical veins were observed and biopsy was performed with cervical biopsy forceps. Patients with pathological colposcopic findings were treated at our center for treatment or advanced treatment procedures. The materials were sent to the pathology laboratory in formaldehyde. Cervical biopsy specimens were evaluated in the Pathology Unit.

Statistical method

Statistical analyses were performed using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) and R (Version 3.5.0) packages. Descriptive statistics are presented as mean ± standard deviation and median (min-max) for continuous variables and as number and percentage for categorical data.

The statistical distribution of the data was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Homogeneity of variances was evaluated by the Levene test. According to HPV groups, non-parametric Kruskal Wallis test was used to compare the age of the patients. After Kruskal-Wallis test, post-hoc two-way comparison test was used in order to determine which groups caused the difference. Correlations between categorical variables and ratio comparisons were performed with Chi-square test or Fisher exact test. The correlation between smear 1 and smear 2 results was evaluated by McNemar Bowker test. Sensitivity, selectivity, positive predictive value, and negative predictive values were calculated for the evaluation of diagnosis according to the results of HPV DNA, pap smear and colposcopy biopsy. Statistical significance was accepted as $p < 0.05$.

3. Results

A total of 1230 patients with mean age of 43.12 ± 8.80 years for patients referred to our research center, were examined. The youngest patient was 20 years, while the oldest patient was 66 years old. HPV DNA test groups were significantly different in terms of age ($p = 0.004$). According to the post-hoc pairs comparison test results, there was no significant difference between patients in the low-middle and medium-high HPV DNA test groups (respectively, $p = 1.000$, $p = 0.557$). The age of the patients in the low and high HPV DNA test groups was significantly different ($p = 0.005$). The age group with high-risk HPV DNA test had lower median age (Fig.1). Age comparisons with HPV DNA test groups are given in Table 1. Of the cases, 435 (35.4%) had no education other than primary school, 690 (56.1%) were secondary school/high school graduates and 105 (8.5%) were university graduates. Only 129 (10.5%) of the cases had good socioeconomic status. In terms of smoking, 154 (12.5) of the patients smoked. No significant relationship was found between smoking status, educational status and financial status and HPV DNA screening test results ($p = 0.123$, $p = 0.201$, $p = 0.244$, respectively) (Table 2). The most common HPV types were HPV 16 in 546 (44.4%), and HPV 18 in 160 (13%). The frequency distribution of other HPV types in the low, middle and high-risk groups is shown in detail in the table. According to HPV types, the rate of those with high risk for cervical cancer was 86.7% (n = 1066), while 57 had moderate risk were (4.6%) and 8.7% had low risk (n = 107) (Table 3). As a result of the colposcopy procedure applied to patients included in the study, colposcopy of 464 patients (37%) was normal and colposcopy of 766 (63%) was evaluated as problematic. Of the 1230 patients, 766 patients underwent biopsy. The sensitivity of colposcopy in determining CPL was 99.2% and positive predictive value (PPV) was 74.1%. Considering colposcopy as a screening tool, the sensitivity for CPL was found to be high (99.2%), and unhealthy cervix (high/low grade lesion) was 99.2% sensitive to differentiation from healthy cervix (Table 4). In the cervical smear evaluation of 766 cervical biopsies; ASCUS was detected in 124 (16.2%), LSIL in 93 (12.1%), HSIL in 47 (6.1%), ASC-H in 26 (3.4%), and AGC in 11 (1.4%). When smear results were separated as normal and pathological, 301 cases were evaluated as pathological based on cervical biopsy results. According to Table 5, the sensitivity of pap smear for CPL was 41.3% and specificity was 66.5%, positive predictive value (PPV) was 78.1% and negative predictive value (NPV) was 28.2% (Table 5). Results of colposcopic biopsy revealed a total of 766 patients with HPV results, with 39 patients having low-risk HPV and 530 patients with moderate and high-risk HPV. In our study, the sensitivity of the HPV test for CPL determination was 93.1%, specificity 86%, PPV 74% and NPV 30%. The accuracy of HPV types in determining the cervical cell was found to be (530 + 17) /766=71.4% (Table 6).

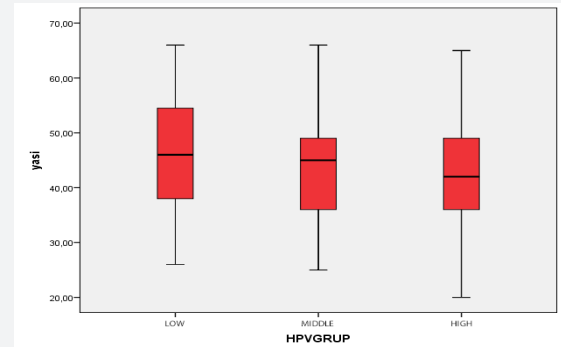

Fig. 1. Boxplot of the distribution of HPV levels according to the age of patients.

Table 1. Age comparisons according to HPV groups.

HPV Group	N	Mean ± SD	Median (min-max)	*p*	*p* value
Minimum (1)	107	45.77 ± 9.47	46 (26-66)		1-2: 1.000*
Average (2)	57	44.51 ± 9.59	45 (25-66)	**0.004***	**1-3: 0.005***
Maximum (3)	1066	42.78 ± 8.64	42 (20-65)		2-3: 0.557

* Kruskal Wallis test statistically significant (p<0.05)

Table 2. Demographic data and evaluation of HPV type.

			HPV			Total	p value
			Minimum	Average	Maximum		
School	**Primary school**	n	44	20	371	435	0.201
		%	10.1	4.6	85.3	100.0	
	Secondary school	n	56	36	598	690	
		%	8.1	5.2	86.7	100.0	
	University	n	7	1	97	105	
		%	6.7	1.0	92.4	100.0	
Wage	**Minimum Wage**	n	69	33	631	733	0.244
		%	9.4	4.5	86.1	100.0	
	Double Minimum Wage	n	28	22	318	368	
		%	7.6	6.0	86.4	100.0	
	Triple Minimum Wage	n	10	2	117	129	
		%	7.8	1.6	90.7	100.0	
Smoking habit	**Smoking**	n	7	6	141	154	0.123
		%	4.5	3.9	91.6	100.0	
	Non-smoking	n	100	51	925	1076	
		%	9.3	4.7	86.0	100.0	
Total		n	107	57	1066	1230	
		%	8.7	4.6	86.7	100.0	

* Chi-square test

Table 3. Distribution of HPV types.

HPV type	Frequency	Percent
16	546	44.4
18	160	13.0
31	28	2.3
33	15	1.2
35	31	2.5
36	1	0.1
38	1	0.1
39	36	2.9
41	3	0.2
42	14	1.1
43	1	0.1
45	12	1.0
46	5	0.4
49	6	0.5
51	61	5.0
52	37	3.0
53	24	2.0
54	13	1.1
55	6	0.5
56	49	4.0
58	39	3.2
59	33	2.7
60	1	0.1
61	16	1.3
62	7	0.6
66	33	2.7
68	18	1.5
69	4	0.3
70	17	1.4
76	1	0.1
81	8	0.7
82	2	0.2
84	2	0.2
Total	**1230**	**100**
Minimum	107	8.7
Average	57	4.6
Maximum	1066	86.7
Total	**1230**	**100**

Table 4. Evaluation of colposcopy.

			Biopsy		Total
			Normal	Pathologic	
Colposcopy	Normal results	n	0	4	4
	Problematic	n	197	565	762
Total		n	197	569	766

Sensitivity	0.992 (0.981-0.998)
Specificity	-
PPV	0.741 (0.709-0.772)
NPV	-

Table 5. Evaluation of smear.

Valid	**Normal Results**	507	66,8
	ascus	124	16,2
	lsıl	93	12,1
	asc-h	26	3,4
	hsıl	47	6,1
	agc	11	1,4
	Total	766	100,0

Comparison of smear and biopsy:

			Biopsy		Total
			Normal	Pathological	
smear1	Normal	Count	131	334	465
	Pathological	Count	66	235	301
Total		Count	197	569	766

Sensitivity	0.413 (0.372-0.455)
Specificity	0.665 (0.594-0.730)
PPV	0.781 (0.729-0.825)
NPV	0.282 (0.242-0.325)

Table 6. Comparison of HPV biopsy.

			Biopsy		Total
			Normal	Pathological	
HPV	Normal	n	17	39	56
	Pathological	n	180	530	710
Total		n	197	569	766

Sensitivity	0.931 (0.907-0.950)
Specificity	0.086 (0.053-0.137)
PPV	0.746 (0.712-0.778)
NPV	0.304 (0.192-0.443)

4. Discussion

KETEM employees and family medicine centers are the most common ways to be correctly informed about the importance of positive cervical smear by pap Smear test screening in our country. In this way, more effective results are obtained for cancer prevention, early diagnosis and treatment methods. In addition, the provision of Pap Smear and oncogenic HPV DNA typing by the state and targeting this service to reach the whole community will positively affect service delivery and healthy community development. For this purpose, our primary aim should be to ensure that all women are properly informed about cervical cancer and pap smear screening at KETEM and family medicine centers. In recent years, many studies have been completed in Turkey and around the world to evaluate the information including cervical cancer risk factors, clinical findings, early diagnosis and prevention methods of cervical cancer, and to increase awareness. In many studies on this subject, it is known that health practitioners working in KETEM and family medicine centers are well aware of their knowledge about the subject and they are sensitive to the patients who apply for these or other reasons (Dönmez, 2007; Can et al., 2010). As seen in many studies, the application of pap smear screening tests in our country and developing countries, unlike developed countries, was found to be extremely inadequate. Paradoxically, in our country, sociocultural level and level of knowledge about cervical cancer was found to be much lower than expected. This may be due to monogamy, ignorance, value judgments and avoidance of examination (Dönmez, 2007; Can et al., 2010).

HPV infection is the most common infectious disease among sexually transmitted infections. HPV has more than forty types which lead to genital tract infections. Approximately 90% of these infections are asymptomatic and spontaneously regress within two years. However, recurrent infections due to some HPV types can lead to cervical cancer and genital warts. HPV types 16 and 18 are associated with approximately 70% of cervical cancers worldwide; HPV types 6, 11, 16, 18 are related to 90% of cases of genital warts (Milutin et al., 2008). Studies conducted in Turkey show that the prevalence of HPV infection in women ranges from 2% to 20% (Akhan, 2007). In addition, the most common type, with or without cytological abnormalities, is HPV type 16. Cervical cancer is the tenth most common cancer among women in our country (T. C. Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı, 2015). There are about 2000 new cases of cervical cancer in our country every year. Although the prevalence of HPV infection and cervical cancer is considered to be lower in Turkey than in the world, some studies have found that the prevalence of HPV infection in women has similar to rates to the rest of the world (Akhan, 2007). This shows us that cervical cancer is going to become one of the prominent cancers in addition to others. Vaccination is the most effective method of preventing HPV infection and related diseases. This suggests that it is not enough to increase the family physician's knowledge or increase vaccination rates in order to achieve a certain level of cervical cancer prevention. It also points out the need to focus on other methods.

High rates of HPV DNA are found in cervical cancer patients. Especially HPV 16 and 18 positivity were higher than 70%. Of women, 50-80% experience HPV infection at least once in their lifetime; 50% of these are oncogenic HPV types (Munoz et al., 2003). Many HPV infections are eliminated by the immune system with 70% in 1 year and 90% in 2 years. Especially if the infection caused by high-risk HPV types (types 16 and 18) does not improve, it takes 15-20 years to develop cervical cancer. Therefore, in order to determine people at risk and to perform the appropriate clinical follow-up, cervical smear is widely used, in addition to the detection and typing of HPV infection (Munoz et al., 2003). For this purpose, various methods were developed for the identification and types of HPV infection.

The most well-known HPV types associated with cervical cancer and cancer precursor lesions are HPV 16 and 18, and less frequently HPV 31, 33, 45, 52, 58, and 59. Interregional changes are observed in the frequency of types other than the most common HPV 16 and 18 in the world (Dönmez, 2007). In our study, when HPV 16 and 18 were combined together, those infected with these viruses accounted for 57% of our study patients. In our country, there are few studies which include both cytological abnormality and frequency of HPV infection. We planned our work in this direction to emphasize the importance of other HPV types. In our study, the relationship between age, smoking, economic status and HPV was evaluated. There was a significant relationship between age and HPV oncogenic high type, but no relationship was found with the other factors. There was no statistically significant relationship between HPV DNA positivity and age in the study by Özçelik et al. (2003). In our study, the risk factors for cervical cancer were consistent with most studies in the literature. A statistically significant relationship was found between age and HPV infection.

In a study of 53 patients presenting with the complaint of genital discharge and having cervical erosion by Aktepe et al. (2007), HPV positivity was reported in 1 (1.8%) case who had cytologically detected HSIL in cervical smear. In the study by Ergünay et al. (2007), HPV positivity was found in 80% of cases with pathologic cervical smear and HPV 16 in 50% of HPV types, HPV 18 in 10.7%, and HPV 53 in 7.1%. In the study by Sapmaz et al. (2003), HPV positivity was 38% (33% HPV 16 and 5% HPV 18) in cervical intraepithelial neoplasia (CIN) and 7.5% in the control group (5% HPV 16 and 2.5% HPV 18) respectively. In our study, the prevalence of high oncogenic HPV was 86.7% (Table 3). The reason for this may be the fact that it is a tertiary care center in the region and the oncology clinic is offered as a separate

service from other branches. In our study, the prevalence of high oncogenic HPV was 86.7% (Table 3). Another reason for the high oncogenic risk HPV positivity may be the fact that the study was performed in cases with risk for cervical cancer and HPV. The most common types of HPV infections were 44.4% HPV 16 and 13% HPV 18, then HPV 31, 33.35, 39, 45, 51, 52, 56, 58, 59, 68, and 82 (Table 3). In our study, in addition to the most common HPV types, other high-risk types of HPV are different from other studies. Since other rare HPV types may cause cervical cancer, these patients should also be referred to a gynecological oncology center without delay and should be directed to biopsy if necessary.

The slow natural course of cervical cancer reveals the importance of screening programs for the early recognition of dysplastic lesions and prevention of progression to invasive cancer. Many clinicians support the combination of cytology and colposcopy in primary screening, hoping to reduce false negative results. Colposcopy is an easily applicable method that requires education and determines cancer lesions (Kyrgiou et al., 2006). In our study, colposcopy was used as a secondary screening tool to confirm the cases diagnosed as pathological on pap smear. In a meta-analysis, the sensitivity was found to be between 87-99% (Mitchell et al., 1998). Similar sensitivities were reported in many other studies. On the other hand, as a colposcopy screening tool, high sensitivity and negative predictive value were calculated as 74% and 99%, respectively. In a recent study of 1850 patients, the sensitivity of colposcopy as diagnostic procedure was 52-98% and specificity was 45-87%. The effect of the number of colposcopic biopsies on the biopsy sensitivity was first examined by Gage and was 68.3% when one biopsy was performed, 81.8% when two biopsies were performed, and 83.3% when three biopsies were performed. In the study performed by Pretorius, the sensitivity was found to be 52.6% for 0-2 biopsy and 85.2% for 3 to 4 biopsies (Pretorius et al., 2006). A large number of biopsies from different quadrants (3 or 4) are associated with high sensitivity. In our study, sensitivity of the study group to high HPV type cases may be high (Table 4) due the fact that biopsy was obtained from at least four quadrants, and the study group contained more high-risk HPV type.

In 301 cases with cytological abnormalities in cervical smear samples, HPV positivity was found to be 37.46%. Although the rates were different in our study, the most common types were HPV 16 and 18 in accordance with other studies in our country. The difference in both HPV positivity and type distribution in studies can be attributed to the sample population, age, examination area, application complaint, and presence of non-homogeneous cases such as presence of risk factors for cervical cancer and different techniques used. The cervical cytological abnormality rate was found to be 1.2% in a cervical vaginal cytology study performed by Ergeneli et al. (2001). In a study of 4122 cases by Bozkurt et al. (2007), cervical cytologic abnormality rate was found to be 4.3%. In a study which evaluated 6706 cervico-vaginal smears by Özdamar et al. (2006) cytological abnormality rate was evaluated as 1.5%. In our study, 33.2% of the epithelial cell abnormalities in cervical smear may be due to the fact that the sampled group consists of few and risky cases (Table 5). According to Wright et al., high-risk HPV DNA positivity is 74-88% for ASC-H and 76.6% for LSIL. High HPV (+) in ASC-H, HSIL, and LSIL lesions decreases the diagnostic value of HPV test in these cytological results. Colposcopy should be the first attempt at diagnosis for these lesions (Thomas et al., 2007). In our study, 124 ASCUS and 93 LSIL cases were detected in 766 patients who underwent biopsy. A number of factors should be considered in the management of women diagnosed with ASC-H. The prevalence of HSIL was higher in women with ASC-H compared to ASCUS. Although the prevalence of CIN II-III in women with ASC in the USA is 7-12%, the prevalence of CIN II-III in ASC-H is 26-68%. These rates reflect the importance of the diagnosis of ASC-H. Of the biopsy patients, 26 (3.4%) were HPC-DNA positive and had ASC-H. As a result, ASC-H should be evaluated as equivalent to HSIL and should be followed closely (Ergunay et al., 2007). Patients who attend with suspicious smears should be given importance even if the severity of the lesion is relatively low (Thomas et al., 2007). In our results, the sensitivity of the smear for diagnosis of cervical pathologies was 66%, and this test was found to be indispensable in cancer screening for women in the practice of family medicine and gynecology oncology.

When the population is screened, approximately 10% of women have minor cytological abnormalities (such as ASCUS, LSIL) in their cervical smears (Wright et al., 2002). Many authors suggested monitoring these cytological abnormalities, postponed referral, and thought that spontaneous regression would be a treatment option. In this case, there may be a hidden high-grade lesion, but this may be masked as a low-grade cytologic phenotype or may occur during screening intervals, in which case monitoring policies may compromise some women in terms of invasive disease development (Kyrgiou et al., 2006). According to the evidence that we found, in 5-47% of lesions with low-grade phenotype, histologically high-grade lesion was revealed in reality. One of the management options is to carry out colposcopy urgently in order to distinguish all women who have minor cytological findings or those with high-risk disease. Accordingly, patients should be immediately referred to colposcopy after a low-grade smear result (Kyrgiou et al., 2006).

HPV testing allows rapid diagnosis in cervical premalignant event detection. It is known that there was increased risk of high-grade lesions, low-grade lesions and carcinoma in HPV (+) cases. In another study, the CIN2/3 ratio in HPV (+) was reported as 15-27% and

in HPV (-) the same ratio was less than 2% (Arbyn et al., 2005). In addition to the 100% negative predictive value of the HPV DNA screening test, continuous smear control, colposcopy and biopsy ensure that patients can safely avoid this condition (Syrjanen and Syrjanen, 1999). In many studies, researchers have found the HPV DNA screening test to be more sensitive than PAP smears in determining PML (Schneider et al., 2000). In another study that included 46009 women, the sensitivity of HPV DNA for PML was stated as 89.2% and the sensitivity of PAP smear was 76.2% (Manos et al., 1999). In the ALTS group study which was conducted in 2003, Guido et al. (2003) examined 1539 patients who had oncogenically risky HPV infection.

In conclusion, women who are at risk of cervical cancer should be closely monitored and precautions should be taken for women with cervical cancer due to high positivity especially with oncogenic HPV types. In fact, the greatest risk for cervical cancer is not having any pap-smear and HPV type assessment, or not recurring at the required frequency. Colposcopy-guided biopsy is the gold standard for the diagnosis of cervical premalignant lesions. Cytological, colposcopic and histological data should be examined together and the right approach should be provided for the patient.

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