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A Study on the Utility of Screening Tests in Squamous Cell Carcinoma (SCC) and High-grade Intraepithelial Lesions (HSIL) of the Cervix: Evaluation of 447 Cases with Histopathological Diagnosis

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ABSTRACT

Introduction: Cervical cancer is one of the most common cancers in women. Precancerous lesions of the cervix can be detected with the combined use of smear testing and HPV (Human Papillomavirus) testing. International guidelines have been developed to indicate at what intervals and in which situations the tests should be performed. In this study, we examined the clinical utility of screening tests in patients with histopathological diagnosed SCC (squamous cell carcinoma) and HSIL.

Methods: Between January 2022 and June 2023, 447 patients aged 19-73 years (mean 37) with cervical biopsy results of SCC and HSIL were evaluated for the use of diagnostic tests (PAP smear and HPV test).

Results: PAP smears were performed in 98.2% and HPV tests in 39.1% of all cases before histopathologic diagnosis. The most frequently detected high-risk HPV (hrHPV) was type 16. HPV testing significantly decreased with age. HPV testing was not performed in 74.2% of patients aged 51-60 years and 80.9% of patients over 60 years.

Conclusion: These cases the clinical utility and pathologic evaluation of the PAP smear were optimal. However, HPV testing practice was decreasing, especially with age. Cytologic evaluation may be misleading due to age-related hormonal withdrawal, difficulty in obtaining adequate smears, and atrophic changes. Our recommendation is to use HPV testing in all age groups, but especially in the population over 50 years of age, where cytologic difficulties may occur, HPV testing should be performed optimally until 65 years of age.

Keywords: HSIL, SCC, HPV, hrHPV, PAP smear, elderly woman.

ÖZET

Giriş: Serviks kanseri kadınlarda en sık görülen kanserlerden biridir. Serviksin prekanseröz lezyonları smear ve HPV (Human Papillomavirus) testlerinin kombine kullanımı ile saptanabilir. Uluslararası kılavuzlar, testlerin hangi aralıklarla ve hangi durumlarda yapılması gerektiğini belirtmek için geliştirilmiştir. Bu çalışmada, histopatolojik olarak SCC (skuamöz hücreli karsinom) ve HSIL (yüksek dereceli skuamöz intraepitelyal lezyon) tanısı alan hastalarda tarama testlerinin klinik yararlanımını inceledik.

Yöntem: Ocak 2022 ile Haziran 2023 arasında, yaşları 19-73 arasında değişen (ortalama 37), servikal biyopsi sonuçları SCC ve HSIL olan 447 olgu üzerinde, tanı testlerinin (PAP smear ve HPV testi) kullanımını değerlendirildi.

Bulgular: Histopatolojik inceleme öncesinde tüm olguların %98,2'sine PAP smear ve %39,1'ine HPV testi yapılmıştı. En sık tespit edilen yüksek riskli HPV (hrHPV) tipi; HPV 16 idi. HPV testinin yapılma oranı yaşla birlikte önemli ölçüde azalmaktaydı. 51-60 yaş arası hastaların %74,2'sine, 60 yaş ve üstü hastaların %80,9'u HPV testi yapılmamıştı.

Sonuç: Çalışma olgularında PAP smearın klinik yararlanımı ve patolojik değerlendirmesi optimaldi. Ancak, HPV testi uygulaması özellikle yaşla birlikte azalmaktaydı. Sitolojik değerlendirme, yaşa bağlı hormonal geri çekilme, yeterli yayma elde etme zorluğu ve atrofik değişiklikler nedeniyle yanıltıcı olabilir. Önerimiz HPV testinin tüm yaş gruplarında kullanılması, ancak özellikle sitolojik zorlukların yaşanabileceği 50 yaş üstü popülasyonda HPV testinin 65 yaşına kadar yapılmasıdır.

Anahtar Kelimeler: HSIL, SCC, HPV, hrHPV, PAP smear, ileri yaş kadın.

Although screening tests for the detection of precancerous lesions of the cervix are now more widely used, cervical cancer is still one of the most common cancers in women[1-7]. More than 90% of cervical cancers and precancerous lesions are caused by HPV infection[1,8-10]. More than 450 HPV types have been reported[1]. However, 15 genotypes are carcinogenic and considered as high-risk HPV subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82)[9,11]. HPV, a DNA virus, activates the cell cycle with its oncoproteins and inhibits apoptosis, a programmed cell death that allows the damaged cell to die[1,8-10]. HPV infection can cause permanent or recurrent infections by settling in the reserve cells in the basal layer in the squamocolumnar zone of the cervix[1,12]. Cervical cancer is a preventable disease due to the protective effect of the HPV vaccine from high-risk HPV subtypes for cancer and the long period of transition from dysplasia to invasive tumor[13,1,14]. The Papanicolaou (PAP) smear test is an easy-to-administer, low-cost, non-invasive screening test that aims to detect cervical dysplasia and early detection of cancer[15]. The Bethesda system for reporting cervical cytology was first developed in 1988, and different versions were published in the following years, increasing the clinical utility of the cervical screening test[16,17]. The major innovation of the Bethesda system is the classification of cervical dysplasia into two main groups according to the risk of malignancy development: high-grade and low-grade intraepithelial lesions. According to this classification, moderate to severe dysplasia is considered a high-grade cervical intraepithelial lesion (HSIL), and mild dysplasia is considered a low-grade cervical intraepithelial lesion (LSIL). In addition, this system introduces ASC-H (Atypical squamous cells -cannot exclude high grade squamous intraepithelial lesion) and ASCUS (Atypical squamous cells of undetermined significance) into cervical cytology reports. While the new terminology and classification made it easier for cytopathologists to identify atypical cells, it also led to the need to update clinical practices. For a standardized practice all over the world, the post-Bethesda terminology clinical practice guideline was updated according to the new terminology and announced as a consensus in 2012 with risk calculations[18]. This consensus provides road maps by evaluating the clinical approach to the cases and how to follow up the cases, especially according to age and abnormal cytology results, by evaluating the risk rates. 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) updated the guidelines for clinical approach to cases with the joint use of HPV testing and HPV/cytology tests[19]. Risk analyses and the Bethesda system have contributed to the standardization of rapid intervention, colposcopy examination, and Loop electrosurgical excision (LEEP) after examination for lesions cytologically diagnosed as HSIL or ASC-H. Studies have shown that the HPV test is more effective (with higher sensitivity) in detecting high-grade dysplasia precancerous lesions, than the PAP test[4]. While the PAP test has a detection rate of 50-70% for precancerous lesions, the HPV test has a rate of over 90%[1,10.] The HPV test is considered more advantageous due to its high sensitivity in detecting precancerous lesions, the ability to extend the control interval to 5 years after a negative test result, and the ability to perform the test on oneself [4]. The PAP smear test, on the other hand, is advantageous over the HPV test because of its shorter turnaround time and lower cost[4]. The combined use of both tests in the diagnosis of HSIL cases has a higher success rate than the use of the HPV test alone and therefore the combined use of both tests is recommended[10]. Algorithms are based on the advantages and disadvantages of both tests, the patient's clinical history, and risk analysis. The requirement is to repeat negative HPV tests at 5-year intervals and negative cervical smears at 3-year intervals[1]. It is said that there is no need for screening tests in women over 65 years of age when both tests are negative[1,19]. Despite the cervical screening test and HPV test, histopathology is still the standard diagnostic method for the definitive and final diagnosis of cervical dysplasia and invasive tumors[20-22]. In cases with smear results reported as HSIL, ASC-H, ASCH+LSIL, and HPV high-risk positive cases, the biopsy is indicated and histopathological examination is absolutely necessary[1,18,19]. With histopathology, tissue integrity can be seen, immunohistochemical studies can be performed and differential diagnosis can be made more easily. Histopathologic sampling is invasive and is never used as the first choice for diagnosis because of the desire to preserve cervical tissue, especially in young women. Standardized guidelines have established waiting periods and conditions after cervical cytology and HPV testing before invasive intervention, especially in women expecting pregnancy.

In this study, we aimed to evaluate how effectively screening tests are used in routine practices in line with the literature. Are cervical cytology results and practices in the light of common guidelines sufficient to catch HSIL and early invasive tumors? What are the preanalytical rates of HPV testing in precancerous or precursor lesions and cancer cases? Most studies to date have focused on the

effectiveness of cervical cytology and HPV tests. In this study, we aimed to analyze the clinical use of screening tests in patients diagnosed with HSIL and invasive tumors based on histopathological specimens in our center and to analyze the results comparatively with the data in the literature.

Material and Method

Study Population and Ethics Approval

This retrospective study was approved on 17.08.2023 by Acıbadem University Clinical Research Ethics Committee under study number 2023-13/455.

Between the dates of January 2022 and June 2023, 447 cases between the ages of 19-73 (mean 37) with high-grade intraepithelial lesion (HSIL/CIN 2-CIN3) and squamous cell carcinoma on cervical biopsy were included in our study population. Smear results, HPV co-test results, HPV subtypes, and additional immunohistochemical studies utilized in the diagnostic phase were analyzed in each case before histopathologic diagnosis.

Histopathological Samples and Immunostaining

All samples were fixed in a 10% neutral-buffered formalin solution and processed with a Tissue-Tek Vip® 6 AI device (Sakura Finetek Japan Co., Ltd., Tokyo, Japan) to prepare paraffin blocks. Three-µm-thick sections were prepared from all the blocks and stained with hematoxylin and eosin (H&E) using a Shandon Gemini stainer. Immunohistochemical staining was performed using antibodies against P-16 (805-4713 Monoclonal Mouse-anti-Human, clone: E6H4, Ventana) and Ki-67 (Monoclonal Mouse anti-Human Clone MIB-1, Dako) using a Ventana Benchmark XT device (Roche Diagnostics, Basel, Switzerland)[23]. All the slides were morphologically evaluated and reported by pathologists who were experienced in the field of gynecological pathology using a light microscope (LM) (Olympus BX51) and digital pathology.

Cytopathologic Sampling and HPV Co-Test

The Thinprepprocessuses Preserv Cytand Cyto Lytsolutions (Aptima, Canada). Cytology preparations were prepared by Thinprep (Cytyc Corp., Boxborough, MA, USA) technique. ThinPrep5000 automated processor was used for preparation. The reserve materials were stored in Thinprepsolution (Cytyc's ThinPrep PreservCytmedium). Aptima Panther test was used as an HR-HPV co-test. The Aptima Panther test detects a total of 14 hrHPV (high-risk Human Papillomavirus) types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68) with type 16 alone, 18/45 in a mixture of two, and the remaining 11 types together.

All of the slides were reevaluated and reported by cytopathologists who are experienced in the field of gynecological cytopathology using a light microscope (LM) (Olympus BX51). PAP smears were reported according to the 2016 version of the Bethesda system[24,25].

Statistical Analysis

Statistical analyses were conducted using SPSS 21.0 software (IBM Corp., Armonk, NY, USA; licensed to Istanbul University). Pearson's χ2 test or Fisher's exact test was used to compare categorical data. Results were presented as frequency and percentage and a p-value of <0.05 was considered significant.

Results

Biopsy Results

The patients in our study group were between 19-73 years of age (mean 37), 393 (87.9%) were 49 years and younger, and 54 (12%) were 50 years and older. 37 of 447 cases (8.3%) were squamous cell carcinoma (SCC). 410 of them were HSIL cases. Of the HSIL cases, 254 (62%) had CIN3 or CIN3 accompanied by CIN2 and/or CIN1. 156 cases (38%) had CIN2 or CIN1 accompanying CIN2. 8 patients had no smear and HPV test before biopsy. These 8 cases were 51 years of age or older (mean 65.5) and 5 cases had hysterectomy for prolapse or myoma uteri and were incidentally diagnosed with HSIL. 3 cases were SCC cases who underwent urgent cervical biopsy due to clinical history and findings. P-16 immunohistochemistry was utilized in 33.2%, and P-16 and Ki-67 were utilized in 21.7% of HSIL cases (Figure 1,2).

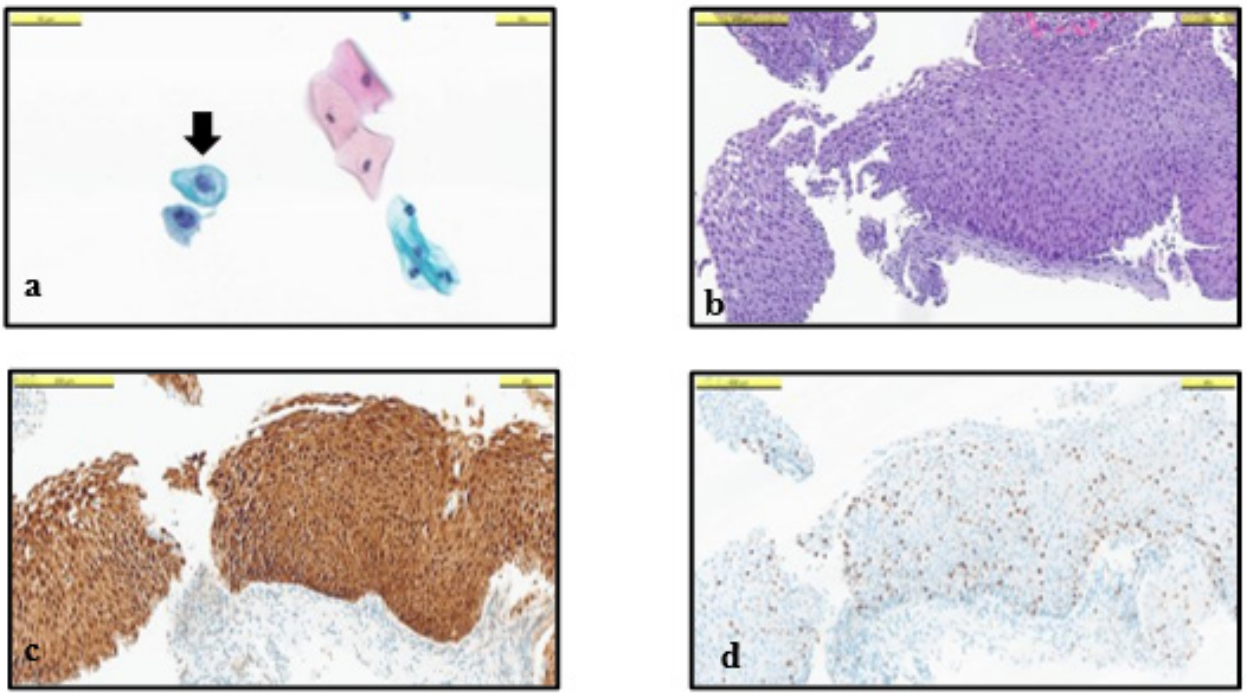

Figure 1: 29 y, HPV 16 (+), smear result LSIL, biopsy result HSIL (CIN 3). a: 2 dysplastic intermediate cells (50 µm PAP) evaluated as LSIL, b: Squamous epithelium with severe dysplasia (200µm H&E), c: same area P-16 cytoplasmic full- thickness strongly positive (200µm), d: same area Ki-67 full-thickness nuclear positive (200µm).

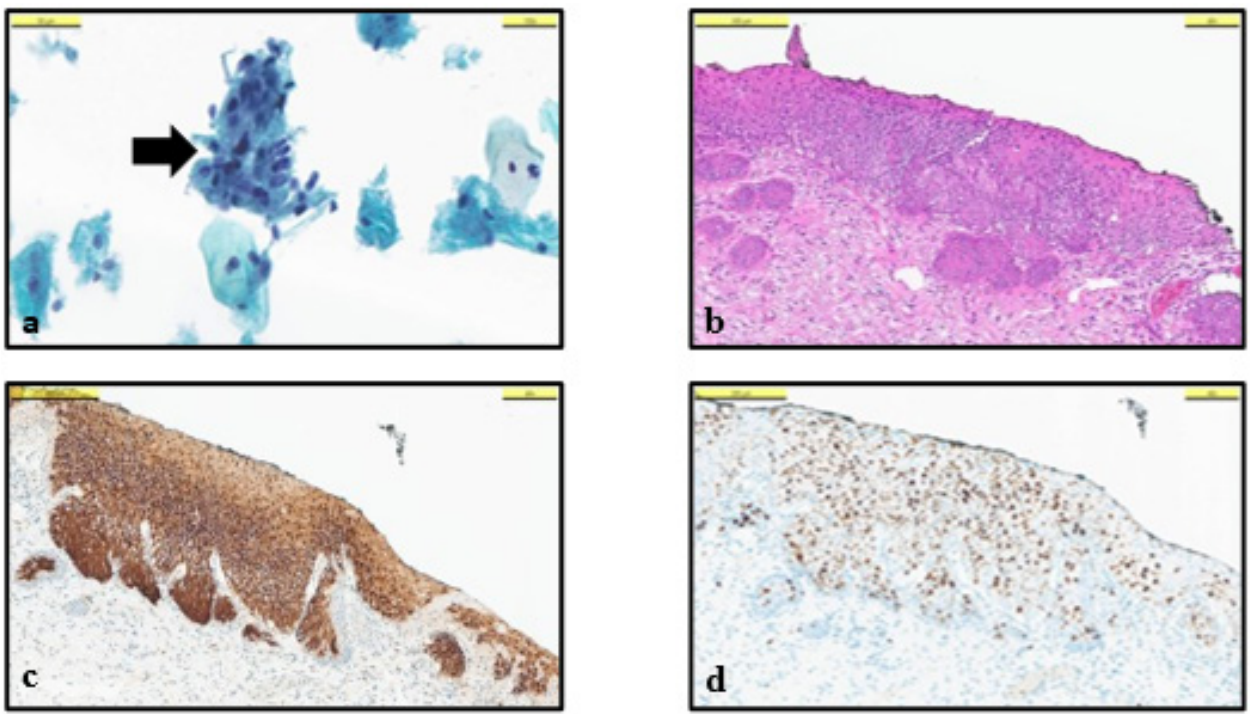

Figure 2: 30 y, HPV 16 (+), smear result HSIL, biopsy result HSIL (CIN 3) a: Dysplastic cell group with large hyperchromatic nuclei and irregular nuclear membrane (50 µm PAP). b: Squamous epithelium with severe dysplasia (200µm H&E), c: same area P-16 cytoplasmic full-thickness strongly positive (200µm), d: same area Ki-67 full-fold nuclear positive (200µm).

Smear Test Results

The smear test was not performed in 8 cases with an age range of 51-73 years (mean 65.5). Of the 439 smears, there were 33 (7.5%) NILM, 76 (17.3%) LSIL, 141 (32.5%) HSIL, 71 (16.1%) ASC-US, 116 (26.4%) ASC-H and ASC-H+LSIL, 2 (0.5%) AGC.

Table 1 shows the distribution of smear results according to biopsy results.

Table 1: Distribution of smear results and biopsy results

	CIN2	CIN3	SCC	Total
NILM	13 (39.4%)	16 (48.5)	4 (12.1%)	33 (100%)
LSIL	43 (56.6%)	32 (42.1%)	1 (1.3%)	76 (100%)
HSIL	28 (19.9%)	99 (70.2%)	14 (9.9%)	141(100%)
ASC-US	39 (54.9%)	29 (40.8%)	3 (4.2%)	71 (100%)
ASC-H	19 (25.3%)	46 (61.3%)	10 (13.3)	75 (100%)
ASC-H+LSIL	13 (31.7%)	27 (65.9%)	1 (2.4%)	41 (100%)
AGC	0	1 (50%)	1 (50%)	2 (100%)
No test	1 (12.5%)	4 (50%)	3 (37.5)	8 (100%)
Total	156 (34.9%)	254 (56.8%)	37 (8.3%)	447 (100%)

NILM *(Negative for intraepithelial lesion or malignancy),* ***LSIL*** *(Low grade squamous intraepithelial lesion),* ***HSIL*** *(High grade squamous intraepithelial lesion),* ***ASC-US*** *(Atypical squamous cells of undetermined significance),* ***ASC-H*** *(Atypical squamous cells – cannot exclude high grade squamous intraepithelial lesion),* ***AGC*** *(Atypical Glandular Cell),* ***CIN2:*** *Cervical moderate dysplasia,* ***CIN3:*** *severe dysplasia and carcinoma in situ,* ***SCC:*** *squamous cell carcinoma*

According to the guidelines, the biopsy was indicated in cases with smear results of HSIL, ASC-H, and AGC regardless of HPV testing. Smear results of NILM, ASCUS, and LSIL could have followed up with smear controls. In our study, when the smear results were analyzed according to the indication for biopsy, the indication for biopsy increased with the smear result as the degree of dysplasia increased. The distribution of biopsy-indicated smear results and cases that could have followed up with smear control according to biopsy results is presented in Table 2.

Table 2: Distribution of smear results to biopsy results according to biopsy indication

	NILM, ASCUS, LSIL	HSIL, ASC-H, AGC (biopsy indication+)	Total
CIN2	95 (61.3%)	60 (38.7%)	155 (100%)
CIN3	77 (30.8%)	173 (69.2%)	250 (100%)
SCC	8 (23.5%)	26 (76.5%)	34 (100%)
Total	180 (41%)	259 (59%)	439 (100%)

NILM *(Negative for intraepithelial lesion or malignancy),* ***LSIL*** *(Low grade squamous intraepithelial lesion), 2:* ***HSIL*** *(High grade squamous intraepithelial lesion),* ***ASC-US*** *(Atypical squamous cells of undetermined significance),* ***ASC-H*** *(Atypical squamous cells – cannot exclude high grade squamous intraepithelial lesion),* ***AGC*** *(Atypical Glandular Cell),* ***CIN2:*** *Cervical moderate dysplasia,* ***CIN3:*** *severe dysplasia and carcinoma in situ,* ***SCC:*** *squamous cell carcinoma*

HPV Test Results

HPV test was performed together with cytology in only 39.1% of the cases (175 cases). Of the 175 patients who underwent HPV testing, only 5 cases were found to be negative for high-risk HPV despite the biopsy result of HSIL. HPV was tested in only 33.6% (138 cases) of HSIL cases and only 27% (11 cases) of SCC cases. HPV testing was significantly decreasing especially in cases over 40 years of age. The distribution of HPV testing according to age is presented in Table 3. HPV testing was particularly high in cases with negative smear results (63.6%) and ASCUS (60.6%). The distribution of HPV testing according to smear results is summarized in Table 4.

Table 3: Distribution of HPV testing by age

Age	hrHPV(-)	hrHPV(+)	HPV no test	Total
19-29	1 (1%)	49 (49.5%)	49 (49.5%)	99 (100%)
30-39	0	81 (39.5%)	124 (60.5%)	205 (100%)
40-49	2 (2.2%)	29 (32.6%)	58 (65.2%)	89 (100%)
50-59	1 (3%)	8 (24.3%)	24 (72.7%)	33 (100%)
60 ≤	1 (4.8%)	3 (14.2%)	17 (81%)	21 (100%)
Total	5 (1.1%)	170 (38%)	272 (60.9%)	447 (100%)

hrHPV *(high-risk Human Papillomavirus)*

Table 4: Distribution of HPV test according to smear results

Smear	hrHPV(-)	hrHPV(+)	HPV no test	Total
NLIM	0	21 (63.6%)	12 (34.6%)	33 (100%)
LSIL	1 (1.3%)	30 (39.5%)	45 (59.2%)	76 (100%)
HSIL	1 (0.8%)	37 (26.2%)	103 (73%)	141 (100%)
ASC-US	2 (2.8%)	43 (60.6%)	26 (36.6%)	71 (100%)
ASC-H/ ASC-H +LSIL	1 (0.9%)	39 (33.6%)	76 (65.5%)	116 (100%)
AGC	0	0	2 (100%)	2 (100%)
Total	5 (1.2%)	170 (38.7%)	264 (60.1%)	439 (100%)

hrHPV *(high-risk Human Papillomavirus),* ***NILM*** *(Negative for intraepithelial lesion or malignancy),* ***LSIL*** *(Low grade squamous intraepithelial lesion), 2:* ***HSIL*** *(High grade squamous intraepithelial lesion),* ***ASC-US*** *(Atypical squamous cells of undetermined significance),* ***ASC-H*** *(Atypical squamous cells – cannot exclude high grade squamous intraepithelial lesion),* ***AGC*** *(Atypical Glandular Cell).*

Of the 439 patients who underwent smear testing, 175 (39.9%) were also tested for hrHPV. Biopsy was also indicated in 170 cases with a positive high-risk HPV test regardless of the smear result. In 2 cases with NILM smear result, biopsy was indicated due to HPV high-risk positivity. In 94 cases, although the smear result was not an absolute indication for biopsy, biopsy was indicated due to HPV high-risk positivity. In 83 cases (20.7%), HPV test was not performed and smear results did not require absolute biopsy. Among these 83 cases, 12 were NILM, their cases could be followed up with smear controls. Biopsy was performed in these cases due to clinical findings and clinical approach.

Evaluation of SCC Cases

The age range of 37 cases with SCC biopsy results was 31 and 73 years with a mean age of 58.1 years. When SCC cases were evaluated by P-16 expression, 35 were associated with HPV and 2 were negative. HVP. Smear test was not performed in 3 cases (8.1%) and hrHPV test was not performed in 26 cases (70.7%). The result was NLIM in 4 of 34 patients who underwent smear test (Figure 3). Of these cases, 2 of 11 patients who underwent HPV testing were negative. HPV test and Smear test results of SCC cases are presented in Table 5.

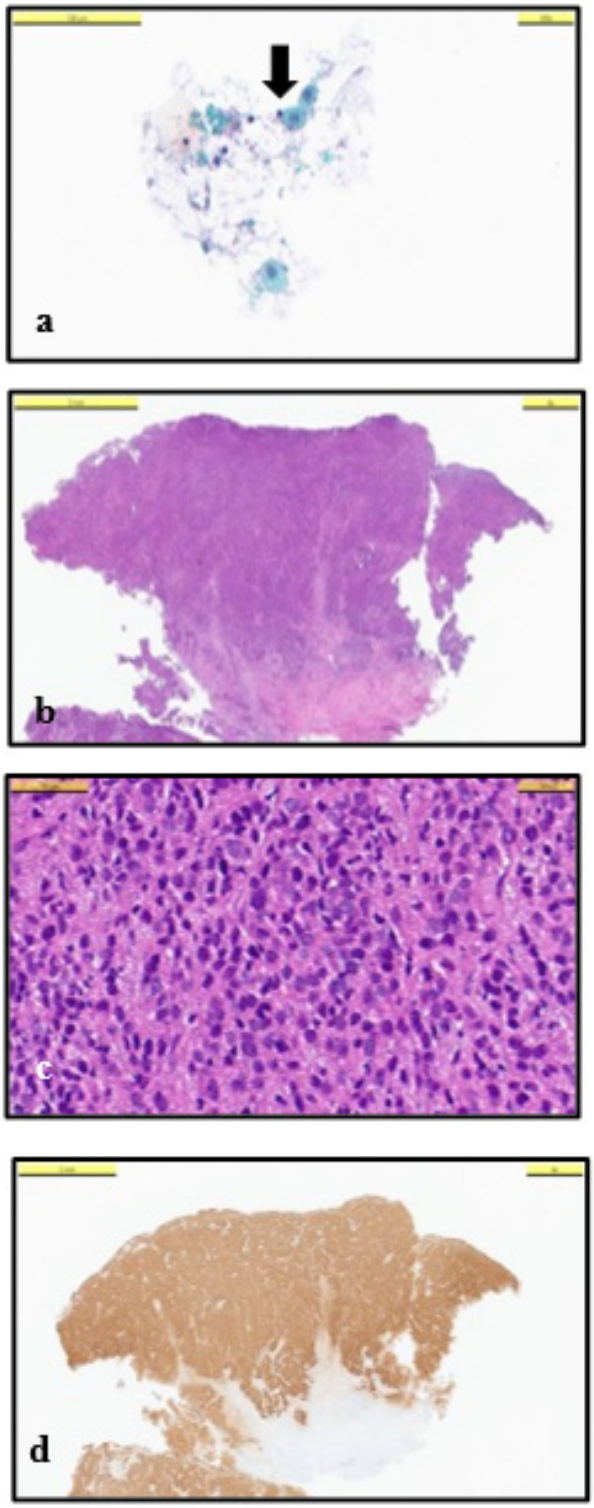

Figure 3: 73 y, smear result NILM, biopsy result SCC. a: Few squamous cells in smear without transformation zone, (arrow) parabasal cells (100 µm PAP). b: HPV-associated SCC (2mm H&E), c: Magnification of area b, hyperchromatic, pleomorphic small nucleated tumor cells d: Same area in b, P-16 cytoplasmic full-fold strongly positive (2mm).

Table 5: Distribution of SCC cases according to smear and hrHPV test results

Smear	hrHPV (+)	HPV no test	hrHPV (-)	Total
NLIM, ASC-US, LSIL	2	5	1	8
HSIL, ASC-H, AGC	7	18	1	26
Smear no test	0	3	0	3
Total	9	26	2	37

hrHPV *(high-risk Human Papillomavirus),* ***NILM*** *(Negative for intraepithelial lesion or malignancy),* ***LSIL*** *(Low grade squamous intraepithelial lesion),* ***HSIL*** *(High grade squamous intraepithelial lesion),* ***ASC-US*** *(Atypical squamous cells of undetermined significance),* ***ASC-H*** *(Atypical squamous cells -cannot exclude high grade squamous intraepithelial lesion),* ***AGC*** *(Atypical Glandular Cell)*

Discussion

In our study, we found that cervical smear was used as a screening test for precancerous lesions of the cervix in 97.5% (439 cases). Only 8 cases did not have a smear test and these 8 cases were aged 50 years or older (mean 65.6). The detection rate of a precancerous lesion was 56% (259 cases including HSIL, ASC-H, and AGC) and the detection rate of a cytologic abnormality was 92.4% (406 cases). In a study by Perkins et al. in which a large number of studies were analyzed, the rate of detection of precancerous lesions by smear was reported to be 50-70% and 53% in the study by Bhatla et al.[1,10]. Cox et al. and Hogarts et al. reported that the smear may also give false negativity at a rate of 15-50%[10,26]. Of the 33 cases in which cytologic evaluation was reported as NILM, 3 had no transformation zone, 2 had a small number of squamous cells that were not sufficient for diagnosis and these 5 cases were insufficient for evaluation. The 28 NILM cases, which we will consider as false negatives, were 6.4% of all smears. Crothers et al. reported a false negative rate of 4.7%-7.8% and infections, reactive changes due to repair, and/or atrophic changes were shown as conditions affecting false negativity[27]. In our cases, 8 out of 28 NILM cases had atrophic findings, trichomonas vaginalis and candida infection were detected in 10 cases, and in the other 10 cases, smears containing reactive changes with inflammatory cell predominance were seen. The utilization rate, precancerous lesion detection rate, and false negativity rate of the smear test in our cases were within the values presented in the literature, and in line with these results, the clinical use and pathology evaluation of the smear test was at an optimal level.

The rate of HPV testing as a screening test was very low at 39.1%. The rate of HPV test utilization was highest in the 19-29 age group with 55.5%, while this rate decreased to 27.3% in women aged 50-59 years and to 19% in women over 60 years, and the rate of HPV test utilization decreased dramatically with increasing age.

Only 5 of 175 cases of HSIL and SCC who underwent HPV testing were hrHPV negative. The detection rate of HPV test for precancerous lesions was reported to be 90% in the study by Perkins et al. and 93.1% in the study by Bhatla et al.[1,10]. In our patients who underwent HPV testing, 97.1% were positive for high-risk HPV. The reason why the hrHPV test was not positive in all precancerous lesions and squamous cell carcinomas in our study and in the literature is that hrHPV has not yet been defined all types or there may be technical deficiencies. Among the high-risk HPV subtypes, HPV type 16 was the most common type with a rate of 42.4%. HPV 16 was again the most common subtype in 6 (54.5%) of 11 SCC cases who underwent HPV testing. In the study of Guan et al. including a large case series, the most common subtype in HSIL cases was HPV 16 and the percentage of HPV 16 increased in the increase of lesions from CIN2 (40-47%) to invasive tumor (58-63%) as in our study[8]. In the study of Dursun et al., the most common hrHPV type in Turkish women was HPV type 16 (36%), which is consistent with our study[28].

The most problematic group among our cases was 83 cases in which HPV testing was not performed and biopsy was not indicated according to smear results (12 NILM, 45 LSIL, 26 ASCUS). In these cases, biopsy sampling was performed with the right clinical approach.

In summary, we can say that the smear test was used effectively in the detection of cervical precancerous lesions in our study, the smear results were as accurate as expected, and the false negativity rate was lower than acceptable rates. The use of HPV test was remarkably low (34.1%). This rate was significantly lower, especially in patients over 50 years of age. Paradoxically, while the risk of cervical cancer increased with age[22,29,30], the rate of HPV

test utilization decreased. Atrophic changes after menopause, sampling, and cytologic evaluation difficulties decrease the sensitivity of PAP smear in detecting percutaneous lesions [29,31]. In our study, the smear was reported as NILM in 4 (10.8%) SCC cases aged 61-73 years (mean 65.7). In addition, 8 cases without smear were in the age range of 51-73 years (mean 65.5). In conclusion, while the incidence of SCC was higher in patients aged 50 years and older, according to our results, the rates of smear and HPV test were decreasing, and the predictive power of smear for cellular abnormality was decreasing if only smear was performed. The highest prevalence of high-risk HPV was reported in women aged 20-23 years (46%) and the lowest in women aged 65 years and older (5.7%) in the study by Kjar et al[2]. In the HPV prevalence study of Dursun et al. in Turkish women, HPV positivity was high before the age of 30 years and decreased after menopause[28]. It has been reported that HPV infection decreases with age and there is a change in the incidence of hrHPV types after menopause. However, in our cases, more careful screening tests should be performed especially in patients over 50 years of age to detect precancerous lesions of cervical cancer, which is among the preventable cancers after HPV vaccination. Because this age group has lost the chance of vaccination. In addition, considering that HPV infection is the most common sexually transmitted infection (70-85% in all age groups)[11,32] women aged 50 years and older have most likely been latently exposed to HPV infection for many years. Cervical cancer is said to develop in 5% of the population without screening tests and effective use of screening tests is said to reduce this risk to less than 0.05% [1]. Recent studies on the implementation of tests recommend the effective use of both tests up to the age of 65 years. 2 negative HPV results or 3 negative smear results in the last 10 years are emphasized as conditions for discontinuation of testing in women over 65 years[1]. In our study, the smear screening test was 100% (393) in the group under 50 years of age and 85.2% (46 cases) in the group aged 50 years and over, and the HPV test was 41.2% in the group under 50 years of age and 24% in the group aged 50 years and over.

Our recommendation and hope is that HPV vaccination should be provided free of charge to the entire population, both male and female, under the age of 25 years to prevent cervical cancer and other HPV-associated cancers. The HPV test, which is an effective test in detecting precancerous lesions, should be performed on all women, and both tests should be used effectively, especially in women aged 50 and over.

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Conflicts of Interest

The authors declare no conflict of interest.

Author Contribution

SE designed the study. SE and DS evaluated and prepared the data. SE, MA, and EB ensured the data collection and the accuracy of the information. ST performed the statistical analysis. DS, UI, and SEr contributed critical comments on the interpretation of the study. SE wrote the manuscript. All authors read and approved the final version of the article.

Data Availability Statement

The data supporting this study's findings are available at a reasonable request from the corresponding author, SE.

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