# The Relationship between Cervical Smear and HPV Results with Colposcopic Biopsy Results

## Servikal Smear ve HPV Sonuçları ile Kolposkopik Biyopsi Sonuçları Arasındaki İlişki

Mehmet Ünsal, Alp Tokalıoğlu, Okan Aytekin, Fatih Çelik, Fatih Kılıç, Burak Ersak, Sevgi Ayhan, Serra Akar, Hakan Raşit Yalçın Günsu Kimyon Cömert, Taner Turan, Osman Türkmen

Ankara City Hospital, Gynecological Oncology Surgery Clinic, Ankara, Turkiye

**ABSTRACT**

**Objective:** Cervical cancer-related deaths can be significantly reduced by early diagnosis and screening methods. Human papillomavirus (human papillomavirus; HPV) is the main risk factor in the development of cervical cancer. The aim of this study is to investigate the histopathological results of patients who underwent colposcopic evaluation due to abnormal cervical smear results and/or HPV test positivity, and to define the relationship between cervical smear and HPV results and the detection of HSIL and higher lesions.
**Method:** The study included 1490 patients who underwent colposcopy in Ankara City Hospital Gynecological Oncology Surgery Outpatient Clinic between August 2019 and January 2021.
**Results:** Cervical smear results were pathological in 59.3% of the study group, and 1.5% of them were interpreted as HSIL. Colposcopic biopsy result was determined as HSIL and above in 59.1% of those whose cervical smear result was HSIL. High-risk HPV type was found to be positive in 69.7% of the patients who had HPV typing. HPV type was found to be type 16 and/or 18 in 44% of these patients. In the presence of type 16 and/or 18, the probability of HSIL and higher lesion increased from 8.1% to 28%.
**Conclusion:** Cervical smear, especially when performed with HPV typing, is decisive in the identification of HSIL and above lesions. In the presence of HPV 16 and/or 18, approximately one-fourth of those with negative smear results have HSIL and higher lesions. For this reason, it would be appropriate to use co-test for screening cervical pathologies instead of cervical smear alone.

**Keywords:** Cervical Smear, HPV, Co-test, Colposcopy, Cervical Pre-invasive Lesion, Cervical cancer

**Received:** 01.27.2022 **Accepted:** 04.19.2022

**ÖZET**

**Amaç:** Erken tanı ve tarama yöntemleriyle serviks kanserine bağlı ölümler önemli bir ölçüde azaltılabilmektedir. Serviks kanseri gelişmesinde insan papilloma virüsü (human papillomavirus; HPV) ana risk faktörüdür. Bu çalışmanın amacı anormal servikal smear sonucu ve/veya HPV testi pozitifliği nedeniyle kolposkopik değerlendirme yapılan hastaların histopatolojik sonuçlarının araştırılması, servikal smear ve HPV sonuçlarıyla HSIL ve üzeri lezyonların saptanması arasındaki ilişkinin tanımlanmasıdır.
**Metod:** Çalışmaya Ağustos 2019 ve Ocak 2021 tarihleri arasında Ankara Şehir Hastanesi Jinekolojik Onkoloji Cerrahisi Polikliniği'nde kolposkopi yapılan 1490 hasta dahil edilmiştir.
**Sonuçlar:** Servikal smear sonuçları çalışma grubunun %59.3'ünde patolojikti ve %1.5'i HSIL olarak yorumlanmıştı. Servikal smear sonucu HSIL olanların %59.1'inde kolposkopik biyopsi sonucu HSIL ve üzeri olarak belirlenmişti. HPV tiplendirmesinin yapılmış olduğu hastaların %69.7'sinde yüksek riskli HPV tipinin pozitif olduğu görüldü. Bunların %44'ünde HPV tipinin tip 16 ve/veya 18 olduğu saptandı. Tip 16 ve/veya 18 varlığında HSIL ve üzeri lezyon olasılığı %8.1'den %28'e çıkmaktaydı.
**Sonuç:** Servikal smear ve özellikle HPV tipi HSIL ve üzeri lezyonların tanımlanmasında belirleyicidir. Smear sonucu negatif olanların yaklaşık dörtte birinde HPV 16 ve/veya 18 varlığında HSIL ve üzeri lezyonların olduğu görülmektedir. Bu nedenle tek başına servikal smear yerine co-test'in servikal patolojilerin taranmasında kullanılması uygun olacaktır.

**Anahtar Sözcükler:** Servikal Smear, HPV, Co-test, Kolposkopi, Servikal Pre-invaziv Lezyon, Servikal kanser

**Geliş Tarihi**: 27.01.2022 **Kabul Tarihi:** 19.04.2022



**ORCID IDs:** M.Ü.0000-0002-9920-6804,A.T.0000-0002-1776-2744.O.A.0000-0002-6430-4607,F.Ç.0000-0002-9523-180X, F.K.0000-0002-7333-4883, B.E.0000-0003-3301-062X, S.A.0000-0003-1697-8583, S.A.0000-0002-0466-140X, H.R.Y.0000-0002-9027-1351, G.K.C.0000-0003-0178-4196, T.T.0000-0001-8120-1143, O.T.0000-0002-1470-7731

**Address for Correspondence / Yazışma Adresi:** Mehmet Ünsal, MD Ankara City Hospital, Gynecological Oncology Surgery Clinic, Universiteler Mahallesi, 06800, Ankara, Turkiye E-mail: munsal174@hotmail.com

doi:http://dx.doi.org/10.12996/gmj.2023.32

## INTRODUCTION

According to GLOBACAN 2020 data, cervical cancer is the fourth most common cancer in women, with 604,000 new cases diagnosed annually worldwide and 342,000 women die from this cancer (1). Human papillomavirus (human papillomavirus; HPV) is the main risk factor in cervical cancer tumorigenesis and is detected in 99.7% of cervical cancers (2). More than 200 types of HPV have been identified. HPV is divided into groups as high (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68) and low risk depending on whether it is responsible for malignant transformation. Of these types, 16 and 18 are the most frequently isolated types in cervical cancer (3). HPV infection typically resolves within 12 months (4). Persistent infections lasting more than 2 months are responsible for the development of preinvasive cervical lesions and subsequent cancer. Cytologically detected cervical preinvasive lesions occur approximately 10 years after contact with HPV (5). Therefore, screening and early detection of preinvasive lesions is very important.

By performing cytological examination with cervical smear, which is used in the early diagnosis and screening of cervical cancer, early detection of cervical preinvasive lesions has been achieved and thus the incidence of cervical cancer has been reduced (6). However, cervical smear alone is not considered sufficient. Test strategies including detection of HPV DNA have been developed to improve the efficiency of cytological evaluation alone (7). In many studies, it has been shown that the sensitivity of the use of cervical smear test and HPV DNA together (co-test) in cervical cancer screening is higher than each of the cervical smear and HPV DNA test separately (8).

Neoplastic changes in HPV-related tissue begin as cervical intraepithelial neoplasia (cervical intraepithelial neoplasia; CIN) before invasive cancer develops. After starting as CIN 1, it progresses to CIN 2 and CIN 3. This grading system is divided into two groups: low-grade squamous intraepithelial neoplasia (low-grade squamous intraepithelial lesion; LSIL) for CIN 1 and high-grade intraepithelial neoplasia (high-grade squamous intraepithelial lesion; HSIL) for CIN 2 and CIN 3. This distinction has made the system clinically and pathologically simpler. While clinical follow-up is recommended for LSIL, surgical intervention is preferred for HSIL (9).

The aim of this study is to investigate the histopathological results of patients who underwent colposcopic evaluation due to abnormal cervical smear results and/or HPV test positivity, and to define the relationship between cervical smear and HPV results and the detection of HSIL and higher lesions.

## MATERIAL and METHOD

One thousand four hundred and ninety patients who underwent colposcopy between August 2019 and January 2021 in Ankara City Hospital Gynecological Oncology Surgery Outpatient Clinic were included in the study. Colposcopy indications; abnormal cervical smear sampling, HPV 16 and/or 18 positivity, cervical smear normal/abnormal but other high risk type positivity other than HPV 16 and 18, and clinical suspicion. Patient data were reviewed retrospectively Pregnant patients, those who had previous surgery for gynecological malignancy and were under cytology follow-up, those who had vaginal cuff cytology, those without smear or pathology results, and those who had previously been treated for cervical preinvasive lesion were excluded from the study.

At Ankara City Hospital Pathology Clinic, cervical cytology samples are prepared with the liquid-based Thin Prep Pap Test technique and reported according to the Bethesda classification. HPV 16, 18 and other high-risk HPV (31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68) genotypes are analyzed using Hybrid Capture 2. Colposcopy-guided cervical biopsy material is evaluated by staining with hematoxylin & eosin after standard tissue follow-up. All participants provided written informed consent to the study procedures. Ethics committee approval of the study was received by the local ethics committee (E2-22-2972).

*Statistical Analysis*

The mean±standard deviation was given for the variables with normal distribution, the median (minimum-maximum) for the variables with non-normal distribution, and the percentage (%) for categorical variables. Among the values that did not fit the normal distribution, the Mann Whitney U test was used when the number of groups was two. Chi-square test was used to compare categorical variables. Results for a P value <0.05 were considered statistically significant. IBM SPSS 23 program was used for data analysis.

## RESULTS

The mean age of 1490 patients in the study group was 41.80±10.353. Atypical squamous cells of undetermined significance (ASCUS) and higher pathology were detected in 884 (59.3%) patients in cervical smear. Cervical smear results were analyzed. Results: Negative cytology in 567 (38.1%) patients, negative cytology but insufficient transformation zone in 39 (2.6%) patients, ASCUS in 574 (38.5%) patients, LSIL in 210 (14.1%) patients, atypical squamous cells high-grade cannot be excluded from high-grade squamous intraepithelial lesion (ASC-H) in 60 (4%) patients., HSIL in 22 (1.5%) patients, atypical glandular cells not otherwise specified (AGC-NOS) in 18 (1.2%) patients. It was determined that HPV typing was performed in 1233 of the patients and high-risk HPV type was positive in 1039 (69.7%) patients.

In 457 (44%) of these patients, positive HPV type was found to be 16 and/or 18. The results of colposcopic biopsy showed chronic cervicitis in 628 (42.1%) patients, LSIL (CIN1) in 646 (43.4%), HSIL (CIN2) in 106 (7.1%), HSIL (CIN3) in 98 (6.6%), AIS in 2 (0.1%), SCC in 8 (0.5%) and adenocarcinoma in 2 (0.1%). Cervical smear, HPV and colposcopic biopsy results of the patients are given in Table 1.

**Table 1.** Characteristics of the study group

| Parameters | | n | % |
|---|---|---|---|
| Cervical Smear Results | Negative Cytology | 567 | 38.1 |
| | Negative cytology but insufficient TZ | 39 | 2.6 |
| | ASCUS | 574 | 38.5 |
| | LSIL | 210 | 14.1 |
| | ASC-H | 60 | 4 |
| | HSIL | 22 | 1.5 |
| | AGC-NOS | 18 | 1.2 |
| | Negative | 194 | 13 |
| HPV Status | Positive | 1039 | 69.7 |
| HPV Types [1] | Unlabored | 255 | 17.1 |
| | HPV 16 only | 354 | 34.1 |
| | HPV 18 only | 74 | 7.1 |
| | HPV 16-18 together | 29 | 2.8 |
| | Other high risk except HPV 16 and 18 | 582 | 56 |
| Colposcopic Biopsy Results | Chronic cervicitis | 628 | 42.1 |
| | LSIL | 646 | 43.4 |
| | HSIL (CIN 2) | 106 | 7.1 |
| | HSIL (CIN 3) | 98 | 6.6 |
| | AIS | 2 | 0.1 |
| | SCC | 8 | 0.5 |
| | Adenocarcinoma | 2 | 0.1 |

[1]HPV positive patients (1039), HPV: Human Papillomavirus, LSIL: Low-Grade Squamous Intraepithelial Lesion, HSIL: High-Grade Squamous Intraepithelial Lesion

AIS: Adenocarcinoma In situ, SCC: Squamous Cell Cancer, ASCUS: Atypical Squamous Cells of Undetermined Significance, ASC-H: Atypical Squamous Cells High-Grade Cannot Be Excluded, AGC-NOS: Atypical Glandular Cells- Not Otherwise Specified, CIN: Cervical Intraepithelial Neoplasia, TZ: Transformation Zone

While the biopsy result was HSIL and above in 13.9% of the patients whose smear result was reported as negative, this rate was 15.4% in negative cytology where no transformation zone was observed. This rate was defined as 9.9% in ASCUS, 19% in LSIL, 35% in ASC-H and 59.1% in HSIL (p<0.0001). Smear results and colposcopic biopsy results are given in Table 2 in detail.

**Table 2.** Colposcopic biopsy results according to cervical smear results

| Cervical Smear Results | Colposcopic Biopsy Results | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chronic cervicitis | LSIL (CIN1) | HSIL (CIN2) | HSIL (CIN3) | AIS | SCC | Adenocarcinoma |
| Negative cytology | 223 (%39.3) | 265 (%46.7) | 37 (%6.5) | 39 (%6.9) | - | 2 (%0.4) | 1 (%0.2) |
| Negative cytology but insufficient TZ | 18 (%46.2) | 15 (%38.5) | 3 (%7.7) | 2 (%5.1) | 1 (%2.6) | - | - |
| ASCUS | 291 (%50.7) | 226 (%39.4) | 32 (%5.6) | 23 (%4) | - | 2 (%0.3) | - |
| LSIL | 65 (%31) | 105 (%50) | 25 (%11.9) | 15 (%7.1) | - | - | - |
| ASC-H | 11 (%18.3) | 28 (%46.7) | 5 (%8.3) | 12 (%20) | - | 4 (%6.7) | - |
| HSIL | 6 (%27.3) | 3 (%13.6) | 4 (%18.2) | 7 (%31.8) | 1 (%4.5) | - | 1 (%4.5) |
| AGC-NOS | 14 (%77.8) | 4 (%22.2) | - | - | - | - | - |

LSIL: Low-Grade Squamous Intraepithelial Lesion,HSIL: High-Grade Squamous Intraepithelial Lesion,AIS: Adenocarcinoma In situ,SCC: Squamous Cell Cancer
ASCUS: Atypical Squamous Cells of Undetermined Significance,ASC-H: Atypical Squamous Cells High-Grade Cannot Be Excluded,AGC-NOS: Atypical Glandular Cells- Not Otherwise Specified,CIN: Cervical Intraepithelial Neoplasia, TZ: Transformation Zone

High-risk HPV type determined the results of colposcopic biopsy. In 1039 patients with high-risk HPV positive, the probability of having a biopsy result of HSIL and above in those with HPV type 16 and/or 18 increased from 8.1% to 28% (p<0.0001).

Similarly, HPV type was associated with colposcopic biopsy result in 567 patients whose smear result was negative in subgroup analysis. High-risk HPV was positive in 98% of this patient group, and 14% of this patient group had HSIL and above lesions in colposcopic biopsy. While this rate was 23.2% in HPV types 16 and/or 18, it was 6.8% in other high-risk types (p<0.0001). HPV type and biopsy results are shown in Table 3.

**Table 3.** Colposcopic biopsy results by HPV types

| HPV Types | Colposcopic Biopsy Result | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chronic cervicitis | LSIL (CIN1) | HSIL (CIN2) | HSIL (CIN3) | AIS | SCC | Adenocarcinoma |
| HPV 16-18 | 129 (%28.2) | 200 (%43.8) | 54 (%11.8) | 67 (%14.7) | 2 (%0.4) | 4 (%0.9) | 1 (%0.2) |
| HPV other | 228 (%39.2) | 307 (%52.7) | 29 (%5) | 16 (%2.7) | - | 2 (%0.3) | - |

HPV: Human Papillomavirus, LSIL: Low-Grade Squamous Intraepithelial Lesion, HSIL: High-Grade Squamous Intraepithelial Lesion, AIS: Adenocarcinoma In situ
SCC: Squamous Cell Cancer, CIN: Cervical Intraepithelial Neoplasia

Cervical pathology was determined to be cervical cancer in 10 patients in the study group. The tumor type in 8 of them was squamous cell cancer, while 2 of them were adenocarcinoma. Cervical smear cytology was found to be normal in 3 of these 10 patients.

On the other hand, cervical smear results were reported as HSIL in 1 patient, ASC-H in 4 patients, and ASCUS in 2 patients. It was observed that 8 of these 10 patients had been tested for high-risk HPV. It was determined that the result of the test was negative in one of those who were tested for HPV. HPV type was type 16 in 4 of 7 patients with positive test results, type 18 in 1, and high-type except HPV 16-18 in 2 (Table 4).

**Table 4.** Age, cervical smear and HPV results of cervical cancer cases

| Patient No. | Histopathology | Age | Cervical Smear | HPV Positivity | HPV Type |
|---|---|---|---|---|---|
| 1 | Adenocarcinoma | 43 | Negative cytology | Positive | 18 |
| 2 | Adenocarcinoma | 65 | HSIL | Unlabored | - |
| 3 | SCC | 44 | Negative cytology | Positive | Other high-risk except HPV 16 and 18 |
| 4 | SCC | 40 | ASCUS | Positive | Other high-risk except HPV 16 and 18 |
| 5 | SCC | 47 | Negative cytology | Positive | 16 |
| 6 | SCC | 34 | ASCUS | Positive | 16 |
| 7 | SCC | 28 | ASC-H | Positive | 16 |
| 8 | SCC | 55 | ASC-H | Positive | 16 |
| 9 | SCC | 48 | ASC-H | Negative | - |
| 10 | SCC | 49 | ASC-H | Unlabored | - |

HPV: Human Papillomavirus,HSIL: High-Grade Squamous Intraepithelial Lesion, SCC: Squamous Cell Cancer, ASCUS: Atypical Squamous Cells of Undetermined Significance ASC-H: Atypical Squamous Cells High-Grade Cannot Be Excluded

## DISCUSSION

Cervical cancer-related deaths can be significantly reduced by early diagnosis and screening methods (10). Cervical smear results were pathological in 59.3% of the study group and 1.5% of this group were interpreted as HSIL. Cervical smear results determined the probability of having a HSIL or higher lesion in colposcopic biopsy. Colposcopic biopsy result was determined as HSIL and above in 59.1% of those whose cervical smear result was HSIL. High-risk HPV type was found to be positive in 69.7% of the patients who had HPV typing. HPV type was found to be type 16 and/or 18 in 44% of them. HPV types 16 and 18 determined the presence of HSIL and higher lesions in colposcopic biopsy. In the presence of type 16 and/or 18, the probability of HSIL and higher lesion increased from 8.1% to 28%.This was also valid for patients whose smear results were reported as negative. Presence of type 16 and/or 18 in this patient group increased the probability of HSIL and higher lesion more than 3 times. In the study group, it was observed that the smear result was negative in 3 of 10 patients with cervical cancer, and HPV typing was reported as negative in 1 of them.

With the cervical smear test, which is the primary step of screening tests, cervical preinvasive lesions can be diagnosed and treated before invasive cancer develops (11,12). In the population-based screening study of the Turkish Cervical Cancer and Cervical Cytology Research Group, the detection rate of abnormal cervical cytology was found to be approximately 1.8% (13). Tiziano Maggino et al. found this rate to be 2.6% (14). In our study, approximately 60% of the study group had pathologically reported cervical smear results. The reason for this significant difference is that our study group consisted of those who had colposcopy due to pathological smear and/or positive HPV.

Cervical cancer occurs with the persistence of HPV infection (15,16). Since it takes 5-10 years for cervical cancer to develop following infection, this wide time interval provides an opportunity for the detection of persistent HPV infections (17,18). Today, the use of HPV as the primary screening method is accepted (19). The sensitivity of the cervical smear test is less than 50%, and the potential to bypass CIN or invasive cancer is over 35% (20). In addition, HPV-based screening has been shown to be 60-70% more sensitive in detecting invasive cancer than cytology-based screening (21). In our present study, HPV typing was found to be important in the patient group whose cervical smear results were reported as negative. In the presence of HPV 16 and/or 18 in 23.2% of this patient group, HSIL and above lesions were detected in colposcopic biopsy.

Determining the prevalence and types of HPV, which plays a role in the etiology of cervical cancer, is very important from regional management to national-international management. According to a study conducted in our country in 2020 involving approximately 4 million women from all regions, the most common HPV type was found to be type 16 (22). Similarly, in a European-centered study conducted in 14 countries, it was found that HPV type 16 was the most common with 29.8% (23).

Cervical smear pathologies and HPV positivity are associated with pathological results in colposcopic biopsy. In our study, in which the patient group consisted of those who underwent colposcopy due to cervical smear anomaly and/or HPV positivity, it was found that 39.4% of the patients had LSIL (CIN1) and 9.6% of them had HSIL (CIN2-3) in the colposcopic biopsy of those with ASCUS as a result of cervical smear. In the study of Massad et al., in which the general population was screened, it was determined that only 10% of those who received ASCUS as a result of cervical smear had LSIL and 4% had HSIL (24). In the study of Ikesu et al. in a single center with 729 patients, it was observed that the cervical biopsy result of 7.8% of HPV 16 positive and 5.7% of HPV 18 positive patients was reported as CIN 2 (25). In our study, the cervical biopsy result was reported as CIN 2 in 11.8% of HPV 16-18 positive patients.

The strengths of the study are the high volume of the study group, colposcopies performed by gyneco-oncologists, and the presence of experienced gynecopathologists. Its retrospective nature is the most important limitation of the study. In addition, the fact that HPV typing was not performed on every patient is another limitation of the study.

In conclusion, cervical smear and especially HPV typing are determinative in the identification of HSIL and above lesions. In the presence of HPV 16 and/or 18, approximately one-fourth of those with negative smear results have HSIL and higher lesions. For this reason, it would be appropriate to use co-test for screening cervical pathologies instead of cervical smear alone.

**Conflict of Interest**

The authors declared no conflict of interest.

## REFERENCES

**1.**Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

**2.**Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-9.

**3.**de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-56.

**4.**Rodríguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst. 2008 Apr 2;100(7):513-7.

**5.**Castle PE, Fetterman B, Akhtar I, Husain M, Gold MA, Guido R, et al. Age-appropriate use of human papillomavirus vaccines in the U.S. Gynecol Oncol. 2009 Aug;114(2):365-9.

**6.**Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol. 2013 Apr;121(4):829-846.
**7.**Nayar R, Goulart RA, Tiscornia-Wasserman PG, Davey DD. Primary human papillomavirus screening for cervical cancer in the United States-US Food and Drug Administration approval, clinical trials, and where we are today. Cancer Cytopathol. 2014 Oct;122(10):720-9.
**8.**Altun E, Usta A, Bülbül ÇB, Turan G. HPV-DNA Alt Tiplerinin Smear ve Kolposkopik Biyopsi Sonuçlarının Korelasyonunun Değerlendirilmesi. Van Tıp Derg. 2018;25:472-76.
**9.**Çoban Ö, Durukan H, DİLEK UK, Doruk A, Dilek S. Determination of Recurrent/Residual CIN-II and CIN-III After Leep, Cytology or HPV-DNA? Zeynep Kamil Tıp Bülteni.47(4):101-105.
**10.**Sopracordevole F, Cadorin L, Muffato G, De Benetti L, Parin A. Papanicolau smear chances to be diagnostic for cervical squamous intraepithelial lesions (SIL) with or without detectable HPV DNA at in situ hybridization analysis. Eur J Gynaecol Oncol. 1993;14(4):336-8.
**11.**Erdoğdu İH. Moleküler Hpv Uygulanan Olgularda Hpv Sonuçları ile Patolojik Materyallerin Karşılaştırılması. Dicle Tıp Dergisi. 2019;46(1):167-172.
**12.**Koçarslan S, Altunbas BE, Güldür ME, Camuzcuoglu A, Bitiren M. Servikal Smear Sitolojisi ile Servikal Biyopsilerin Sitohistolojik Korelasyonu/Cytohistorical Correlation of Cervical Smear Cytology and Cervical Biopsies. Türkiye Klinikleri Tip Bilimleri Dergisi. 2014;34(1):65.
**13.**Prevalence of cervical cytological abnormalities in Turkey. Int J Gynaecol Obstet. 2009 Sep;106(3):206-9.
**14.**Maggino T, Sciarrone R, Murer B, Dei Rossi MR, Fedato C, Maran M, et al. Screening women for cervical cancer carcinoma with a HPV mRNA test: first results from the Venice pilot program. Br J Cancer. 2016 Aug 23;115(5):525-32.
**15.**Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PLoS One. 2010 Mar 9;5(3):e9584.
**16.**Wright TC, Jr., Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol. 2012 Jan;206(1):46.e1-46.e11.
**17.**Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. World J Clin Oncol. 2015 Dec 10;6(6):281-90.
**18.**Lee S, Kim JW, Hong JH, Song JY, Lee JK, Kim IS, et al. Clinical significance of HPV DNA cotesting in Korean women with ASCUS or ASC-H. Diagn Cytopathol. 2014 Dec;42(12):1058-62.
**19.**Tracht J, Wrenn A, Eltoum IE. Primary HPV testing verification: A retrospective ad-hoc analysis of screening algorithms on women doubly tested for cytology and HPV. Diagn Cytopathol. 2017 Jul;45(7):580-586.
**20.**ACOG Practice Bulletin No. 99: management of abnormal cervical cytology and histology. Obstet Gynecol. 2008 Dec;112(6):1419-1444.
**21.**Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014 Feb 8;383(9916):524-32.
**22.**Gultekin M, Dundar S, Keskinkilic B, Turkyilmaz M, Ozgul N, Yuce K, et al. How to triage HPV positive cases: Results of four million females. Gynecologic oncology. 2020;158(1):105-111.
**23.**De Vuyst H, Clifford G, Li N, Franceschi S. HPV infection in Europe. Eur J Cancer. 2009 Oct;45(15):2632-9.
**24.**Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. Gynecol Oncol. 2001 Sep;82(3):516-22.
**25.**Ikesu R, Taguchi A, Hara K, Kawana K, Tsuruga T, Tomio J, et al. Prognosis of high-risk human papillomavirus-related cervical lesions: A hidden Markov model analysis of a single-center cohort in Japan. Cancer Med. 2021 Dec 17.