İSTANBUL ÜNİVERSİTESİ YAYINEVİ

ARAŞTIRMA / RESEARCH
DOI: 10.26650/IUITFD.2018.0026
İst Tıp Fak Derg 2019 / J Ist Faculty Med 2019

COLPOSCOPIC EXAMINATION IN CYTOLOGY NEGATIVE WOMEN WHO TESTED POSITIVE FOR NON-16/18 HPV TYPES

HPV TİP 16 VE 18 DIŞINDA POZİTİF, SMEAR SONUCU NORMAL HASTALARIN KOLPOSKOPİK İNCELENMESİ

Ramazan DENİZLİ[1], Önder SAKİN[2], Ali Doğukan ANĞIN[2], Muzaffer Seyhan ÇIKMAN[2], Zehra Meltem PİRİMOĞLU[2]

[1]Arhavi State Hospital, Department of Obstetrics and Gynecology, Artvin, Turkey
[2]Istanbul Kartal Dr. Lütfi Kırdar Education and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey

ORCID IDs of the authors: R.D. 0000-0003-1128-7169; Ö.S. 0000-0001-6036-9975; A.D.A. 0000-0003-1954-8546; M.S.C. 0000-0003-2485-568X; Z.M.P. 0000-0002-4660-3267

Cite this article as: Denizli R, Sakin O, Angin AD, Cikman MS, Pirimoglu ZM. Colposcopic examination in cytology negative women who tested positive for non-16/18 HPV types. J Ist Faculty Med 2019;82(4):212-8. doi: 10.26650/IUITFD.2018.0026

ABSTRACT

Objective: To assess the colposcopic examination findings and biopsy results in women who tested positive for oncogenic Human Papilloma Virus (HPV) types other than HPV-16 and 18 while having otherwise normal Pap test results.

Material and Method: This paper analyzes the results from a total of 300 women who tested positive for non-16/18 HPV types but had otherwise normal Pap test and underwent a colposcopic examination in our hospital between January 2017 and December 2017. The study subjects presented with postcoital bleeding, had a family history of cancer or exhibited macroscopic examination findings which were suspected to be malign. A co-test was scheduled one year later for 39 patients (13%) who had no lesions suspected of malignancy and a colposcopy-guided tissue sample was performed on 261 patients.

Results: Histological examination results included inflammation (in 186 patients [62%]), CIN 1 (in 61 patients [20.33%]), CIN 2 (in 9 patients [3%], CIN 3 (in 3 patients [1%]) and cervical cancer (in 2 patients [%0.67]).

Conclusion: One should keep in mind that a diagnosis of CIN 2 or more severe lesions or even cervical cancer can be made using a colposcopy-guided biopsy in women who test positive for non 16/18 HPV types but have otherwise normal Pap smear test.

Keywords: Human papilloma virus (HPV), diagnosis, screening, colposcopy

ÖZET

Amaç: Human Papilloma Virüs (HPV) tip 16 ve 18 dışında pozitifliği olup, smear sonucu normal olan hastaların kolposkopik muayene ve biyopsi sonuçlarını incelemek

Gereç ve Yöntem: Çalışmamızda smear sonucu normal, ancak HPV tip 16-18 dışında pozitifliği olan ve Ocak 2017- Aralık 2017 tarihleri arasında hastanemizde kolposkopi yapılan 300 hasta incelendi. Hastalarımızın genel olarak kolposkopi endikasyonu postkoital kanama, ailede jinekolojik malignite öyküsü ve makroskopik şüpheli lezyon bulunması idi. Kolposkopi sırasında şüpheli lezyonu olmayan 39 hastaya (% 13) bir yıl sonra ko-test için kontrole çağrılırken, 261 hastaya kolposkopi kılavuzlu doku örneklemesi yapıldı.

Bulgular: Histolojik inceleme sonuçları 186 hastada (%62) inflamasyon, 61 hastada (%20,33) CIN 1, 9 hastada (%3) CIN 2, 3 hastada (%1) CIN 3 ve 2 hastada (%0,67) servikal kanser olarak rapor edilmiştir.

Sonuç: HPV tip 16-18 dışında pozitifliği olup smear sonucu normal olan hastalarda CIN 2 ve üstü lezyon, hatta kanser teşhisi konulabileceği unutulmamalıdır.

Anahtar Kelimeler: Human papilloma virus (HPV), Smear tabakası, uterin servikal displazi, serviks kanseri, kolposkopi

Corresponding author/İletişim kurulacak yazar: dr.ramazn@hotmail.com

Submitted/Başvuru: 19.11.2018 • **Revision Requested/Revizyon Talebi:** 12.03.2019 •
Last Revision Received/Son Revizyon: 16.03.2019 • **Accepted/Kabul:** 26.03.2019 • **Published Online/Online Yayın:** 19.07.2019

INTRODUCTION

The use of Human papillomavirus (HPV) tests in cervical cancer screening is subject to ongoing debates and investigations. A number of countries use HPV testing alone for cervical cancer screening, while other countries currently use cytology-based screening along with HPV testing for cervical cancer screening (1-3).

A HPV test is considered safer than cervical cytology test in cervical cancer screening. Regular screening for high-risk HPV types has been reported to be 60 to 70% more effective in preventing cervical cancer, in comparison to cytology-based screening (4, 5).

HPV testing is more effective than cytology-based screening in early detection of high-grade cervical intraepithelial neoplasia (CIN) and provides a more significant reduction in the incidence of cervical cancer (5-8).

The sensitivity of cytology-based screening to detect CIN 2 and 3 is 65% while this rate increases to 94% in HPV testing (9, 10).

However, the specificity of HPV testing to detect CIN-2+ lesions is 2 to 5 % lower than the cytology test (11, 12). This fact cannot be ignored and therefore, currently co-testing is a widely accepted approach worldwide.

"Cytology negative-non-16/18 high risk HPV positive" results are the most prevalent results reported with co-testing (9, 10).

The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends direct referral to colposcopy in HPV positive patients with abnormal cytology, regardless of the type of HPV. A direct referral to colposcopy is also recommended for women who test positive for HPV type16/18, even in women with negative cytology. However repeat cotesting one year later is recommended, if high-risk non 16/18 oncogenic HPV types are detected (13-15). This recommendation is mainly based on the potentially transient nature of HPV infections and the possibility of spontaneous regression (16).

Currently, HPV types 16 and 18 together account for about 70% of cervical cancers (15). A direct referral to colposcopy is an established approach if HPV types16 and 18 are detected. However, research investigating the significance, follow-up, and management of other high-risk oncogenic HPV types is still in progress (1-3).

Thirty two out of 60 patients who developed cervical cancer despite a negative cytology had adenocarcinomas. Furthermore, it was noted that cytology negative women might develop adenocarcinoma as Pap smears were less effective in detecting adonocarcinoma precursors (16, 17).

It is certain that direct referrals of all HPV positive women to a colposcopic examination would be associated with increased medical costs as well as discomfort from the patient's perfective (4). Furthermore, this might double biopsy rates (18). While rapid advances in HPV screening are evident, the direct colposcopy referral option should be considered with caution. As new programs and algorithms are being developed, considerable uncertainty remains with regard to the screening frequency of HPV positive women, how to approach women positive for non 16/18 HPV types and whether HPV counts are significant.

Based on this knowledge, we aimed to analyze our results from colposcopy-guided biopsies in cytology negative – non 16/18 high risk HPV positive women.

MATERIALS AND METHODS

Women who had tested positive for non 16/18 HPV types but had otherwise normal Pap test results, were referred to our hospital between January 2017 and December 2017. They underwent a colposcopic examination in the case of a history of postcoital bleeding, a family history of cancer or if macroscopic examination found suspected malignancy. Patients had no history of previously known cervical dysplasia. Patients whose colposcopy examination was normal and patients without cervical sampling were excluded. A repeat co-test was scheduled 1 year later in patients with normal colposcopy without suspicious lesions. If a suspicious lesion was detected during the colposcopy, tissue sampling was performed, and the treatment management was planned based on histological examination results. We determined that 300 women were appropriate for our study and to be explored retrospectively. Approval was obtained from the Kartal education and research hospital ethics committee for the study.

On the basis of the national HPV screening program conducted in our country, women aged 30 to 64 undergo HPV testing with the next screening test being scheduled for 5 years later in those who test negative for HPV, while HPV genotypes are identified and cytology-based screening is performed on those who test positive for HPV.

HPV screening includes 14 high-risk HPV types. Twelve high-risk HPV types including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 are also screened, in addition to HPV types 16 and 18.

Since the average age of the menopause is 45-47 years in our country, we have divided the patients into two groups under the age of 45 and over 45 years (19). If the HPV test was positive for non 16/18 HPV types, then a further stratification was performed based on the number of e HPV types detected in the samples: patients who tested positive for one HPV type and patients who tested positive for multiple HPV types. Patients who tested positive

for multiple HPV types were excluded from the study if they tested positive for HPV type16/18.

Patients were divided into 5 categories based on cervical biopsy and endocervical canal curettage (ECC): normal, inflammation, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3 and cervical cancer.

The cervical biopsy, endocervical canal curettage and the maximum dysplasia results were evaluated. The maximum dysplasia result was based on the assessment of the outcome of the patient with the highest degree of dysplasia from the cervix or ECC biopsies.

RESULTS

163 patients (54.33%) were under 45 years of age and 137 patients (45.67%) were over 45 years of age. 229 (76.33%) patients tested positive for a single HPV type while 71 (23. 67%) patients tested positive for multiple HPV types.

The demographic characteristics of study subjects are shown in Table 1.

Comparisons between the age groups in the number of HPV types detected, the cervical biopsy (BX) results and the ECC results, and the maximum dysplasia results revealed that there were no statistically significant differences between the two age groups in the number of HPV types detected, biopsy (BX) results, ECC results and the maximum dysplasia results ($p>0.05$ for all) (Table 2).

Comparisons between the group which tested positive for one HPV type and the group which tested positive for multiple HPV types regarding BX, ECC and maximum dysplasia results revealed a significant association between ECC results and the number of positive HPV types. The rate of CIN 1 results in the ECC assessments was significantly lower in the group which tested positive for one HPV type (2.62%) than the group which tested positive for multiple HPV types (8.45%). The rate of inflammation

Table 1: Demographic characteristics of the patients

		n	%
Age	**Under 45 years of age**	163	(54.33)
	Over 45 years of age	137	(45.67)
Number of HPV-types detected	**One (1)**	229	(76.33)
	Multiple	71	(23.67)
Biopsy results	**Normal**	65	(21.67)
	Inflammation	165	(55.00)
	CIN 1	56	(18.67)
	CIN 2	9	(3.00)
	CIN 3	3	(1.00)
	Cancer	2	(.67)
Endocervical canal curettage	**Normal**	177	(59.00)
	Inflammation	109	(36.33)
	CIN 1	12	(4.00)
	CIN 2	0	(.00)
	CIN 3	2	(.67)
	Cancer	0	(.00)
Maximum dysplasia results	**Normal**	39	(13.00)
	Inflammation	186	(62.00)
	CIN 1	61	(20.33)
	CIN 2	9	(3.00)
	CIN 3	3	(1.00)
	Cancer	2	(0.67)

Table 2: The distribution of number of HPV types, cervical biopsy results, endocervical canal curettage and maximum dysplasia results in the age groups

		Under 45 years of age		Over 45 years of age		p
		n	%	n	%	
Number of HPV-types detected	**One (1)**	123	(75.46)	106	(77.37)	0.698
	Multiple	40	(24.54)	31	(22.63)	
Biopsy results	**Normal**	31	(19.02)	34	(24.82)	0.133
	Inflammation	85	(52.15)	80	(58.39)	
	CIN 1	36	(22.09)	20	(14.60)	
	CIN 2	8	(4.91)	1	(.73)	
	CIN 3	2	(1.23)	1	(.73)	
	Cancer	1	(.61)	1	(.73)	
Endocervical canal curettage	**Normal**	95	(58.28)	82	(59.85)	0,168
	Inflammation	64	(39.26)	45	(32.85)	
	CIN 1	3	(1.84)	9	(6.57)	
	CIN 3	1	(.61)	1	(.73)	
Maximum dysplasia results	**Normal**	20	(12.27)	19	(13.87)	0.198
	Inflammation	94	(57.67)	92	(67.15)	
	CIN 1	38	(23.31)	23	(16.79)	
	CIN 2	8	(4.91)	1	(.73)	
	CIN 3	2	(1.23)	1	(.73)	
	Cancer	1	(.61)	1	(.73)	

in the ECC assessments was higher in the group which tested positive for one HPV type (39.74%) than the group which tested positive for multiple HPV types (25.35%) (p:0,029). No statistically significant associations were found regarding the number of positive HPV types and age, BX or results (p>0.05 for all) (Table 3).

Over the course of 1 year, a colposcopic examination was performed on 300 women who had been recommended to undergo a cotest, based on the results of the HPV screening program. Based on the colposcopic examination results, 39 patients (13%) who had no lesions suspected of malignancy were advised to have a repeat cotest in one year and a colposcopy-guided tissue sample was performed on 261 patients. The histological examination results were: inflammation in 186 patients (62%), CIN 1 in 61 patients (20.33%), CIN 2 in 9 patients (3%), CIN 3 in 3 patients (1%) and cervical cancer in 2 patients (%0.67). Fourteen patients who had a biopsy result indicating CIN 2 or more severe lesions received further treatment.

DISCUSSION

Non 16/18 HPV types have an important place in HPV screening programs. In the assessment of the colposcopic biopsy results from 300 patients who tested positive for oncogenic non 16/18 HPV types, no significant associations were found in the colposcopic biopsy results between the age groups and in the number of HPV types detected.

False negative cervical cytology leads to a decrease in the success rates in cervical cancer, notably in cases of adenocarcinoma. Two cases of cervical cancer were detected in this study and this rate is clinically, (but not statistically) significant. It was possible to make these two diagnoses of cervical cancer thanks to the colposcopic examination performed directly on those women with negative cytology who tested positive for non 16/18 HPV.

Whether a colposcopy should be directly preferred or not is a matter of debate worldwide. Currently a routine colposcopic examination is not recommended for all HPV

Table 3: Intergroup comparisons of cervical biopsy results, endocervical canal curettage and maximum dysplasia results based on the number of HPV types detected

		Number of HPV-types detected				
		One		Multiple		p
		n	%	n	%	
Age	**Under 45 years of age**	123	(53.71)	40	(56.34)	0.698
	Over 45 years of age	106	(46.29)	31	(43.66)	
Biopsy results	**Normal**	53	(23.14)	12	(16.90)	0.120
	Inflammation	126	(55.02)	39	(54.93)	
	CIN 1	37	(16.16)	19	(26.76)	
	CIN 2	9	(3.93)	0	(.00)	
	CIN 3	3	(1.31)	0	(.00)	
	Cancer	1	(.44)	1	(1.41)	
Endocervical canal curettage	**Normal**	131	(57.21)	46	(64,79)	0.029
	Inflammation	91	(39.74)	18	(25.35)	
	CIN 1	6	(2.62)	6	(8.45)	
	CIN 3	1	(.44)	1	(1.41)	
Maximum dysplasia results	**Normal**	34	(14.85)	5	(7.04)	0.079
	Inflammation	141	(61.57)	45	(63.38)	
	CIN 1	41	(17.90)	20	(28.17)	
	CIN 2	9	(3.93)	0	(.00)	
	CIN 3	3	(1.31)	0	(.00)	
	Cancer	1	(.44)	1	(1.41)	

positive patients. The most preferred approaches are those recommended in the ASCCP guidelines. Certainly, costs, labor loses, the excessive number of interventions, and the excessive number of biopsies need to be questioned in terms of cost effectiveness.

The assessment of patients over 45 years of age who tested positive for multiple HPV types revealed that there were no statistically significant differences between the age groups in the rate of patients who tested positive for multiple HPV types. Considering the concerns of clinicians for positive test results indicating the presence of multiple HPV types and consequent questioning of a need for colposcopy, we also assessed any associations between the number of HPV types detected and the colposcopic biopsy results. Significant differences were found between the ECC result categories regarding the number of positive HPV types. However, no significant differences were found between the group which tested positive for a single HPV type and the group which tested positive for multiple HPV types in the rate of CIN 2+ lesions. We conclude that further studies with larger study samples are required to assess any relationships between these categories.

Some studies show that 14-15% of CIN II + lesions tested negative for HPV (8, 21, 22). According to these results, it is not correct to claim that the HPV test is both safe and sufficient. Therefore, in routine practice, cytology and HPV are recommended and applied together.

The aim of this study was to evaluate the differences in high-oncogenic risk HPV types, to evaluate their compatibility with the cervicovaginal smear, to evaluate biopsy indications in clinical practice and to evaluate their relationship through colposcopic examination and biopsy results.

There are some limitations in this research. The risk factors of the patients are not fully known, and, furthermore, the biopsy results and long-term follow-up of the patients are not included in our records.

CONCLUSION

One should keep in mind that CIN 2+ lesions or even cervical cancer can be detected by colposcopy-guided biopsy in women who test positive for non 16/18 HPV types but have an otherwise normal Pap smear test. In order to avoid overlooking a potential malignancy in these patients, further assessment including a risk analysis based on the medical history, a repeat macroscopic examination and acetic acid application, colposcopy and colposcopy-guided biopsy should be performed before scheduling a co-test one year later.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Data Acquisition- A.D.A., M.S.Ç.; Data Analysis/Interpretation- R.D., Ö.S., Z.M.P.; Drafting Manuscript- R.D., Ö.S.; Critical Revision of Manuscript- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Final Approval and Accountability- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Technical or Material Support- R.D., Ö.S., A.D.A., M.S.Ç.; Supervision- Z.M.P.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı alınmıştır.

Bilgilendirilmiş Onam: Retrospektif bir çalışma olduğundan bilgilendirilmiş onam alınmamıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Veri Toplama- A.D.A., M.S.Ç.; Veri Analizi/Yorumlama- R.D., Ö.S., Z.M.P.; Yazı Taslağı- R.D., Ö.S.; İçeriğin Eleştirel İncelemesi- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Son Onay ve Sorumluluk- R.D., Ö.S., A.D.A., M.S.Ç., Z.M.P.; Malzeme ve Teknik Destek- R.D., Ö.S., A.D.A., M.S.Ç.; Süpervizyon- Z.M.P.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

REFERENCES

1. Basu P, Meheus F, Chami Y, Hariprasad R, Zhao F, Sankaranarayanan R. Management algorithms for cervical cancer screening and precancer treatment for resource-limited settings. Int J Gynaecol Obstet 2017;138(Suppl 1): 26-32. [CrossRef]
2. 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;45(7):580-6. [CrossRef]
3. MarianiL , Igidbashian S, Sandri MT, Vici P, Landoni F. The clinical implementation of primary HPV screening. Int J Gynaecol Obstet 2017;136(3):266-71. [CrossRef]
4. Tshomo U, Franceschi S, Tshokey T, Tobgay T, Baussano I, Tenet V, et al. Evaluation of cytology versus human papillomavirus-based cervical cancer screening algorithms in Bhutan. Oncotarget 2017;8(42):72438-46. [CrossRef]
5. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomized controlled trials. Lancet 2014;383(9916):524-32. [CrossRef]
6. Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357(16):1589-97. [CrossRef]
7. Horn J, Denecke A, Luyten A, Rothe B, Reinecke-Lüthge A, Mikolajczyk R, et al. Reduction of cervical cancer incidence within a primary HPV screening pilot project (WOLPHSCREEN) in Wolfsburg, Germany. Br J Cancer. 2019 Apr 16. [CrossRef]
8. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomized controlled trial. Lancet Oncol. 2012;13(1):78-88. [CrossRef]
9. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer 2006;119(5):1095-101. [CrossRef]
10. Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 2012;30(Suppl 5):F88-99. [CrossRef]
11. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. New Technologies for Cervical Cancer Screening Working Group. Results at recruitment from a randomized controlled trial comparing human papilloma virus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst 2008;100(7):492-501. [CrossRef]
12. Cox JT, Schiffman M, Solomon D; ASCUS-LSIL Triage Study (ALTS) Group. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. Am J Obstet Gynecol 2003;188(6):1406-12. [CrossRef]
13. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol 2013;121(4):829-46. [CrossRef]
14. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Désy M, et al. Epidemiology of acquisition and clearance of cervical human papilloma virus infection in women from a high-risk area for cervical cancer. J Infect Dis 1999;180(5):1415-23. [CrossRef]

15. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papilloma virus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 2011;12(7):663-72. [CrossRef]
16. Karaca İ, Öztürk M, Comba C, Demirayak G, Alay İ, Erdoğan VŞ, et al. Immediate biopsy of cervical cytology-negative and non-HPV-16/18 oncogenic types positive patients. Diagn Cytopathol 2018;46(4):326-30. [CrossRef]
17. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. J Low Genit Tract Dis 2012;(16(3):175-204. [CrossRef]
18. Ronco G, Zappa M, Franceschi S, Tunesi S, Caprioglio A, Confortini M, et al. Italian HPV Survey Working Group. Impact of variations in triage cytology interpretation on human papillomavirus-based cervical screening and implications for screening algorithms. Eur J Cancer 2016;68:148-55. [CrossRef]
19. Çelik AS, Pasinlioğlu T. Klimakterik dönemdeki kadınların yaşadıkları menopozal semptomlar ve etkileyen faktörler. Hacettepe Üniversitesi Hemşirelik Fakültesi Dergisi 2014;16-29.
20. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 2009;10(7):672-82. [CrossRef]
21. Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357(16):1589-97. [CrossRef]