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Original Article

Human papillomavirus (HPV) subtypes and their relationships with cervical smear results in cervical cancer screening: a community-based study from the central Anatolia region of Turkey

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Abstract: Objective: Cervical cancer can be diagnosed early by cancer screening programs. The aim of this study was to evaluate the cervical smear test results of healthy women. Methods: We enrolled 94,848 healthy women from 30-65 years of age in whom both HPV typing and a cervical smear test was performed between 2014 and 2017. Results: HPV was detected in 3001 women (3.16%). The mean age was 42 ± 8.94 years old. Positive HPV types were HPV16; HPV16 and multiple infection; HPV31; HPV51; HPV39; HPV52; HPV56; HPV18; HPV68; HPV35; HPV18 and multiple infection; HPV58; HPV45; HPV59; HPV16, HPV18 and multiple infection; HPV16 and 18; and HPV33, in descending order. Cytology results were normal in 63.61%. We also identified atypical squamous cells of undetermined significance in 6.60%, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion in 0.73%, low-grade squamous intraepithelial lesion in 10%, high-grade squamous intraepithelial lesion and atypical glandular cells in 0.53%, and adenocarcinoma in situ in 0.03%. In terms of HPV subtypes, abnormal smear results were divided into an HPV16, HPV18, and multiple infection group (25%), an HPV35 group (23.61%), an HPV 16 and multiple infection group (22%), and an HPV16-only group (21.85%). Most cases of HPV (39.02%) and abnormal cytology (43.04%) were detected between the ages of 30 and 40. Conclusions: This study is remarkable because it is a community-based study and includes a large population of healthy women to detect HPV prevalence, its subtype, and abnormal smear results.

Keywords: Papanicolaou test, human papilloma virus, primary care, screening

Introduction

Cervical cancer is the fourth most common malignant tumor seen in women in the world. Approximately 527,624 women are affected by this tumor each year. The death toll from the disease is estimated to be approximately 265,672 annually [1].

Nearly 87% of cervical cancer deaths occur in underdeveloped countries, where it is the third most common cause of death among women [1-3]. This trend is due to the inadequacy of screening programs in underdeveloped countries [4, 5].

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide [6]. HPV infection is responsible for almost all cervical cancers. Currently, about 79 million men and women are infected with HPV and approximately 14 million will become newly infected each year in the United States (US) [7]. In the US, HPV was detected in nearly 99.7% of cervical cancers, and cervical cancer developed in 11,000 HPV-positive women [7, 8].

There are more than 40 sexually transmitted types of HPV that infect the skin and mucous membranes. In infected individuals, the immune system normally eliminates the virus within two years, but in some individuals, persistent HPV infection causes cervical cancer and genital warts [9]. HPVs are divided into three groups as low, potentially high, and high-risk types. HPV6, HPV11, HPV40, HPV42,

HPV43, HPV44, HPV54, HPV61, HPV70, HPV-72, HPV81, and CP6108 are low risk; HPV26, HPV53, and HPV66 are potentially high risk, and HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68, HPV73, and HPV82 are high-risk types [10].

An HPV infection takes 10-20 years to transform into invasive carcinoma. This long process allows us to capture the disease in the premalignant period when treatment is most effective. Premalignant cervical lesions are asymptomatic and therefore can only be detected by appropriate screening tests. Cervical cancer screening aims to detect high-grade lesions in asymptomatic women, to treat these lesions, and to prevent them from becoming invasive carcinoma [11].

Precancerous lesions can be detected by Papanicolaou (Pap) smear cytologic testing and can be treated early before progression to cancer. Early detection of the disease reduces mortality rates. Patients treated with precancerous lesions have approximately a 100% 5-year survival rate [12, 13].

With the development of screening and treatment programs in the last 30 years worldwide, cervical cancer rates have decreased. The World Health Organization suggests screening programs in developed countries beginning at the age of 30 [14]. For this reason, HPV-DNA testing and concurrent cytology results are being studied in the context of cervical cancer screening programs in women over 30 years of age [15, 16]. According to the National Cervical Screening Program, HPV testing once every five years and Pap smear evaluation in HPV-positive cases is recommended for every woman from 30-65 years of age.

In this study, HPV-DNA tests were performed on healthy women as the first step of health services within the cervical cancer screening program envisaged by the Ministry of Health, and HPV-positive cases were further evaluated by Pap smear.

Materials and methods

In this retrospective study, the screening records of 94,848 healthy women between the ages of 30-65 were analyzed. The study protocol was approved by the Necmettin Erbakan University Ethical Committee and Institutional Review Board (23.11.2017/14567952-050). From 2014-2017, two different samples were obtained for the HPV DNA test and the Pap smear from 94,848 healthy women between the ages of 30-65 by family physicians trained in primary healthcare in our city. Cases who had vaginal bleeding, used suppositories, reported vaginal douching in last 72 hours or had engaged in sexual activity in the last 24 hours, were not included in the screening. Cervical smears were prepared using a cervical brush fixed in 95% alcohol. The second sample was taken with a different brush. The samples obtained for HPV (HPV-DNA specimen collection kits with (Qiagen HC2) and cervical smear samples (with smear containers) were transferred to a laboratory. Genotyping was performed using a CLART kit (Genomica) on women with Hybrid Capture2 (Qiagen), and HPV-positive samples were sent to the National Central HPV Laboratory within the Cancer Early Detection and Education Center of the Ministry of Health. Cervical smear samples of HPV-positive cases were stained with conventional methods and examined under a microscope by a pathologist. Cytological evaluations were reported according to the Bethesda Classification System in the following categories: Normal cells, atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), adenocarcinoma in situ (AIS), and inadequate material.

In this study, the cases were grouped into those with a single HPV infection, HPV16 and HPV18, HPV16 and multiple infections, HPV18 and multiple infections, HPV16, HPV18 and multiple infections and others. The cases were divided into age groups from 30-40, 40-50, 50-60 and 60-65 years.

Age data are presented as the mean ± standard deviation. The results of HPV types and cervical smear results were analyzed as a frequency and percentage. For comparing groups, the χ^2 test or Fisher's exact test were used. *P*-values smaller than 0.05 are considered significant. The data were analyzed with SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Table 1. The relationship between HPV subtypes and smear results

HPV types	Smear results			
	Abnormal n (%)	Normal n (%)	U.M. n (%)	Total n
HPV 16	97 (21.85)	273 (61.49)	74 (16.66)	444
HPV 18	12 (14.12)	55 (64.71)	18 (21.17)	85
HPV 16, 18	1 (10.00)	5 (50.00)	4 (40.00)	10
HPV 16, others	77 (22.00)	211 (60.29)	62 (17.71)	350
HPV 18, others	8 (11.43)	46 (65.71)	16 (22.86)	70
HPV 16, 18, others	4 (25.00)	8 (50.00)	4 (25.00)	16
HPV 31	30 (19.61)	103 (67.32)	20 (13.07)	153
HPV-33	2 (7.41)	20 (74.07)	5 (18.52)	27
HPV-35	17 (23.61)	37 (51.39)	18 (25.00)	72
HPV-39	18 (16.82)	67 (62.62)	22 (20.56)	107
HPV-45	9 (14.75)	41 (67.21)	11 (18.04)	61
HPV-51	19 (13.29)	91 (63.64)	33 (23.07)	143
HPV-52	11 (10.89)	70 (69.31)	20 (19.80)	101
HPV-56	12 (12.90)	62 (66.67)	19 (20.43)	93
HPV-58	14 (20.90)	42 (62.69)	11 (16.41)	67
HPV-59	5 (10.87)	35 (76.09)	6 (13.04)	46
HPV-68	10 (13.70)	52 (71.23)	11 (15.07)	73
Others	207 (19.12)	691 (63.80)	185 (17.08)	1083

HPV = human papillomavirus; U.M. = unsatisfactory material.

Results

Within the screening program, HPV was found in 3,001 out of 94,848 (3.16%) women. The median age of HPV-positive women was 42 ± 8.94 years.

Of the HPV-positive types, 444 (14.8%) were HPV16; 350 (11.66%) were HPV16 and multiple infections; 153 (5%) were HPV31; 143 (4.7%) were HPV51; 107 (3.5%) were HPV39; 101 (3.3%) were HPV52; 93 (3.09%) were HPV56; 85 (2.83%) were HPV18; 73 (2.43%) were HPV68; 72 (2.4%) were HPV35; 70 (2.33%) were HPV18 and multiple infections; 67 (2.2%) were HPV58; 61 (2.03%) were HPV45; 46 (1.5%) were HPV59; 16 (0.53%) were HPV16, HPV18 and multiple infections; 10 (0.33%) were HPV16 and HPV18; and 27 (0.9%) were HPV33. Other types of HPV made up 1083 cases at a rate of 36.08%.

Cytologic abnormalities were found in 553 (18.3%) of HPV-positive cases. The cytology results were determined to be normal in 1909 (63.61%), ASCUS in 198 (6.60%), ASC-H in 22 (0.73%), LSIL in 300 (10%), HSIL in 16 (0.53%), AGC in 16 (0.53%), AIS in 1 (0.03%), and unsatisfactory material in 539 (17.96%).

Abnormal smear results in terms of HPV subtypes were found in 25% of the HPV16, HPV18 and multiple infection group, in 23.61% of the HPV35 group, in 22% of the HPV16 and multiple infection group and in 21.85% of the HPV16 group only (**Table 1**).

In one case with AIS, HPV16 was the single causative factor. Singular HPV16 and the HPV 16 and multiple infection group were responsible for 53% of the cases that resulted in AGC, 75% of HSIL cases, 30.3% of LSIL cases, 32% of ASC-H cases, and 27.8% of ASCUS cases. After HPV16, the HPV35, HPV58 and HPV31 types were determined to be the most prevalent factor in abnormal smear results (**Table 2**).

The most common HPV-positive rates were found in the 30-40 age group in 1171 (39.02%) patients, followed by 1014 (33.79%) in 40-50 year olds, 648 (21.59%) in 50-60 year olds and 168 (5.60%) in 60-65 year olds (**Table 3**).

Abnormal cytology results in terms of age group were seen in 238 (43.04%) people from 30-40 years, 209 (37.79%) patients from 40-50 years, 92 (16.64%) participants from 50-60 years, and 14 (2.53%) people from 60-65 years (**Table 4**).

Discussion

Cervical cancers have a long pre-invasive phase. High-risk HPV genotypes and persistent infections are preventable risk factors in the development of cervical intraepithelial neoplasia and cervical cancer [17, 18].

HPV-DNA testing and Pap smears are effective screening methods for detecting high-risk HPV infection. The detection of pre-invasive lesions by screening methods and appropriate treatment reduces the cervical cancer mortality rate [19, 20]. In Turkey, a global cervical cancer screening program that includes cervical Pap smear testing has been applied by the De-

Table 2. HPV genotype and cervical smear results

HPV types	Cases n (%)	Cervikal smear results							
		Normal n (%)	ASCUS n (%)	ASC-H n (%)	LSIL n (%)	HSIL n (%)	AGC n (%)	AIS n (%)	U.M. n (%)
HPV 16	444 (14.80)	273 (61.49)	23 (5.18)	4 (0.90)	57 (12.84)	8 (1.80)	4 (0.90)	1 (0.23)	74 (16.67)
HPV 18	85 (2.83)	55 (64.71)	7 (8.24)	1 (1.18)	4 (4.71)	0	0	0	18 (21.18)
HPV 16, 18	10 (0.33)	5 (50.00)	1 (10.00)	0	0	0	0	0	4 (40.00)
HPV 16, others	350 (11.66)	211 (60.29)	32 (9.14)	3 (0.86)	34 (9.71)	4 (1.14)	4 (1.14)	0	62 (17.71)
HPV 18, others	70 (2.33)	46 (65.71)	3 (4.29)	1 (1.43)	3 (4.29)	1 (1.43)	0	0	16 (22.86)
HPV 16, 18, others	16 (0.53)	8 (50)	1 (6.25)	0	3 (18.75)	0	0	0	4 (25)
HPV 31	153 (5.00)	103 (67.32)	10 (6.54)	2 (1.31)	17 (11.11)	1 (0.65)	0	0	20 (13.07)
HPV-33	27 (0.90)	20 (74.07)	0	0	2 (7.41)	0	0	0	5 (18.52)
HPV-35	72 (2.40)	37 (51.39)	6 (8.33)	1 (1.39)	9 (12.50)	0	1 (1.39)	0	18 (25)
HPV-39	107 (3.5)	67 (62.62)	7 (6.54)	1 (0.93)	9 (8.41)	0	0	0	22 (20.56)
HPV-45	61 (2.03)	41 (67.21)	5 (8.20)	0	4 (6.56)	0	0	0	11 (18.03)
HPV-51	143 (4.70)	91 (63.64)	11 (7.69)	0	7 (4.90)	0	1 (0.70)	0	33 (23.08)
HPV-52	101 (3.30)	70 (69.31)	4 (3.96)	2 (1.98)	4 (3.96)	0	1 (0.99)	0	20 (19.80)
HPV-56	93 (3.09)	62 (66.67)	5 (5.38)	0	7 (7.53)	0	0	0	19 (20.43)
HPV-58	67 (2.20)	42 (62.69)	5 (7.46)	1 (1.49)	8 (11.94)	0	0	0	11 (16.42)
HPV-59	46 (1.50)	35 (76.09)	1 (2.17)	0	4 (8.70)	0	0	0	6 (13.04)
HPV-68	73 (2.43)	52 (71.23)	7 (9.59)	0	3 (4.11)	0	0	0	11 (15.07)
Others	1,083 (36.08)	691 (63.80)	70 (6.46)	6 (0.55)	125 (11.54)	2 (0.18)	4 (0.37)	0	185 (17.08)

HPV = human papillomavirus; ASCUS = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; AGC = atypical glandular cells; AIS: adenocarcinoma in situ; U.M. = unsatisfactory material.

Table 3. The relationship between HPV subtypes and age groups

HPV types	Age groups				Total (n, %)
	30-40 years old (n, %)	40-50 years old (n, %)	50-60 years old (n, %)	60-65 years old (n, %)	
HPV 16	194 (43.69)	137 (30.86)	100 (22.52)	13 (2.93)	444 (14.8)
HPV 18	35 (41.18)	28 (32.94)	18 (21.18)	4 (4.70)	85 (2.83)
HPV 16, 18	5 (50.00)	2 (20.00)	2 (20.00)	1 (10.00)	10 (0.33)
HPV 16, thers	152 (43.43)	105 (30.00)	66 (18.86)	27 (7.71)	350 (11.66)
HPV 18, others	23 (32.86)	29 (41.43)	16 (22.86)	2 (2.85)	70 (2.33)
HPV 16, 18, others	7 (43.75)	7 (43.75)	2 (12.50)	0	16 (0.53)
HPV 31	74 (48.37)	42 (27.45)	31 (20.26)	6 (3.92)	153 (5.1)
HPV-33	10 (37.04)	8 (29.63)	9 (33.33)	0	27 (0.9)
HPV-35	24 (33.33)	34 (47.22)	12 (16.67)	2 (2.78)	72 (2.4)
HPV-39	45 (42.06)	42 (39.25)	15 (14.02)	5 (4.67)	107 (3.57)
HPV-45	23 (37.70)	29 (47.55)	9 (14.75)	0	61 (2.03)
HPV-51	58 (40.55)	50 (34.97)	30 (20.98)	5 (3.50)	143 (4.77)
HPV-52	47 (46.54)	35 (34.65)	15 (14.85)	4 (3.96)	101 (3.37)
HPV-56	29 (31.18)	28 (30.11)	25 (26.88)	11 (11.83)	93 (3.1)
HPV-58	18 (26.87)	29 (43.28)	14 (20.90)	6 (8.95)	67 (2.23)
HPV-59	15 (32.61)	17 (36.95)	10 (21.74)	4 (8.70)	46 (1.53)
HPV-68	25 (34.25)	29 (39.73)	16 (21.92)	3 (4.10)	73 (2.43)
Others	387 (35.73)	363 (33.52)	258 (23.82)	75 (6.93)	1,083 (36.09)
Total	1,171 (39.02)	1,014 (33.79)	648 (21.59)	168 (5.60)	3,001 (100)

partment of Cancer at the Ministry of Health since 1992 [21].

The global HPV prevalence in cervical cancer patients is 92.4% [22]. In a 2010 study by Bruni

Table 4. Distribution of abnormal smear results according to age groups

Abnormal smear	Age groups				Total (n, %)
	30-40 years old (n, %)	40-50 years old (n, %)	50-60 years old (n, %)	60-65 years old (n, %)	
AGC	6 (37.50)	7 (43.75)	3 (18.75)	0	16 (2.89)
AIS	1 (100)	0	0	0	1 (0.18)
ASC-H	7 (31.82)	10 (45.45)	4 (18.18)	1 (4.55)	22 (3.98)
ASCUS	74 (37.37)	69 (34.85)	47 (23.74)	8 (4.04)	198 (35.8)
HSIL	7 (43.75)	8 (50.00)	1 (6.25)	0	16 (2.89)
LSIL	143 (47.67)	115 (38.33)	37 (12.33)	5 (1.67)	300 (54.25)
Total	238 (43.04)	209 (37.79)	92 (16.64)	14 (2.53)	553

AGC = atypical glandular cells; AIS: adenocarcinoma in situ; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

et al., 1,016,719 cases with normal cytologic results had an HPV prevalence of 11.7%; 24% in Africa, 21.4% in Eastern Europe and 16.1% in Latin America [23].

Studies performed in Turkey have reported varying rates of HPV; some indicate a HPV prevalence from 2-6%, while others claim that it is near the world average [24-28]. In studies from still different regions of Turkey, the HPV rates were reported as 23%, 17.9%, and 12.8% [29-31]. Beyazıt et al. found a HPV prevalence rate of 45.2% in 201 Turkish women from a western region of Turkey [32]. However, the reason for this high rate was that the study was performed in patients who came to the obstetrics and gynecology polyclinic for gynecologic complaints. These authors suggested that a cervical cancer-screening program should include local results to better determine the rate in Turkey.

In our study, HPV was detected at a rate of 3.16%. This rate is more realistic as it shows the community-based prevalence in healthy women. In addition, the social life style, religious beliefs, and conservative cultural life in our city are factors that can affect the HPV prevalence.

Bruni et al. found the five most common HPV types to be HPV16, HPV18, HPV31, HPV52 and HPV58. HPV16 is the most common type around the world. The second most common type is HPV18 in western countries and HPV58 in Asia [23]. Many studies have attempted to identify the most prevalent HPV types in Turkey. Dursun et al. local study determined the most common types as HPV16, HPV06 and HPV18, while Demir et al. implicated HPV16, HPV06, HPV45, HPV62, and HPV53. Bayram et al. found HPV18, HPV16, HPV06, HPV59, HPV54, and HPV58 to be most prevalent and Beyazıt et al. identified HPV16, HPV58, HPV06, HPV31, HPV 33, and HPV11 [29-32]. In the current study, the most common HPV types were HPV16, HPV31, HPV51, HPV39, HPV52, HPV56, HPV18, HPV68 and HPV35. Therefore, HPV16 appears to be the most common in our study as well as in the world and in Turkey. However, contrary to the literature, our HPV18 prevalence was almost last, which indicates that subtypes differ from region to region.

In our study, the most common subtypes to produce cytologic abnormalities were the HPV16, HPV18 and multiple infection group; HPV35, the HPV16 and multiple infection group; and only HPV16. This result indicates that HPV16 is most responsible for cytologic abnormalities, especially in high-grade lesions, such as HSIL. HPV16 was also responsible for the single cases of AIS and AGC. This finding was consistent with the literature. Dursun et al. found HPV16, HPV06 and HPV18 subtypes most frequently in abnormal cytology samples, while 6.6% of normal cytology samples had a coinfection of both HPV16 and HPV18 [29]. Beyazıt et al. detected HPV16 and HPV58 the most in abnormal cytology [32]. In our study the rates of cytologic abnormalities were increased in HPV18 with HPV16 coinfection. In addition, HPV35 was remarkably the second most common cytologic abnormality, and 61.49% of cases with normal cytologic results were infected with HPV16. Arora et al. argued that if high-risk HPV is present in cases with negative cytol-

ogy, these cases should be followed more closely than HPV-negative cases, even if there are no visible lesions [33]. Considering the high positivity rates of high-risk HPV in negative cytology samples in our study, it is vital that screening programs are carried out properly in our country and the screening intervals in these cases should also be re-examined.

It has been reported in the literature that the HPV prevalence peaks at two separate times at younger and older ages [34, 35]. Age-related sexual behavior and age and menopause-related changes in the cervicovaginal epithelium were responsible for the increases in HPV at advanced ages. In addition, it is thought that there may be a reactivation of latent HPV infections as a result of age-dependent immune suppression [35]. In Turkey, HPV rates decrease with increasing age. In different studies, authors have found that the HPV prevalence was the highest under 30 years of age and the lowest over 54 years of age [29, 30]. In our study, the HPV prevalence was reduced with increasing age, which is consistent with other studies. The HPV frequency and associated abnormal cytology results were found in the lowest age group from 30-40 years of age. The rates continued to decline with every 10 years of age. This result was likely due to the lack of sexual partners in Turkey, which has resulted in low infection rates at young ages and a low level of virus persistence.

The strength of this study is the fact that the research is not hospital-based and involves healthy individuals who do not have gynecologic complaints, so the prevalence of HPV detected in our study is more realistic and noteworthy.

A limitation of this study was that it demonstrates the results of only one city from Turkey, which does not allow generalization of the results to the whole population.

Conclusion

Cervical smear tests in HPV-DNA positive women increase the rates of cervical intraepithelial lesion detection. High-risk HPV types have great value in identifying cervical intraepithelial neoplasia and subsequent cervical cancer development. National and regional screening programs contribute to the reduction of cervical cancer rates with the detection of cervical lesions in pre-invasive stages before cervical lesions are converted to invasive cancers. HPV prevalence and genotypes show differences among countries and even within different regions of the same country. Our study is remarkable because it was a community-based study that included a large population of healthy women to detect the prevalence of HPV and its subtypes and their relationship with abnormal Pap smear results.

Disclosure of conflict of interest

None.

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References

[1] Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human papillomavirus and relateddiseases in the world. http://www.hpvcentre.net/statistics/reports/BRA.pdf. Accessed 20 December 2018.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-86.

[3] IARC TIAfRoC. World Cancer Research Fund International; 2018.

[4] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.

[5] Wittet S, Tsu V. Cervical cancer prevention and the millennium development goals. Bull World Health Organ 2008; 86: 488-90.

[6] Zhang L, Bi Q, Deng H, Xu J, Chen J, Zhang M, Mu X. Human papillomavirus infections among women with cervical lesions and cervical cancer in Eastern China: genotype-specific prevalence and attribution. BMC Infect Dis 2017; 17: 107.

[7] Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among adolescents aged 13-17 years--United States, 2012. MMWR Morb Mortal Wkly Rep 2013; 62: 685-93.

[8] McCormack PL. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vac-

cine (gardasil(®)): a review of its use in the prevention of premalignant anogenital lesions, cervical and anal cancers, and genital warts. Drugs 2014; 74: 1253-83.
[9] CDC. 2018. https://www.cdc.gov/hpv/parents/whatishpv.html
[10] Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003; 348: 518-27.
[11] Basu P, Mittal S, Bhadra Vale D, Chami Kharaji Y. Secondary prevention of cervical cancer. Best Pract Res Clin Obstet Gynaecol 2018; 47: 73-85.
[12] ACS. Key statistics for cervical cancer. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html. Accessed 20 December 2018.
[13] ACS. Cancer facts and figures 2018. Atlanta, Ga: American Cancer Society; 2018.
[14] WHO Guidelines Approved by the Guidelines Review Committee. Comprehensive cervical cancer control: a guide to essential practice. Geneva: World Health OrganizationCopyright (c) World Health Organization 2014.
[15] Boulet GA, Horvath CA, Berghmans S, Bogers J. Human papillomavirus in cervical cancer screening: important role as biomarker. Cancer Epidemiol Biomarkers Prev 2008; 17: 810-7.
[16] Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol 2011; 12: 880-90.
[17] zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst 2000; 92: 690-8.
[18] Millikan RC. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. J Natl Cancer Inst 1994; 86: 392-3.
[19] Sigurdsson K, Sigvaldason H. Longitudinal trends in cervical cytological lesions and the effect of risk factors. A 30-year overview. Acta Obstet Gynecol Scand 2006; 85: 350-8.
[20] Celik C, Gezginc K, Toy H, Findik S, Yilmaz O. A comparison of liquid-based cytology with conventional cytology. Int J Gynaecol Obstet 2008; 100: 163-6.
[21] Acikgoz A, Ergor G. Cervical cancer risk levels in Turkey and compliance to the national cervical cancer screening standard. Asian Pac J Cancer Prev 2011; 12: 923-7.
[22] Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. Int J Cancer 2011; 128: 927-35.
[23] Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010; 202: 1789-99.
[24] Inal MM, Kose S, Yildirim Y, Ozdemir Y, Toz E, Ertopcu K, Ozelmas I, Tinar S. The relationship between human papillomavirus infection and cervical intraepithelial neoplasia in Turkish women. Int J Gynecol Cancer 2007; 17: 1266-70.
[25] Ozcelik B, Serin IS, Gokahmetoglu S, Basbug M, Erez R. Human papillomavirus frequency of women at low risk of developing cervical cancer: a preliminary study from a Turkish university hospital. Eur J Gynaecol Oncol 2003; 24: 157-9.
[26] Tuncer S, Başaran M, Ustaçelebi Ş, Mocan-Kuzey G. High-risk Human Papilloma Virus (HPV) infection determined by Hybrid Capture II assay in a Turkish university hospital outpatient clinic. Gynecol Obstet Reprod Med 2006; 12.
[27] Safi Z, Demirezen S, Beksac MS, Kuzey GM, Kocagoz T, Ustaçelebi S, Hascelik G, Cakar AN. İnsan Papilloma Virusunun (IPV) Polimeraz Zincir Reaksiyonu Tekniği İle Servikal Ve Vajinal Akıntı Örneklerinde Saptanması. MN-Klinik Bilimler & Doktor 2002; 8.
[28] Seçkin S, Aksoy F, Yıldırım M. Servikal Smearlerde HPV İnfeksiyonu Görülme İndisansı. Ankara Numune Eğitim ve Araştırma Hastanesi Tıp Dergisi 1996; 36.
[29] Dursun P, Senger SS, Arslan H, Kuscu E, Ayhan A. Human papillomavirus (HPV) prevalence and types among Turkish women at a gynecology outpatient unit. BMC Infect Dis 2009; 9: 191.
[30] Demir ET, Ceyhan M, Simsek M, Gunduz T, Arlier S, Aytac R, Aycan AE, Gurbuz V. The prevalence of different HPV types in Turkish women with a normal Pap smear. J Med Virol 2012; 84: 1242-7.
[31] Bayram A, Erkilic S, Balat O, Eksi F, Ugur MG, Ozturk E, Kaya G. Prevalence and genotype distribution of human papillomavirus in non-neoplastic cervical tissue lesion: cervical erosion. J Med Virol 2011; 83: 1997-2003.
[32] Beyazit F, Silan F, Gencer M, Aydin B, Paksoy B, Unsal MA, Ozdemir O. The prevelance of human papillomavirus (HPV) genotypes detected by PCR in women with normal and abnormal cervico-vaginal cytology. Ginekol Pol 2018; 89: 62-67.

[33] Arora R, Kumar A, Prusty BK, Kailash U, Batra S, Das BC. Prevalence of high-risk human papillomavirus (HR-HPV) types 16 and 18 in healthy women with cytologically negative Pap smear. Eur J Obstet Gynecol Reprod Biol 2005; 121: 104-9.

[34] Pham TH, Nguyen TH, Herrero R, Vaccarella S, Smith JS, Nguyen Thuy TT, Nguyen HN, Nguyen BD, Ashley R, Snijders PJ, Meijer CJ, Muñoz N, Parkin DM, Franceschi S. Human papillomavirus infection among women in South and North Vietnam. Int J Cancer 2003; 104: 213-20.

[35] Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol 2005; 32 Suppl 1: S16-24.