



HPV Types in Turkey: Multicenter Hospital Based Evaluation of 6388 Patients in Turkish Gynecologic Oncology Group Centers

Türkiye'deki HPV Tipleri: Türk Jinekolojik Onkoloji Grubuna Üye Merkezlere Başvuran 6388 Hastanın Retrospektif Analizi

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ABSTRACT

Objective: To evaluate the prevalence of HPV DNA and cervical cytological abnormalities, to compare cervical cytology results and HPV DNA and to define HPV types distribution in a large series of Turkish women who have undergone HPV analysis in hospitals that are members of the Turkish Gynecological Oncology Group.

Material and Method: Between 2006 and 2010, a total of 6388 patients' data was retrospectively evaluated at 12 healthcare centers in Turkey. Demographic characteristics, cervical cytology results, HPV status and types were compared.

Results: The mean age of the patients was 38.9±10.2. Overall, 25% of the women were found to be HPV positive. Presence of HPV-DNA among patients with abnormal and normal cytology was 52% and 27%, respectively. There was significant difference with respect to decades of life and HPV positivity ($p < 0.05$). HPV was positive in (within the HPV (+) patients) 37%, 9%, 27%, 20%, 22%, and 41% of the ASCUS, ASC-H, LSIL, HSIL, glandular cell abnormalities, and SCC cases respectively. The most common HPV types in our study were as follows; HPV 16 (32%), HPV 6 (17%), HPV 11 (9%), HPV 18 (8%), HPV 31 (6%), HPV 51 (5%), HPV 33 (3%).

Conclusion: In this hospital based retrospective analysis, HPV genotypes in Turkish women with normal and abnormal cytology are similar to those reported from western countries. Further population based prospective multicenter studies are necessary to determine non-hospital based HPV prevalence in Turkish women.

Key Words: Human papillomavirus DNA tests, Mass screening, Uterine cervical neoplasms, Vaginal smears, Turkey

ÖZ

Amaç: Türkiyedeki HPV tiplerinin geniş bir seri ile ortaya konması ile Türk Jinekolojik Onkoloji grubuna üye hastanelerde HPV analizi yapılan hastaların sonuçlarının retrospektif olarak değerlendirilmesi ve sitolojik anormalliklerdeki HPV tiplerinin belirlenmesi.

Gereç ve Yöntem: 2006 ve 2010 yılları arasında 12 ayrı merkeze başvuran smear ve HPV analizi yapılan toplam 6388 hasta retrospektif olarak incelenmiştir. Hastaların demografik bilgileri, smear sonuçları, HPV tipleri online olarak toplanıp analiz edilmiştir.

Bulgular: Ortalama hasta yaşı 38.9±10.2 idi. Tüm grup değerlendirildiğinde, %25 hastada HPV pozitif olarak saptandı. Anormal sitolojisi olanlarda HPV pozitifliği %57 iken normal pap testi olanlarda HPV pozitifliği %27 oranında tespit edildi. Hastaların yaşam dekadrları ile HPV pozitifliği arasında anlamlı bir ilişki bulundu ($p < 0,05$) HPV pozitifliği ASCUS, ASC-H, LSIL, HSIL, glandüler anormallikler ve skuamöz hücreli karsinom için sırasıyla %37, %9, %27, %20, %22, %41 idi. En sık görülen HPV tipleri sırasıyla HPV 16 (%32), HPV 6 (%17), HPV 11 (%9), HPV 18 (%8), HPV 31 (%6), HPV 51 (%5), HPV 33 (%3) idi.

Sonuç: Bu hastane temelli retrospektif analizde HPV tipleri gelişmiş batı ülkelerinde rapor edilen tiplerle benzer olarak tespit edildi. Ülkemizdeki gerçek popülasyon temelli HPV prevalansı ve tiplerinin belirlenmesi için hastane temelli olmayan çok merkezli geniş sayıda hasta içeren serilere ihtiyaç vardır.

Anahtar Sözcükler: Human papillomavirus DNA testleri, Kitle taraması, Uterin servikal tümörler, Vaginal yayma, Türkiye

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INTRODUCTION

Worldwide, cervical cancer is the second most common and the fifth deadliest cancer in women (1, 2). It affects about 16 per 100,000 women per year and kills about 9 per 100,000 per year (3). Worldwide, in 2008, it was estimated that there were 473,000 cases of cervical cancer, and 253,500 deaths per year majority of which is preventable with the HPV vaccine (4). The vaccine is also effective against type 6 and 11 which cause more than 90% of anogenital warts and recurrent respiratory papillomatosis. Therefore accurate information about HPV prevalence is needed to make vaccination recommendations. The widespread use of cervical screening programs has dramatically reduced the incidence of invasive cervical cancer (5).

What is less known in Turkey is the prevalence of cervical abnormalities and HPV type distribution. This information is important for a better understanding of which prevention strategies, such as screening programs, public health education and vaccines are likely to be effective. Previous studies have reported that HPV prevalence among low-risk Turkish women ranges between 2- 20 % (6). However, reliable data on HPV type distribution in this population is lacking. Therefore we performed a multicenter study with the aim of improving knowledge with regard to the prevalence of the HPV DNA and to determine the distribution of HPV types among women with normal and abnormal cytology.

MATERIAL and METHODS

This is a multicenter retrospective study, which was conducted in twelve tertiary gynecology centers in Turkey. After obtaining the ethical approval of Başkent University Ethics Committee, a total of 12 healthcare centers in Turkey agreed to participate in the study. Between January 2006 and December 2010, a total of 6388 consecutive patients who underwent a pelvic examination by a gynecologist were recruited for this retrospective analysis. Current pregnancy, previous diagnosis, or treatments for cervical, vulva or vaginal cancer, previous hysterectomy or cervical conisation, previous history of chemo-radiotherapy for cervical carcinoma were excluded from the analysis. Very few virgins underwent a gynecological examination. Therefore, the following analyses were restricted to those women who reported being sexually active. Data were collected from patient files, pathology/cytology reports, and hospital records. Patients' demographic characteristics, cervical cytology results, HPV status, and types were collected from each participating center. These data were sent to the principal investigators, thus final analysis was

performed at Başkent University School of Medicine. All cervical specimens were collected via the same standardized protocol. Samples of exfoliated cervical cells were obtained using a cytobrush. After preparation of a standard cervical smear, the remaining cells were placed in tubes with 0.9% saline. These tubes were transferred to the microbiology laboratory for HPV-DNA analysis. Papanicolaou or liquid-based cytology smears were stained and read by local cytopathologists and classified according to the Bethesda system (7). HPV DNA detection and genotyping performed by Hybrid Capture-II (used only at Hacettepe University) and PCR as described previously and just patients who underwent genotype identification included this analysis (8). HPV DNA detection in cervical swabs was conducted by using real-time polymerase chain reaction (PCR) with a commercial kit (Fluorion, Iontek, Turkey). For DNA extraction, the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) was used in accordance with the instructions of the manufacturer. A 150 bp fragment of the L1 gene was amplified using GP5 and GP6 primers. An amplified gene product was identified via melting curve analysis and visualized by incorporation of Sybr Green dye during amplification. HPV genotyping was performed with DYEnamic ET Terminator Cycle Sequencing Kit (Amersham Biosciences Corp., NJ, USA) and ABI PRISM 310 Genetic Analyzer at Iontek Ltd, Turkey.

Statistical analysis: Chi-square method and Fisher's exact test were used for most of the analysis. Since age distribution on HPV positivity was not normally distributed, the Mann-Whitney-U Test was utilized. All tests of significance were done at the 5% two-sided significance level. Statistical analysis was performed using SPSS 17 (Statistical Package for Social Sciences, Chicago, US).

RESULTS

A total of 6388 women who applied for regular gynecological examination were analyzed for HPV at twelve Health Centers in Turkey. Of these, 218 women were excluded from the analysis due to missing HPV DNA assessment and incomplete data. The study included data from 7 (58%) university clinics and 5 (42%) government hospitals. Sixty seven percent of the patients were married, while the remaining 33% were single or widowed. Fifty nine percent of the study population consisted of nulliparous women and the remaining 41% had at least one delivery. The vast majority of patients were between the 3rd and 5th decades and the mean age of the patients was 38.9 ± 10.2 (range 15-76) years. While 81% of the study population was premenopausal, the remaining 19% was menopausal. Overall, 25% of the women were found to be HPV positive.

Presence of HPV-DNA among patients with abnormal and normal cytology was 52% and 27%, respectively. There was a statistically significant negative relationship between age and HPV positivity ($p < 0.05$). The younger the age, the higher was the chance of HPV positivity. Furthermore as in the presence of significant differences with respect to HPV positivity between women under 30 years old and women older than 30 years old (36.2% vs. 30.4%, $p < 0.001$), there were similar significant differences with respect to decades of life and HPV positivity ($p < 0.05$). HPV prevalence was significantly increased in premenopausal women (32.5%) compared to menopausal women (28.6%) ($p < 0.05$). While there were 76.5% women with normal cervical cytology, only 23.5% women with cervical cytological abnormality

were diagnosed. HPV-DNA positivity among patients with abnormal and normal cytology was 52% and 27%, respectively. HPV was positive in (within the HPV (+) patients) 37%, 9%, 27%, 20%, 22%, and 41% of the ASCUS, ASC-H, LSIL HSIL, glandular cell abnormalities, and SCC respectively. Table I illustrates total distribution of cervical cytology and HPV results in the study population. The most common HPV types in our study were as follows; HPV 16 (32%), HPV 6 (17%), HPV 11 (9%), HPV 18 (8%), HPV 31 (6%), HPV 51 (5%), HPV 33 (3%). Table II illustrates HPV types distribution. Figure 1, demonstrates HPV prevalence by decades and Figure 2 demonstrates High risk HPV prevalence by decades. Table III demonstrates the most common HPV types in different abnormal cytologies.

Table I: Distribution of cervical cytology with regard to HPV status in patients with abnormal cytology

		HPV			
		Negative	Positive	Total	
PAP Results	ASCUS	n, %	406 (35%)	233 (20%)	639 (54%)
	ASC-H	n, %	8 (0.7%)	59 (5%)	67 (6%)
	LSIL	n, %	87 (7%)	170 (14%)	257 (22%)
	HSIL	n, %	29 (3%)	122 (10%)	151 (13%)
	Glandular Cell Abnormalities	n, %	12 (1%)	9 (0.8%)	21 (2%)
	SCC	n, %	8 (0.7%)	33 (3%)	41 (3%)

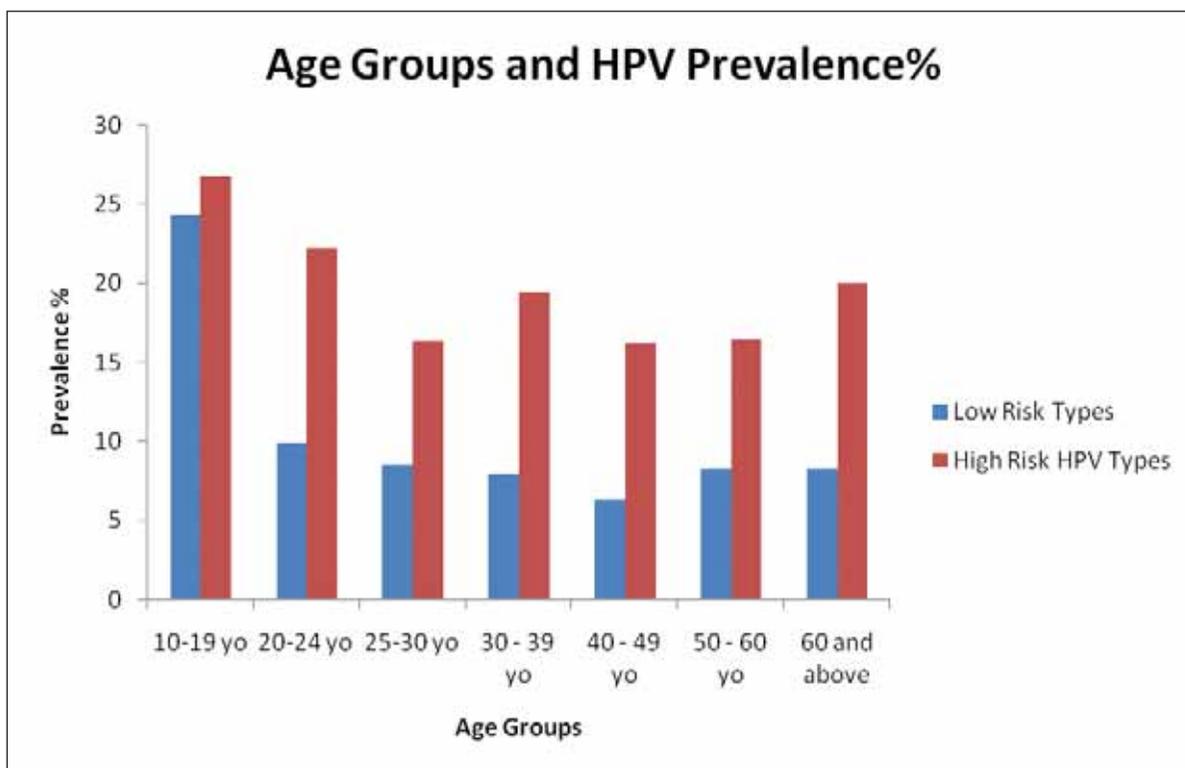


Figure 1: HPV prevalence by decades (yo: “years old”).

DISCUSSION

Historically, two-milestone studies were published related the HPV and cervical cancer. In 1976 zur Hausen published the hypothesis that human papilloma virus plays an important role in the cause of cervical cancer. Thereafter in 1983 and 1984 zur Hausen and his collaborators identified HPV16 and HPV18 in cervical cancer (9). Today the cause and effect relationship between high-risk HPV infection and cervical cancer is clearly established (10). Cervical cancer is an important health problem worldwide, with an annual incidence of 500.000 cases and 50% case fatality rate (2). Over 120 HPV types have been identified and are referred to by number. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are carcinogenic “high-risk” sexually transmitted HPVs and may lead to the development of cervical intraepithelial neoplasia (CIN) (11).

Knowledge of HPV prevalence and type distribution in a selected population is important, as it may affect vaccination and treatment strategies. Earlier studies have reported that HPV prevalence among low risk Turkish women ranges between 2-6 % (12,13). However, reliable data on HPV type distribution in this population is lacking. This study has been conducted to gather reliable data on prevalence and type distribution of HPV-DNA in a Turkish population.

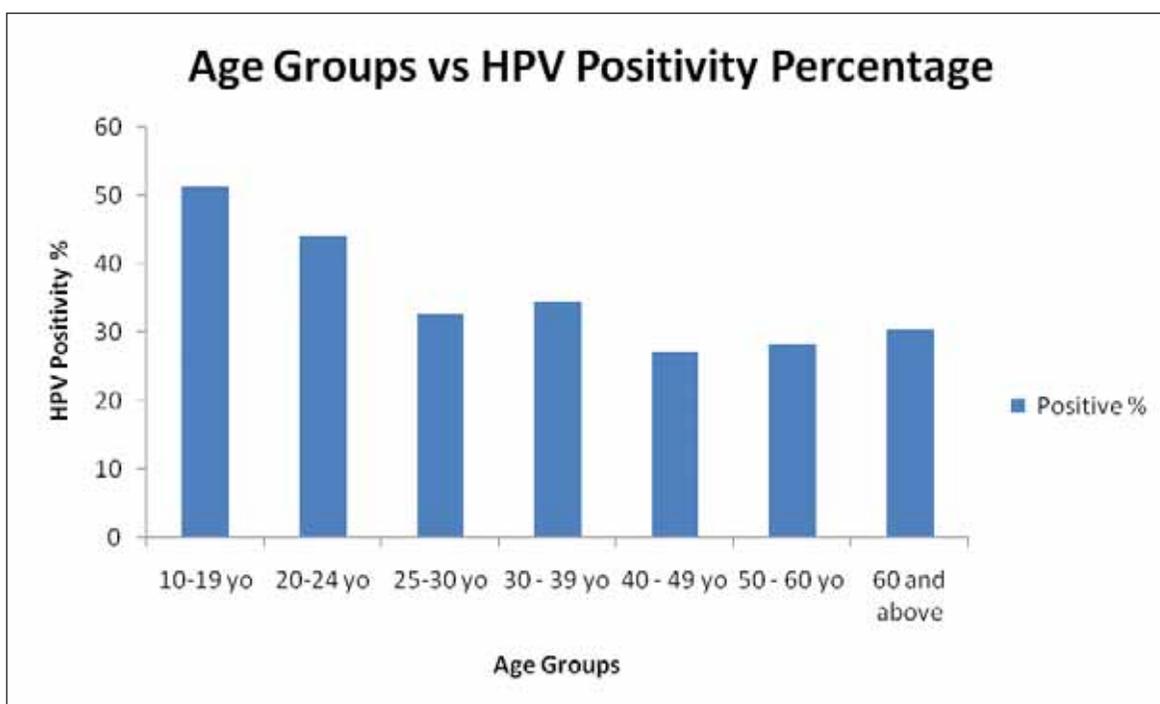
Many studies demonstrated that the prevalence of women infected with human papillomavirus and the distribution of HPV types varies greatly across populations worldwide. Prevalence of HPV in our study was 25%, which is similar to those reported worldwide. However previous studies from Turkey had reported this figure was much lower (between 2%-6%) (13,14,14,16) compared with western countries. But in our study HPV prevalence determined as high as 25% contrary to previous studies. This discrepancy may be explained by the hospital-based accrual of the patients as well as number of patients included in the studies, educational levels and knowledge about HPV and cervical cancer of the subjects (17, 18). Our study is the largest series that we believe is the most reliable results from Turkey with respect to HPV types in Turkey. However, we have to emphasize that this high rate of the prevalence cannot reflect to real HPV prevalence in Turkey. Furthermore technological improvement for the HPV evaluating methods may affect the results (19). Barring the data from Hacettepe University, in our study, all HPV-DNA analysis was performed via PCR methods whereas in three studies previously published from Turkey, HC (Hybrid Capture) was used for the analysis (13,14,15,16). In a pathological evaluation of the cervical cancer specimens, Usubütün et al. (20) reported that HPV prevalence was 93.5% (232/248;

Table II: Distribution of the HPV types in the study population

HPV types	Frequency (n)	Percent (%)
16	509	32
6	274	17
11	141	9
18	124	8
31	103	6
51	75	5
33	48	3
53	39	2
52	35	2
45	31	2
66	30	2
35	26	2
68	23	1
39	14	.9
50	13	.8
56	12	.8
30	9	.6
70	9	.6
54	8	.5
17	7	.3
42	6	.4
58	6	.4
59	6	.3
44	5	.3
16,18	5	.3
26	4	.3
40	4	.3
82	4	.3
32	3	.1
31,33,45,52,58	3	.2
34	2	.1
43	2	.1
90	2	.1
5	1	.1
8	1	.1
61	1	.1
67	1	.1
81	1	.1
95	1	.1
Total	1588	100.0

Table III: Most common HPV types in patients with abnormal cytology

	ASCUS	LSIL	HSIL
HPV-16	67 (29.8%)	55 (41.4%)	66 (68.8%)
HPV-6	28 (12.4%)	12 (9%)	4 (4.2%)
HPV-31	24 (10.7%)	10 (7.5%)	3 (3.1%)
HPV-11	20 (8.9%)	3 (2.3%)	3 (3.1%)
HPV-18	17 (7.6%)	14 (10.5%)	4 (4.2%)
HPV-33	9 (4%)	4 (3%)	4 (4.2%)

**Figure 2:** High risk HPV prevalence by decades (yo: “years old”).

95% confidence interval: 90.5%-96.6%). The five most common HPV types identified as single types among HPV-positive cases were HPV16 (64.7%), HPV18 (9.9%), HPV45 (9.9%), HPV31 (3.0%), and HPV33 (2.2%) (20). Similar to our study, HPV 16 and 18 were the most common high risk HPV in this study as well.

We found the presence of HPV in women with abnormal cytology was 53%, which is consistent with literature. In previous studies, HPV was reported in 29%-61% in women with abnormal cytology results (21,22,23,24,25,26). In our study, the rate of HPV positivity in women with normal cervical cytology was 27%, reflecting hospital based patients' accrual. In 2007 a meta-analysis of 78 studies, in 2008 a meta-analysis of 79 studies in women with normal cervical cytology, overall HPV was reported 10.4% and 14.4% respectively (18). On the other hand, in another meta-analysis including the results of 15,613 women,

overall HPV prevalence was 8.7%, 14.3% and 5.2% for Asia, South America and Europe, respectively (19). The discrepancy between the various studies could be explained by the false negative results of Pap testing and differences in the population with respect to risk factors for HPV and the method used for evaluations. In literature, multiple presences of HPV genotypes have been reported to occur in 10% to 20% of HPV-positive cases (24). As a matter of fact, we only found less than 1% of HPV-infected women with multiple HPV genotypes. We believe that is most likely due to the nature of data collection from different centers retrospectively.

In literature, HPV prevalence in women younger and older than 25 years old has been reported between 32-64% and between 2-4%, respectively (25). Furthermore Sellors et al. reported a significant reduction in HPV prevalence throughout the third decade of life (27). Similarly, in our

study differences between women less than 30 years old and women older than 30 years old with respect to HPV positivity were significant. We also found significant differences in HPV prevalence by the decades of life (Figure 1, 2). HPV prevalence and high risk HPV was more common in women with younger age.

In this study, the most common HPV types were as follows; HPV-16, HPV-6, HPV-11, and HPV-18. Although HPV-16 is known to be the most prevalent type and HPV-18 is the second most common type worldwide, our results show similarity with western countries with respect to HPV type distribution (24). Within the HPV positive patients in our study population the most common cytological abnormalities was as follows: SCC, ASCUS, LSIL, and HSIL. Similarly in the literature, there is a strong association between abnormal cervical cytological results and the presence of carcinogenic types of HPV.

In conclusion, heterogeneity in HPV type distribution among women from different populations should be taken into account when developing screening tests for the virus and predicting the effect of vaccines on the incidence of infection. In spite of higher HPV prevalence in our study compared with previous studies reported from Turkey, HPV prevalence and genotypes in Turkish women with normal and abnormal cytology are similar to those reported from western countries. Population-based data for HPV type distribution is necessary to the development of new HPV screening tests and to assessment of the effect of future vaccination. These results may also provide baseline information about the HPV prevalence and may help to guide vaccination policies in Turkey. Although our data was collected in almost all regions from Turkey, it is important to acknowledge that it was a hospital based study. Therefore further population based prospective multicenter studies are necessary to determine more precise hospital and non-hospital based HPV prevalence in Turkish women.

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