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Prevalence of cervical high-risk human papillomavirus and cytological abnormalities in elderly Turkish women

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ABSTRACT

Objective: Cervical cancer (CC) screening ends at the age of 65 in Turkey, as in many countries. However, about a quarter of CCs occurs in women over the age of 65. Persistent high-risk human papillomavirus(HR-HPV) infection is the most important factor leading to CC. In this study, we aimed to investigate the prevalence of cervical HR-HPV and cytological abnormalities in Turkish women aged 65 and over.

Patients and Methods: A total of 467 women between the ages of 66-84 who were referred to the gynecology outpatient clinics for any reason between January 2010 and December 2021 were included in the study. Pap smears (liquid-based) of patients were screened for HPV DNA typing using the COBAS test system and evaluated cytopathologicaly.

Results: The mean age of women was 72.4 years. The prevalence of HR – HPV was 5.1% (n = 24), HPV-16 and HPV-18 subtypes constituted 58.4% of all positive cases. The rate of cervical HR-HPV and cytological abnormalities were not statistically different between age groups. Of the women with a positive HR-HPV test in Pap smear, cytological abnormalities were found to be more frequent when compared to HR-HPV negatives (95.8%, n=23 vs 4.3%, n=19, p<0.00001).

Conclusion: We demonstrated a strong correlation between HR-HPV positivity and cytological abnormality in the elderly women population. Age groups were not significantly different regarding the prevalence of HR-HPV and abnormal cytology. We also revealed that the prevalence of HR-HPV and cytological abnormalities in the elderly population were not high enough to explain the second peak of cervical cancer seen in older ages. More studies are needed to explain which testing methods should be used in the elderly patient population.

Keywords: Cervical high-risk human papillomavirus, Cytological abnormality, Elderly Turkish women

1. INTRODUCTION

Human papillomavirus (HPV) is a small, non-enveloped double-stranded DNA virus that infects cervicovaginal epithelial cells in women, leading to cervical cancer [1]. There are more than 200 genotypes of HPV and HPV infection is common in the world [2]. Cervical cancer, which occurs because of high-risk Human Papillomavirus (HR-HPV) infection, is the fourth most common cancer after breast cancer, colorectal cancer, and lung cancer in women all over the world, according to GLOBOCAN data [3]. It is estimated that approximately 1.4 million women worldwide are living with cervical cancer. While it is leading cancer among gynecological tract cancers all over the world, it is the third most common in Turkey after endometrial and ovarian cancer [4].

Human papillomavirus infection, which is more common, especially at young ages, is often spontaneously eradicated in middle and advanced ages and does not cause any histological abnormalities. Although, its prevalence varies from society to society, socioeconomic status, age, other concomitant diseases, and sexual life characteristics also affect the frequency of HPV. Knowing the prevalence of HPV by age group may be very useful data that can guide public health policies, epidemiological studies, and screening programs.

Istanbul, with its population of over 20 million, is a small-scale replica of Turkey and most likely represents the country as a whole. The center where the study was conducted, is the largest

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hospital in the Umraniye region, is a large district located on the Anatolian side of Istanbul, and may represent Istanbul with its population density and socioeconomic characteristics.

Turkey has started to use primary HPV screening for population screening in recent years and has been taken as an example by some other countries. The Ministry of Health of Turkey successfully carries out the national cervical cancer screening program based on the HPV test [5]. According to this program, population screening ends at age 65. Opportunistic screening is performed for women over 65 years of age. Cervical cancer shows a bimodal distribution according to age and approximately one-fourth of cervical cancers are seen in women over 65 years of age. In addition, cervical cancer cases over the age of 65 usually present at an advanced stage and the prognosis is poor in this age group [6].

There is a lack of information about the prevalence of HPV and cervical cytological abnormalities in women aged 65 and over.. There is a false prejudice in the general population, and even among health professionals, that the elderly population has very little sex life. However, many international studies show that women over the age of 65 lead an active sexual life [7]. In addition, in many developed countries and developing countries including Turkey, the average life expectancy is getting longer.

Due to the hypoestrogenic state caused by the effect of advancing age and menopause, the cervical transformation zone is pulled into the cervical canal and it becomes difficult to obtain a sufficient smear for cytological evaluation [8]. Therefore, HPV screening may be a more appropriate method for the elderly population [9]. The aim of our study is to reveal the prevalence of HPV and the prevalence of HPV-associated cervical dysplasia in the elderly population, which is outside the social screening age range according to the national screening program, and to discuss the national screening program from this perspective.

2. PATIENTS and METHODS

This retrospective cross-sectional descriptive study is based on 467 women aged between 65–84 years (mean age 72.4 years), attending gynecology or gynecologic oncology outpatient clinic and having an HPV test as part of a routine gynecological examination. Women with a surgically absent cervix (who had a total hysterectomy) or women with a known gynecological malignancy were excluded from the study. Cervicovaginal smears were taken from the patients who applied to the gynecology, gynecological oncology and urogynecology outpatient clinics of our hospital with any complaint and all smears were taken by a gynecologist, gynecological oncology specialist or obstetrics and gynecology assistant. The smear samples were transferred to the pathology department in ThinPrep® PreservCyt® (Hologic Inc., Marlborough, MA) solution. Specimens were evaluated by pathologists for cytological abnormalities and tested for HPV. Samples in which cytological evaluation could not be done, or HPV test could not be performed due to insufficient sample quality were excluded from the study.

As it is known, the national screening program of the Turkish Ministry of Health has two steps. In Pap smears, the HPV test is done first. Cytology is also studied in HPV-positive samples. However, in our study, the screening strategy of our hospital was applied and simultaneous cytological evaluation was performed with the HPV test.

Cytological abnormalities were graded according to the 2014 Bethesda classification [10]. In our study, smear results with atypical squamous cells of uncertain significance (ASCUS) and low-grade disease (LSIL) were categorized as LSIL, while high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells from which high-grade lesion cannot be excluded (ASC-H), and atypical glandular cells (AGC) were categorized as a high-grade disease (HSIL). Women with cytological abnormalities associated with HPV positivity, women with HPV 16 or HPV 18 positivity regardless of cytology, or women with ASC-H, HSIL, or AGC cytological abnormalities even if HPV negative were referred to colposcopy for further evaluation. Patients with normal cytology results and negative HPV, ASCUS, or LSIL cytology results but negative HPV results, and patients with normal cytology but other high-risk HPV positivity other than 16/18 HPV results were referred to have a cotest after 12 to 24 months.

The Cobas4800® HPV testing system (Roche Molecular Systems, Branchburg, NJ, USA) is a fully automated PCR-based HPV test that detects HPV DNA and detects 14 high-risk HPV types from a liquid-based cytology medium. This system is one of five HPV testing systems approved by the US Food and Drug Administration for HPV DNA typing. After detecting 14 high-risk HPVs, the Cobas HPV test reports HPV 16 and HPV 18 separately, while the other 12 HR-HPV types (31,33,35,39,45,51,52,56,58,59, 66,68) reports together as a pool.

The study was approved by the Umraniye Training and Research Hospital Ethical Committee (approval number B.10.1.TKH.4.34.H.GP.0.017281).

Statistical Analysis

All analyzes were performed using SPSS 16.0 software (SPSS INC., Chicago, Il, USA). Quantitative data are expressed as mean ± standard deviation. Categorical data were defined as percentages and numbers. A chi-squared test was used to compare the prevalence of cytological abnormalities and HPV subtypes in different age groups and the prevalence of abnormal cytology in groups according to HR-HPV positivity. p value less than 0.05 was considered significant.

3. RESULTS

The mean age of 467 women was 72.4 years. All participants were grouped according to ages of 65-69 (n=239), 70-74 (n=177), 75-79 (n=45) and 80-84 (n=6) (Table I, Figure 1).

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Table I. *Prevalence of cytological abnormalities between age groups in elderly women*

	Age 66-69 (n=239)	*Age 70-74* (n=177)	*Age 75-79* (n=45)	*Age 80-84* (n=6)	Total (n=467)	p
Unsatisfactory smear, n(%)	28 (11.7)	13 (7.3)	5 (11.1)	1 (16.6)	47 (10.1)	
LSIL (ASCUS or LSIL), n(%)	25 (10.4)	9 (5.1)	2 (4.4)	0 (0)	36 (7.7)	
HSIL (ASCH or HSIL), n(%)	4 (1.7)	1 (0.6)	1 (2.2)	0 (0)	6 (1.3)	**P=0.103**
abnormal Cytology (total),n(%)	29 (12.1)	10 (5.7)	3 (6.6)	0 (0)	42 (9)	

LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion, ASCUS: atypical squamous cells of undetermined significance, ASC-H:atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion

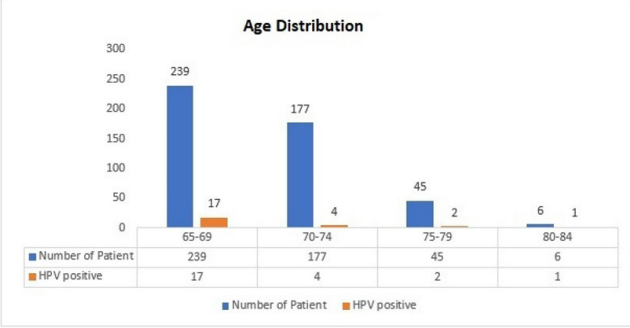

Figure1*. HPV positivity between age groups in elderly women*

Overall, abnormal cytology was found in 9% (n=42) of the population. The smear was reported as insufficient in 10.1%, LSIL were found in 7.7% and high-grade cytological abnormalities were seen in 1.3%. When evaluated according to age groups, the rate of abnormal cytology was 12.1% in '66-69 age', 5.7% in '70-74 age', 6.6% in '75-79 age' and 0% in '80-84 age' groups (Table I). The frequencies were not significantly different between groups (p=0.103).

High-risk human papillomavirus positivity was found in 5.1% (n=24) of the population; 1.7% was associated with HPV-16 /18 and 3.4% with other HR-HPV. When evaluated according to age groups, the rate of HR-HPV was 7.1% in '66-69 age', 2.8% in '70-74 age', 4.4% in '75-79 age' and 16.7% in '80-84 age' groups (Table II, Figure-1). The frequencies were not significantly different between groups (p=0.085).

Table II. *Prevalence of HPV subtypes between age groups in elderly women*

	Age 66-69 (n=239)	*Age 70-74* (n=177)	*Age 75-79* (n=45)	*Age 80-84* (n=6)	Total (n=467)	p
HPV 16/18, n(%)	5 (2.1)	2 (1.1)	1 (2.2)	0 (0)	8 (1.7)	
other HR-HPV, n(%)	12 (5)	2 (1.1)	1 (2.2)	1 (16.7)	16 (3.4)	
HPV positivity (total), n(%)	17 (7.1)	4 (2.8)	2 (4.4)	1 (16.7)	24 (5.1)	**P=0.085**

HPV: human papillomavirus, HR-HPV: high-risk HPV

Of the women with a positive HR-HPV test in Pap smear, cytological abnormalities were found to be more frequent when compared to HR-HPV negatives. (95.8%, n=23 vs 4.3%, n=19) (p=<0.00001) (Table III).

Women who participated in the study and required colposcopic evaluation according to cytology or HPV test results were referred to colposcopy. However, colposcopic evaluation results were excluded from the scope of this study due to insufficient numbers.

Table III. *Prevalence of abnormal cytology according to high-risk HPV positivity in elderly women*

	Abnormal cytology	Normal cytology	Total	P
HR-HPV (+)	**23** (95.8%) *within HR-HPV(+)*	1 (4.2%) *within HR-HPV(+)*	24 (100%)	
HR-HPV (-)	19 (4.3%) *within HR-HPV(-)*	424 (95.7%) *within HR-HPV(-)*	443 (100%)	**<0.00001**
total	42	425	467	

HR-HPV: high-risk human papillomavirus

4. DISCUSSION

To the best of our knowledge, our study is the first study on the prevalence of cervical HR-HPV and the cytological abnormalities in elderly Turkish women. This study reveals a strong association between abnormal cytology and HR-HPV positivity in elderly women despite lower prevalence compared to the younger population.

In our study, almost all of the HR-HPV-positive cases (23/24) had cytological abnormalities, while only 19 of 443 HPV-negative patients had abnormal cytology. The high rate of

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cytological abnormalities in this patient group might be related to inadequate eradication of HPV despite advancing age.

In the total study group, we found the prevalence of HR-HPV was 5.1%. Petignat et al., in their study with a cohort over 60 years of age, found the prevalence of HPV to be 6.7% [11]. In another study, Ferenczy, and friends found that only 1% were HPV positive, out of 306 postmenopausal women aged 50-70 years [12]. Ferenczy et al., claimed that the reason for the low rate in their study was that it was carried out in a Jewish hospital and a private hospital.

Human papillomavirus-based screening programs emerge as a more economical and easily applicable alternative to cytological screening for community screening. This screening program has been used successfully in Turkey for many years. Several studies have shown that HPV DNA detection tests are more sensitive than cytological evaluation for primary screening of premalignant lesions of the cervix. We demonstrated that, in elderly women, cytological abnormalities were strongly associated with cervical HR-HPV, nonetheless we could not support colposcopic histopathologic verification to display any relation with cervical neoplasms. Therefore, HR-HPV testing as a primary cervical cancer screening tool for the elderly women population is arguable and uncertain to carry out which age period. As well known, the age-specific incidence of cervical cancer is bimodal and peaks at 35-40 and 70-80 years of age.

Our study had some limitations. First, the number of patients in some age groups, especially those over the age of 70, was low. Second, this study was single-centered and not carried out on a national basis, contrary to some studies of China and Scandinavian countries, on a larger scale with the participation of higher numbers [13-15]. Nonetheless, the total number of our study was sufficient, and the evaluated women population was representative of Turkey's population. Third, the sexual life and smoking history of the patients could not be questioned. Fourth, we did not include the colposcopic evaluations of the patients with HPV positivity and cytological abnormalities in our study, so we were unable to compare the specificity and sensitivity of HPV testing and liquid-based cytology in the elderly patient population.

In conclusion; we observed a strong correlation between HR-HPV positivity and cytological abnormality in the elderly patient population. Age groups were not significantly different in terms of HR-HPV and abnormal cytology prevalence. We also revealed that the prevalence of HR-HPV and cytological abnormalities in elderly ages are not high enough to explain the second peak of cervical cancer seen in older ages. Because the frequency of unsatisfactory cytology might be highly seen, cytological evaluation alone does not seem to be sufficient for screening cervical neoplasms in elder women. We believe that larger studies, including histological evaluation, are needed to decide whether cytology or HPV testing should be used as a screening test and which age periods are more appropriate to screen in the elderly patient population.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Umraniye Training and Research Hospital Ethical Committee (approval number B.10.1.TKH.4.34.H.GP.0.017281).

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REFERENCES

[1] de Villiers EM. Cross-roads in the classification of papillomaviruses. Virology 2013;445:2-10. doi: 10.1016/j.virol.2013.04.023.

[2] Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12-9. doi: 10.1002/(SICI)1096-9896(199909)189:1<12 :AID-PATH431>3.0.CO;2-F.

[3] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. doi: 10.3322/caac.21660.

[4] Açikgöz A, Ergör 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.

[5] Gultekin M, Karaca MZ, Kucukyildiz I, Dundar S, Keskinkilic B, Turkyilmaz M. Mega Hpv laboratories for cervical cancer control: Challenges and recommendations from a case study of Turkey. Papillomavirus Res 2019;7:118-122. doi: 10.1016/j.pvr.2019.03.002.

[6] Darlin L, Borgfeldt C, Widen E, Kannisto P. Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. Anticancer Res 2014; 34: 5147–51.

[7] Beckman N, Waern M, Gustafson D, Skoog I. Secular trends in self reported sexual activity and satisfaction in Swedish 70 year olds: cross sectional survey of four populations, 1971-2001. BMJ 2008;337(7662):a279. doi: 10.1136/bmj.a279.

[8] Hermansson RS, Olovsson M, Hoxell E, Lindström AK. HPV prevalence and HPV-related dysplasia in elderly women. PLoS One 2018;13:e0189300. doi: 10.1371/journal.pone.0189300.

[9] Meijer CJ, Berkhof J, Castle PE, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer 2009;124:516-20. doi: 10.1002/ijc.24010.

[10] Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). Acta Cytol 2015;59(2):121-32. doi: 10.1159/000381842.

[11] Petignat P, Faltin D, Goffin F, Billieux MH, Stucki D, Sporri S, et al. Age-related performance of human papillomavirus testing used as an adjunct to cytology for cervical carcinoma

screening in a population with a low incidence of cervical carcinoma. Cancer 2005;105:126-32. doi: 10.1002/cncr.21060.

[12] Ferenczy A, Gelfand MM, Franco E, Mansour N. Human papillomavirus infection in postmenopausal women with and without hormone therapy. Obstet Gynecol 1997;90:7-11. doi: 10.1016/S0029-7844(97)00217-2.

[13] You W, Li S, Du R, Zheng J, Shen A. Epidemiological study of high-risk human papillomavirus infection in subjects with abnormal cytological findings in cervical cancer screening. Exp Ther Med 2018;15:412-8. doi: 10.3892/etm.2017.5357.

[14] Andersen B, Christensen BS, Christensen J, Ejersbo D, Heje HN, Jochumsen KM, et al. HPV-prevalence in elderly women in Denmark. Gynecol Oncol 2019;154:118-23. doi: 10.1016/j.ygyno.2019.04.680.

[15] St-Martin G, Viborg PH, Andersen ABT, et al. Histological outcomes in HPV-screened elderly women in Denmark. PLoS One 2021 11;16:e0246902. doi: 10.1371/journal.pone.0246902.