

At what Point is HPV in Cervical Cancer Screening?

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Background: Cervical cancer is the third most frequently seen cancer type after colorectal and breast cancers. It takes the fourth place with respect to mortality rate among the cancers seen in women. The aim of this study is to investigate the association of HPV with cervical premalign lesions and the type of premalignant lesion seen.

Materials and Methods: The study was conducted in the province of Amasya, Turkey between August 2014 and December 2017 with 24,446 women aged between 30 and 65 years of age, by co-test screening using HPV and cervical cytology in combination.

Results: HPV was found at a rate of 26%, HPV18 at a rate of 16.5%, HPV outside 16-18 at a rate of 68.6% and HPV 16-18 combination at a rate of 0.4%. The cytological results of 724 HPV-positive patients revealed that 24.3% were normal, 5.8% had ASC-US, 8% LGSIL, 0.3% HGSIL, 0.3% ASC-H, 0.4% AGC, 45% infection, and 15.9% had insufficient material.

Conclusion: This study demonstrates with which cytological findings we mostly encounter HPV. The HPV screening revealed that the HPV types outside HPV16-18 constituted a large majority and a considerable amount of accompanying cytological abnormalities were present. In conclusion, the possibility of other HPV types to cause cervical premalign lesions and thus their association with cervical cancer is shown to be negligible.

Keywords: HPV, cervical screening test, HSIL, LSIL, ASC-US

Introduction

Human papilloma virus (HPV) is a sexually transmitted disease seen mostly between 20 and 30 years of age. With more than 100 reported subtypes, HPV is a double helical DNA virus. It is divided into two groups as high-risk and low-risk with respect to the risk involved. Looking at the risk groups, 6, 11, 40, 42, 43, 44,

54, 61, 72, and 81 are classified as low-risk and 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 as high-risk. It is seen in a broad spectrum ranging from cervical preinvasive lesions to cancer. It is also closely associated with the cancers of vulva, anus, bladder penis and larynx (1-5). Its most common transmission pattern is sexual and 90% of them regress within 2 years

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(4,5). Persistent HPV infections involve the risk of cancer development. The underlying cause of cancer development is not fully known, but conversion into cancer is more common in those who have, or receive treatment for, an immunosuppressive disease, in smokers and in those over 30 years of age (3,6,7). HPV is a screening test that has replaced the smear test in several countries in their cervical cancer screening programs (8-12). It is an alternative test to the smear test in some countries. The United States Preventive Services Task Force (USPSTF) presented 4 different options for the cervical cancer screening in 2017. These options are;

1. Screening only with cervical cytology every 3 years for women aged between 21 and 29,
2. Only cytology every 3 years or screening for high-risk HPV every 5 years for women aged between 30 and 65,
3. No screening for those younger than 21 and those older than 65 who had no pathology in their previous screening tests,
4. No screening for patients who have no history of high-grade precervical lesion and whose cervix has been removed by way of hysterectomy.

The first three options apply to women who have a cervix regardless of whether or not they have a history of sexuality or vaccination. None of these options are recommended for women with high-grade precancerous lesions. These options are also not recommended for women who were exposed to diethylstilbesterol during their pregnancy or those infected by HIV. Major professional society guidelines and current practical guidelines suggest a cervical cytological screening every 3 years (2,13,14). The USPSTF guidelines do not include co-test

screening models where HPV is combined with cervical cytology screening between ages 30 and 65. The suggestions of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Congress of Obstetricians and Gynecologists (ACOG), which have come to serve as guidelines in the practice of cervical cancer screening in the past few years, do recommend co-test program (2,14,15). They consider, like other professional organizations, the co-test program as a preferable screening method (15,16). According to their studies, co-test does not seem to be an appropriate test in patients younger than 30 as the persistence of HPV in this group is lower (1). HPV-related cancers are mostly associated with the squamous cell cancer of the cervix, but its association with adenocancers has also been evidenced. There are also studies that have evidenced HPV screening as being a more sensitive test in the diagnosis of adenocancers as compared to cervical cytological screening (17-19). The ASCCP and ACOG recommend screening of women aged between 30 and 65 with co-test every 5 years (2, 3).

Materials and Methods

The study was conducted between August 2014 and December 2017 using the co-test screening method combining the HPV and cervical cytology screenings on 24,446 women aged between 30 and 65 within the framework of the public health screening program of the province of Amasya. In the selection of patients to undergo screening, care was taken to include those who did not have active vaginal infection, who had no sexual relation in the last 3 days and who had no prior HPV test. The patients who turned out HPV positive were made subject to a cervical cytological assessment and

the cervical cytological materials taken from those who were HPV negative were left outside such assessment. The statistical analyses were carried out using the SPSS version 22.0, simple frequency analysis.

Results

HPV positivity was found in 724 of a total of 24,446 patients who underwent the HPV screening between August 2014 and December 2017 and from these, 188 (26%) were classified as HPV16⁺, 36(5%) as HPV18, 497(68.6%) as HPVs outside HPV16-18 and 3(0.4%) as HPV16⁺ and HPV18⁺. The cervical cytological results revealed that there were 45%(326) infections, 8%(58) LGSIL (low grade cervical intraepithelial neoplasia), 5.8%(42) ASC-US (atypical squamous cells of undetermined significance), 0.04%(3) AGC (atypical glandular cells), 0.03%(2) ASC-H (atypical squamous cells cannot exclude HGSIL), 0.03%(2) HGSIL (high grade squamous intra epithelial lesion), 24.3%(176) normal cytological findings, and 15.9% (117) insufficient material. Looking at the cytological assessments in a type-specific way, we see that 9% of those HPV16 positive had LGSIL and 6.9% ASC-US;

5.6% of those HPV18 positive had LGSIL and 5.6% ASC-US; and 7.9% of those with other HPVs had LGSIL and 5.2% ASC-US.

Table-2. Crosstab of the HPV types and age interval

Age interval for HPV typing * hpv Crosstabulation						
AGE (years)		HPV				Total
		16 ⁺	18 ⁺	16 ⁺ 18 ⁺	Out	
30-40	N	71	14	1	203	289
	%	24,6	4,8	0,3	70,2	100
41-50	N	54	10	1	145	210
	%	25,7	4,8	0,5	69	100
51-60	N	47	9	0	122	178
	%	26,4	5,1	0	68,5	100
>61	N	17	3	1	26	47
	%	36,2	6,4	2,1	55,3	100
Total	N	189	36	3	496	724
	%	26,1	5	0,4	68,5	100

Discussion

Depending on the smear result and clinical requirements, the screening method with HPV is used either alone or in the form of co-test in various countries. In our country, Turkey, HPV screening is performed as a co-test within the

Table-1. Crosstab of the HPV types and the cervical type

HPV Types			Cervical Type								
			AGC	ASC-H	ASC-US	Infection	HGSIL	LGSIL	Normal	Insufficient Material	Total
HPV	16	N	0	2	13	76	1	17	50	30	189
		%	0%	1,1%	6,9%	40,2%	0,5%	9%	26,5%	15,9%	100%
	18	N	0	0	2	17	0	2	6	9	36
		%	0%	0%	5,6%	47,2%	0,0%	5,6%	16,7%	25%	100%
	16-18	N	0	0	1	0	0	0	1	1	3
		%	0%	0%	33,3%	0%	0,0%	0%	33,3%	33,3%	100%
	Out	N	3	0	26	233	1	39	119	75	496
		%	0,6%	0%	5,2%	47%	0,2%	7,9%	24%	15,1%	100%
Total		N	3	2	42	326	2	58	176	115	724
		%	0,4%	0,3%	5,8%	45%	0,3%	8%	24,3%	15,9%	100%

Table-3. Cervical cytology results in the patients

Variables	HPV 16 ⁺	HPV 18 ⁺	Non-HPV	HPV 16 ⁺ &18 ⁺
ASC-H	2(1,1)	2(5,6)	3(0,6)	*
ASC-US	13(6,9)	*	26(5,2)	1(33,3)
Infection	76(40,4)	17(47,2)	233(47)	*
HGSIL	1(0,5)	*	1(0,2)	*
LGSIL	17(9)	2(5,6)	39(7,9)	*
Normal	49(26,1)	6(16,7)	119(24)	1(33,3)
Insufficient Material	30(16)	9(25)	75(15,1)	1(33,3)
Total	188(100)	36(100)	496(100)	3(100)

**All values are given as N(%).

scope of general public health screening programs in order to standardize our screening programs and to screen also the general prevalence of HPV. Martins et al. have identified that HPV 16 and 56 is most common types in their study on 665 of patients. They found HPV 56 most commonly associated with LSIL. They found that the most prevalent type was HPV 16 in high-grade lesions. They found that HPV 18 was to be associated with low risk and abnormal smear results (21). Otero et al. found that HGSIL prevalence increased in HPV 16, 33 and 58 types and decreased in HPV 51, 53 and 66 types (22). Koliopoulos et al. also concluded that HPV screening was more reassuring than the smear test, and stated that the false negativity of the smear test was high (23).

HPV screenings are important because HPV leads to cervical cancer, the third most common cancer type, and falls in the category of sexually transmitted diseases. Should we as a country think of HPV as a single screening for the purpose of screening cervical cancer or should we do it as cervical smear screening and consider HPV test only when necessary? To answer these questions, we organized regional

co-test screening programs both to determine prevalence of HPV in Turkey and to standardize our cervical cancer screening method that we needed to choose in our country as a screening program. The data we presented in our study belong to the province of Amasya with a female population of 165,494. The results of our screening show that the most common types actually consist of the group including a number of different types that are seen less frequently and are grouped under the heading "other types". We found that HPV type 16, which falls in the category of high-risk HPVs most commonly seen worldwide, was observed at a rate of 26% among all other HPV types. This makes it obvious that type infects regional women most is one classified as "other types".

Conclusion

In this study, we aimed at finding the cervical cytological results of all of the 724 patients who we detected to be HPV positive from the 24,446 women included in the HPV screening program, which cytological type accompanied these and which HPV type was the most common. Given these results, we can say which HPV types we should consider most for our region, the response of our race to HPV, and to what extent they convert to high-grade cervical lesions. Addition of the colposcopic assessment results of the same patients to our study would enable us present more comprehensive information, but since the women consulted healthcare institutions considering themselves as patients suspected of cervical cancer when they found out that they were HPV positive, we were unable to include their cervical biopsy results, which constituted a limitation of our study. Therefore, it was not possible to say how many of the results of those HPV positive involved cervical cancer. However, cervical

cancer was found in only 3 of the 224 patients who had colposcopic biopsies in our clinic in the past 1.5 years and two were adenocarcinomas and 1 squamous cell carcinoma.

Conflict of Interests

The author declares that there is no conflict of interests regarding publication of this paper.

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