

HPV prevention in women aged 30–65 in Istanbul: Effect of early diagnosis of cervical cancer

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ABSTRACT

OBJECTIVE: Earlier detection and timely interventions against cancers are well known to reduce the morbidity and mortality. Screening programs provide opportunity to detect cancers as early as precancerous stages. Cancers of cervix of uterus are one of the cancers that have widely applicable screening methods and are one of the three cancer types that have population-based screening program in Turkiye. In this article, it is aimed to evaluate cervical cancer screenings in Istanbul.

METHODS: The study methodology for cervical cancer screening conducted between 2015 and 2020 in Istanbul, Turkiye's largest city, was introduced. The results obtained in the first round of screening of 723,068 women with the human papillomavirus (HPV) method as a new methodology are discussed.

RESULTS: As a summary of results, the HPV positivity ratio was found to be 6.5% and the positivity rate was higher in younger women. The results also show that majority of the subjects with positive result were infected with more than 1 strains of HPV. Most prevalent subtypes detected were HPV16, HPV51, HPV31, HPV52, and HPV66, respectively. Total detection rate for any of the high-risk HPV subtypes was 29.95%.

CONCLUSION: Although HPV-16 is the highest subtype to be infected and total percentage of infection with any high-risk strains is approximating to one-third of the total positivity, cytological results revealed only 8.1% meaningful results.

Keywords: Cancer screenings; cervical cancer; human papillomavirus.

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Malignancies increasingly keep the lead as a cause of disease burden, morbidity, and mortality worldwide. They account for the first five causes of premature death in approximately in all countries worldwide (179 of 183 UN member countries) and are the first cause of premature death in 55 countries including Turkiye [1].

Malignancies of cervix of uterus are the fourth most common type of cancers seen in women worldwide [1]. Although incidence and mortality rates of cervical can-

cers are at lower end of spectrum in Turkiye when compared to the worldwide statistics, they are still at the top 10 malignancies reported in women with an age adjusted incidence rate of 4.3 cases per 100.000 population [2].

Earlier detection of an intervention toward the malignancies is widely accepted as a measure to reduce the mortality and morbidity rates of almost all malignancies, and when available screening programs provide a great opportunity for early detection and interventions [3].



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Nationwide programs aiming to implement population-based cancer screening in Türkiye dates back to the early years of 2000s [4]. However, particularly cervical cancer, screening rates could not exceed 1–2% of population per year when planned and population-based rates were considered [5, 6]. Those population-based procedures were limited to Centers for Cancer Early Diagnosis and Education Centers (KETEM) mainly and Mother and Children Health Centers (ACSAP). In İstanbul, KETEM's could not be implemented up until the year of 2014 and cancer screening was performed in hospitals in an opportunistic manner.

In 2012, Turkish Ministry of Health revised the screening program and implemented human papillomavirus (HPV) testing as the primary method for cervical cancer screening. In 2014, centralized HPV testing laboratories started to serve in Ankara and İstanbul [7]. To achieve adequate coverage of population, screening procedures started to be performed by family practitioners beyond KETEM's, ACSAP's, and hospitals.

Objective

In this manuscript, we aim to introduce the cervical cancer screening workflow performed in İstanbul as the largest populated city in Türkiye, the challenges encountered during implementation phases and evolution of the steps taken to overcome these challenges in the light of the results and experience gathered through the first 6 years of screening with the novel screening algorithm and methodology incorporating HPV testing through a centralized approach.

MATERIALS AND METHODS

This study was accepted with the Approval letter dated December 25, 2019 and numbered 186 of the Taksim Training and Research Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Cervical cancer screenings in scope of this article were performed in accordance with the national cancer screening standards [8]. Accordingly, women between the ages of 30 and 65 years are eligible for screening. The interval for screening is 5 years.

Main screening points for cervical cancer screening in İstanbul are planned as the family health centers, and the attended family practitioner of the individual is the main responsible of following the screening status of the individual, calling-recalling for the screening, and further

Highlight key points

- HPV positivity rate is higher in younger women.
- The majority of women who were found to be positive were found to be infected with more than one HPV subtype.
- The most common of the subtypes detected in the first round of the screening program is HPV51.

follow-up according to the results. All of the family practitioners are educated for the importance and the workflow of the screening as well as for the interpretation and communicating of the results.

Specimens at the family health centers are collected by the family medicine nurses. All of the family medicine nurses take online theoretical education for specimen collection and 5 days of practical education at gynecology clinics at research and education hospitals.

KETEM's and ACSAP's support the family health system when the physical conditions of the family health center are not suitable for the specimen collection, or until the educations of newly attended family practitioner or family health nurse for the cervical specimen collection techniques were completed.

The second and third line hospitals are also incorporated in screening program to extend the coverage rate.

All kits needed for specimen collection and transport is provided by the national centralized HPV laboratory and distributed to the screening points by the İstanbul Provincial Directorate of Health through logistics networks also used for other laboratory evaluations.

Screening method is based on HPV testing. Two cervical specimens are collected simultaneously during the procedure, one for HPV isolation and sub-typing and one for the reflex cytopathologic evaluation if needed.

The first sample is collected with a brush and transferred to a glass slide for conventional cytology. The second sample is taken with a different brush and placed in 5 ml of standard transport medium for HPV DNA analysis.

Laboratory evaluation is done in three steps. The first step is determination of the presence of HPV-DNA in the specimen. This is done by Hybrid Capture2 (Qiagen) method [9]. If the specimen is found positive for HPV-DNA, genotyping and subtype analysis are performed with the CLART kit (Genomica). Furthermore, reflex cytopathologic evaluation is performed for the samples of all HPV-DNA-positive women by two pathologists in a double-blind manner.

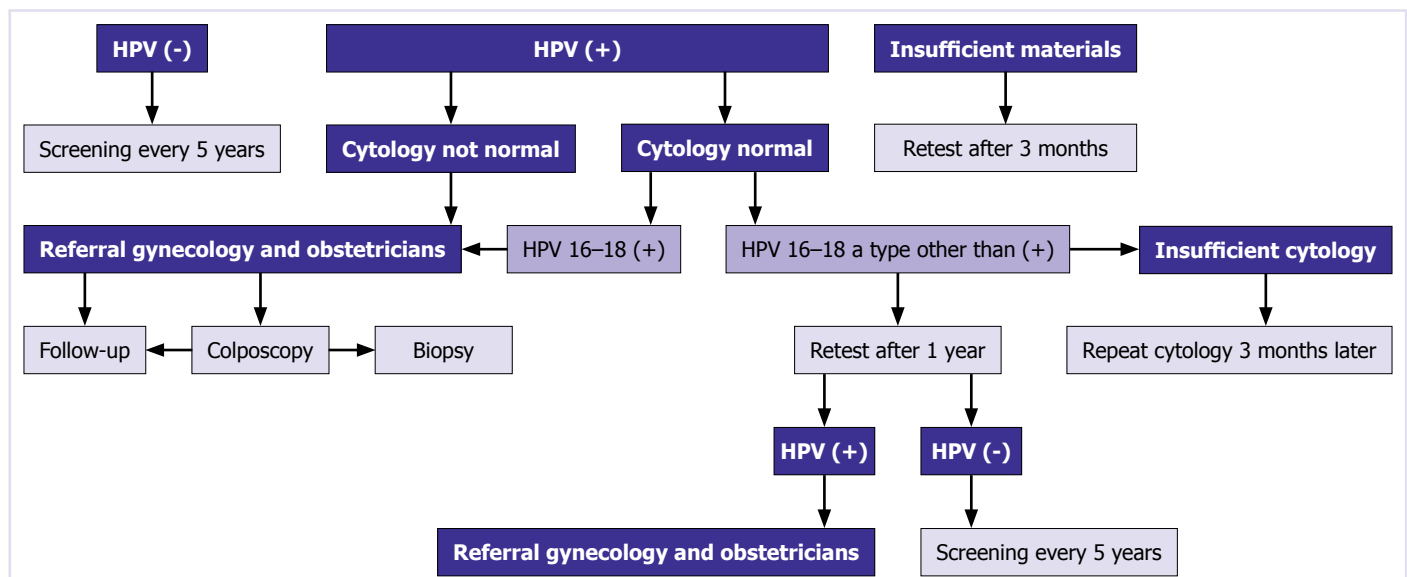


FIGURE 1. HPV algorithm.

In the family medicine practice of Türkiye, each individual has been attended to one family practitioner. All demographic and health-related data of the individual are registered in the local electronic database of the family practitioner which is called Family Medicine Information System (AHBS). AHBS is also capable of filtering and sorting for target populations for screening programs. The screening results of the individual are also pushed and recorded to the AHBS of the family practitioner even the specimen collection is performed out of the family health center where the individual is attended.

If HPV-DNA is resulted as negative, the first round of screening for the individual is completed, and she is dropped from the target population list of the family practitioner for the following 5 years. For individuals who are resulted as HPV-DNA positive, a two side approach is followed according to the subtype analysis or cytopathologic results.

Limitations of the study; covering the scans made between 2015 and 2020, inclusion of women aged 30–65, that only the data of the province of Istanbul have been used, discussion of the results from the first round of scans is the limitations of the study.

Strengths; the province of Istanbul is Türkiye's most populous province, scanning with a new methodology, implementation of a screening program in all institutions providing Primary Health Care and having a large database, and being the first community-based screening program conducted in Family Health Centers and integrated into the system are the strengths of the study.

Women who are positive for HPV-DNA are referred to the diagnostic centers when subtype analysis of whom revealed any of the high-risk HPV strains (HPV16, HPV18, HPV31, and HPV33) or when any abnormalities found in cytopathologic evaluation. Women who are positive for HPV-DNA, but subtype analysis revealed a non-high-risk strain and cytopathologic evaluations does not show any abnormalities, are followed up at the screening in an annual basis (Fig. 1).

Statistical Analysis

In this study were calculated using the Microsoft Excel (2019, Microsoft, New Mexico/ABD) application and analyzed in SPSS.

RESULTS

In grand total, 723.068 screening procedures were performed during the study period involving the years of 2015–2020. Total number of HPV-positive results was 46.993 (6.5%) and total number of HPV-negative results was 670.099 (92.67%), 5.976 tests (0.83%) were reported as insufficient material. Age distribution of screened population is summarized in Table 1.

Maximum number of screening was performed at the 2nd year of the screening program in 2016, and in 2020, a significant reduction was observed due to the COVID-19 pandemics. The year distribution revealed a

TABLE 1. Age distribution of screening population and HPV screening results within age groups

Age group	Total (n)	Negative n=670.099 (%)	Positive n=46.993 (%)	Insufficient material n=5.976 (%)
30–35	155.271	91.16	7.99	0.85
36–40	141.970	92.11	7.14	0.76
41–45	134.424	92.76	6.42	0.82
46–50	105.914	93.29	5.89	0.81
51–55	91.573	93.76	5.37	0.87
56–60	60.281	94.09	5.00	0.90
61–65	33.635	94.27	4.88	0.85
Total	723.068	92.67	6.50	0.83

HPV: Human papillomavirus.

TABLE 2. Year distribution of screening numbers and HPV screening results across years

Age group	Total (n)	Negative n=670.099 (%)	Positive n=46.993 (%)	Insufficient material n=5.976 (%)
2015	60.203	94.05	4.29	1.66
2016	212.657	93.73	5.31	0.95
2017	167.196	92.23	6.57	1.20
2018	129.846	92.34	7.28	0.38
2019	118.283	91.69	8.08	0.23
2020	34.883	90.58	8.90	0.52
Total	723.068	92.67	6.50	0.83

HPV: Human papillomavirus.

trend toward the increase of HPV positivity rates from 4.29% in 2015 to 8.90% in 2020 (Table 2).

Majority (54.59%) of HPV-positive individuals in screening population were infected with more than 1 HPV subtypes (Table 3). General proportion of individuals infected by more than 5 HPV subtypes was 1.78%. Furthermore, 17 individuals were infected by more than 10 HPV subtypes of whom one individual was infected by 14 HPV subtypes, one individual was infected by 12 HPV subtypes, three individuals were infected by 11 HPV subtypes, and 12 individuals were infected by 10 HPV subtypes.

Most prevalent subtypes detected were HPV16, HPV51, HPV31, HPV52, and HPV66, respectively, and this finding was consistent within each age group (Table 4). Total detection rate for any of the high-risk HPV subtypes (HPV16, HPV18, HPV31, and HPV33) was 29.95%.

Cytological investigations were resulted as normal in 64.30% of HPV-positive individuals and infection was only cytological finding in 14.10%. Number of individuals with a meaningful cytological finding was 3.808 (8.1%) (Table 5).

DISCUSSION

HPV testing has eventually become the state-of-the-art cervical cancer screening methodology since the introduction of the WHO's essential practice guidance in 2014 [10]. Türkiye is one of the early adapting countries to this approach, by accepting HPV as the primary

TABLE 3. Distribution of individuals by number of HPV subtypes been infected within age groups

Age group	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	>5 (%)
30–35	46.29	26.23	16.32	6.80	2.51	1.85
36–40	47.09	26.20	15.90	6.45	2.66	1.69
41–45	45.71	27.52	16.03	6.59	2.42	1.74
46–50	44.94	27.43	16.87	6.75	2.58	1.43
51–55	42.59	27.66	17.49	7.36	2.99	1.91
56–60	43.00	25.99	17.57	8.02	3.08	2.32
61–65	41.50	26.39	18.95	7.50	3.66	2.01
Total	45.41	26.76	16.54	6.84	2.66	1.78

HPV: Human papillomavirus.

methodology in 2012 [8], and further developing and implementing a centralized laboratory and practice system in 2014 [7].

Although the guidelines of the Ministry of Health for cervical cancer screening are valid for countrywide, there are some practice differences for the application between provinces and regions due to their differing population profile and infrastructure. In İstanbul, application of new screening scheme is prioritized to be performed in family practice setting due to the wide coverage and acceptance of the system. This approach allowed 4–5 times more population based coverage when compared to the pre-HPV screening era.

TABLE 4. Age group distribution of HPV subtypes detected in screening population

HPV subtype	30–35 (%)	36–40 (%)	41–45 (%)	46–50 (%)	51–55 (%)	56–60 (%)	61–65 (%)	Total
HPV06	1.64	1.38	1.23	1.06	1.00	0.98	0.86	1.29
HPV11	0.62	0.47	0.41	0.42	0.44	0.31	0.32	0.47
HPV16	18.00	18.10	16.42	14.91	14.21	13.47	15.03	16.52
HPV18	4.08	4.23	3.89	3.84	3.40	3.16	2.86	3.87
HPV26	0.21	0.19	0.15	0.17	0.1	0.08	0.21	0.17
HPV31	7.81	7.86	7.49	7.50	7.30	6.83	6.44	7.55
HPV33	1.67	1.95	2.09	2.10	2.30	2.36	2.43	2.00
HPV35	4.97	4.84	4.90	4.83	5.05	4.51	4.90	4.89
HPV39	5.35	4.95	4.62	5.26	4.53	3.94	3.40	4.87
HPV40	0.13	0.19	0.10	0.22	0.21	0.31	0.14	0.17
HPV42	0.33	0.41	0.51	0.43	0.51	0.35	0.75	0.43
HPV43	0.06	0.11	0.12	0.06	0.07	0.18	0.11	0.09
HPV44	0.03	0.08	0.11	0.07	0.04	0.12	0.07	0.07
HPV45	2.40	2.53	2.47	2.57	2.20	2.01	1.82	2.39
HPV51	8.47	8.22	7.82	7.64	8.05	8.83	8.44	8.17
HPV52	6.25	5.92	6.08	5.93	5.95	6.31	6.37	6.08
HPV53	4.10	4.35	4.62	5.07	4.97	5.92	5.80	4.65
HPV54	0.34	0.53	0.59	0.74	0.53	0.78	0.68	0.54
HPV56	4.24	4.20	4.60	5.27	4.88	5.16	5.08	4.59
HPV58	4.25	4.48	4.47	4.91	5.15	6.48	6.08	4.74
HPV59	4.23	3.96	4.09	4.01	4.20	3.77	3.58	4.06
HPV61	0.99	1.03	1.04	1.33	1.59	1.43	1.90	1.18
HPV62	0.20	0.28	0.34	0.37	0.40	0.47	0.32	0.31
HPV66	5.35	5.26	5.49	4.95	5.36	4.75	4.76	5.24
HPV68	3.92	4.00	4.35	4.57	4.53	4.12	3.69	4.17
HPV70	1.57	1.59	1.67	1.69	1.94	1.86	2.25	1.69
HPV71	0.00	0.01	0.00	0.00	0.01	0.00	0.04	0.01
HPV72	0.32	0.25	0.32	0.33	0.47	0.57	0.32	0.34
HPV73	0.14	0.09	0.23	0.19	0.11	0.18	0.14	0.15
HPV81	0.67	0.70	0.93	0.89	1.00	1.15	1.32	0.84
HPV82	1.16	1.05	0.98	0.75	0.78	0.88	0.97	0.98
HPV83	0.64	0.66	0.88	0.95	1.18	1.27	1.07	0.84
HPV84	0.79	0.77	0.80	0.82	0.87	0.68	0.61	0.78
HPV85	0.08	0.05	0.11	0.06	0.07	0.08	0.04	0.07
HPV89	0.13	0.10	0.14	0.16	0.15	0.12	0.14	0.13
Other	4.86	5.20	5.94	5.95	6.47	6.60	7.05	5.64
Total (n)	20.503	16.535	14.016	10.134	8.235	5.121	2.795	77.339

HPV: Human papillomavirus.

One of the key findings of the analysis of 6 years data of the population-based screening is the age distribution of the screened population. Although it is known that higher age groups are more prone to take service from family medicine system in Türkiye, there

was a common trend for younger ages to have a higher uptake for the screening program. This was also a common feedback from family practitioners in meetings set up for the evaluation the screening programs that older women were more hesitant to accept the screen-

TABLE 5. Cytological findings in HPV -positive individuals by age group and general proportion of cytological findings within HPV positivities

Cytological result	30–35 (%)	36–40 (%)	41–45 (%)	46–50 (%)	51–55 (%)	56–60 (%)	61–65 (%)	Total (n)	General proportion within HPV positives
[Agc]	24.56	29.82	20.18	9.65	9.65	3.51	2.63	114	0.24
[Asc-H]	19.44	18.16	19.95	13.55	11.76	12.53	4.60	391	0.83
[Asc-Us]	20.69	18.59	15.63	13.09	15.07	11.04	5.89	2.528	5.38
[Infection]	30.26	22.92	17.82	10.94	9.33	5.52	3.20	6.626	14.10
[Hgsil]	16.67	11.11	16.67	16.67	16.67	11.11	11.11	18	0.04
[Lgsil]	21.53	20.87	16.25	14.40	12.55	10.83	3.57	757	1.61
[Normal]	27.67	22.74	19.34	13.43	9.15	4.90	2.77	30.218	64.30
[Insufficient]	19.73	15.87	15.60	15.01	15.74	11.86	6.20	6.341	13.49
Total	26.41	21.56	18.38	13.28	10.46	6.42	3.49	46.993	100.00

HPV: Human papillomavirus; Asc-H: Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; Agc: Atypical glandular cells; Asc-Us: Atypical squamous cells of undetermined significance; Hgsil: High-grade squamous intraepithelial lesion; Lgsil: Low-grade squamous intraepithelial lesion.

ing. This is a worthy issue for further investigations to detect the causes of hesitancy of older population's and develop countermeasures to overcome. However, when also the higher HPV positivity rates among younger population are considered, ensuring the continuation of higher uptake rates of younger women seems another important paradigm.

When the yearly progress of the screening program analyzed, it is obvious that the 2nd year after the initiation and establishment of the program, the year of 2016, is the year with the highest number of procedures of performed. In the following years, there is a trend for lower procedure rates. This may be attributed to the novelty effect of the program in 2016 that there was a wide conventional and social media coverage and wider awareness events nationwide. These findings, especially the year of 2020 in which inadvertently COVID-19 pandemics congested the agenda of the day both in public and health care as all countries worldwide [11], clearly show that to achieve the desired screening coverage, the topic should always be held aloft of the society.

In contrast to the most of the findings of similar studies [12–15] in literature, our findings show a greater ration of infection with multiple HPV subtypes. Furthermore, there is a trend through the mid age groups for the rate of multiple infection with the years of 51–55 have highest multiple infection percentage. The distribution of coexisting HPV subtypes

and the impact of multiple infection for future clinical outcomes should be further analyzed.

Although HPV-16 is the highest subtype to be infected and total percentage of infection with any high-risk strains is approximating to one-third of the total positivity, cytological results revealed only 8.1% meaningful results. These finding may suggest the superiority for early risk detection role of HPV when compared to cytology. However, this suggestion necessitates the evaluation the long-term follow-up patients with positive results with those subtypes.

Conclusion

HPV testing and centralized approach and involvement of all possible health-care settings to the screening program brought greater coverage traceability. Especially, the traceability of centralized approach is of great advantage for a cosmopolite and crowded population like Istanbul. Although in this article, we aimed to summarize the initial epidemiological data for the first round of novel cervical screening program, this approach is expected to yield further analysis and evaluation of the critical findings with the future follow-up data of the relevant population covered in the first round screening [16, 17]. Furthermore, epidemiologic data acquired from HPV screening program and further long-term risk assessment of the state-of-the-art HPV load of the population are expected to guide for pharmacoepidemiologic and pharmaco-economic analyses needed by the decision-makers for population wide HPV vaccination.

Ethics Committee Approval: The Taksim Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 25.12.2019, number: 186).

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Authorship Contributions: Concept – AEG, AK; Design – AEG, SS; Supervision – AEG, SS; Fundings – AEG; Materials – SK; Data collection and/or processing – KK, SK; Analysis and/or interpretation – KK, SS; Literature review – AEG, SS; Writing – AEG, SS; Critical review – AEG, SS.

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