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Human papillomavirus infection in women with and without cervical cancer in Tehran, Iran

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No data exist on the population prevalence of, or risk factors for, human papillomavirus (HPV) infection in Iran or the Middle East. Cervical specimens were obtained from 825 married women aged 18–59 years from the general population of Tehran, Iran and from 45 locally diagnosed invasive cervical cancers (ICC) according to the standardized protocol of the International Agency for Research on Cancer HPV Prevalence Surveys. HPV was detected and genotyped using a GP5+/6+ PCR-based assay. HPV prevalence in the general population was 7.8% (95% confidence interval: 6.0–9.8) (5.1% of high-risk types), with no significant variation by age. HPV positivity was significantly higher among divorced women, women in polygamous marriages and those reporting husband's absence from home for >7 nights/month. HPV16/18 accounted for 30 and 82.2% of HPV-positive women in the general population and ICC, respectively. Cervical cancer prevention policies should take into account the relatively low HPV prevalence in this population.

To date, there are no data on the population prevalence of, or risk factors for, human papillomavirus (HPV) infection in predominantly Muslim countries in the Middle East, where sexual mores differ from many other world populations.[1] These data are essential to assess the potential relevance of HPV vaccination and HPV test-based screening to invasive cervical cancer (ICC) prevention in the region, as well as to identify any changes in risk occurring in young generations. Thus, a study of women with and without cervical cancer was carried out in Tehran, Iran, according to the standardized protocol of the International Agency for Research on Cancer (IARC) HPV prevalence surveys,[2] which was approved by both the IARC and local ethical review committees.

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Material and Methods

A total of 2,342 married women aged 18–59 years registered in the Public Clinic of Chizar (serving the child and maternal health needs for all families living within a densely populated suburb of Tehran) were invited to the study clinic by mail, phone and/or home visits. Attendance was 81% (95/118), 60% (340/570), 62% (355/574) and 37% (398/1,072) for the eligible population aged <25, 25–34, 35–44 and 45–59 years, respectively. Approximately 100 women were enrolled in each 5-year age group. Once a given age group sample size was met (which occurred for all age groups except <25 years), additional attendees underwent conventional Pap smear screening, but did not participate in the study ($n = 273$). An additional 85 attendees were excluded due to unwillingness (*e.g.*, 16 who were pregnant) or impossibility (*e.g.*, 28 hysterectomized women) of obtaining a sample of cervical exfoliated cells.

All enrolled participants signed an informed consent form and were administered a risk-factor questionnaire. Local staff felt it would have been difficult to ask women about lifetime number of sexual partners; hence this information was not collected. A sample of exfoliated cervical cells was collected from 830 participants and placed into PreservCyt media

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Table 1. Prevalence of HPV types in 825 women from the general population and 45 women with ICC[1] in Tehran, Iran

HPV type	General population							ICC
	Normal cytology			Abnormal cytology				
	Single	Multiple	Total (%)	Single	Multiple	Total (%)	All (%)	All (%)
N			791			34	825	45
HPV+	39	13	52 (6.6)	9	3	12 (35.3)	64 (7.8)	45[1] (100.0)
High-risk								
16	9	5	14 (1.8)	2[2]	1	3 (8.8)	17 (2.1)	27[3] (60.0)
18	0	2	2 (0.3)	0	0	0 (0.0)	2 (0.2)	10[3] (22.2)
31	1	4	5 (0.6)	0	0	0 (0.0)	5 (0.6)	4 (8.9)
39	3	0	3 (0.4)	1	1	2 (5.9)	5 (0.6)	
45	4	2	6 (0.8)	0	0	0 (0.0)	6 (0.7)	2 (4.4)
51	1	1	2 (0.3)	0	0	0 (0.0)	2 (0.2)	
52	2	0	2 (0.3)	0	1	1 (2.9)	3 (0.4)	
56	2	0	2 (0.3)	1	0	1 (2.9)	3 (0.4)	
58	0	1	1 (0.1)	2[2]	1	3 (8.8)	4 (0.5)	2[3] (4.4)
59	0	1	1 (0.1)	1	0	1 (2.9)	2 (0.2)	
73	1	0	1 (0.1)	0	0	0 (0.0)	1 (0.1)	
HR[4]	0	1	1 (0.1)	0	0	0 (0.0)	1 (0.1)	
Any	23	10	33 (4.2)	7	2	9 (26.5)	42 (5.1)	
Low-risk								
6	3	1	4 (0.5)	0	1	1 (2.9)	5 (0.6)	
26	0	0	0 (0.0)	0	0	0 (0.0)	0 (0.0)	1 (2.2)
30	0	0	0 (0.0)	1	0	1 (2.9)	1 (0.1)	
32	0	1	1 (0.1)	0	0	0 (0.0)	1 (0.1)	
40	1	1	2 (0.3)	0	0	0 (0.0)	2 (0.2)	
42	3	2	5 (0.6)	0	1	1 (2.9)	6 (0.7)	
54	1	0	1 (0.1)	0	0	0 (0.0)	1 (0.1)	
66	3	2	5 (0.6)	0	1	1 (2.9)	6 (0.7)	
67	1	1	2 (0.3)	0	0	0 (0.0)	2 (0.2)	
CP6108	1	1	2 (0.3)	0	0	0 (0.0)	2 (0.2)	
JC9710	3	3	6 (0.8)	1	1	2 (5.9)	8 (1.0)	
LR[5]	0	1	1 (0.1)	0	0	0 (0.0)	1 (0.1)	
Any	16	7	23 (2.9)	2	2	4 (11.8)	27 (3.3)	
X	0	1	1 (0.1)	0	0	0 (0.0)	1 (0.1)	

[1]Including 36 squamous cells and 7 adeno/other ICC cases that were infected with HPV18x3, HPV16x2, HPV45 and HPV16/58. [2]Including one woman with high-grade squamous intraepithelial lesion/ICC. [3]Including one multiple infection, HPV16/58. [4]Tested positive for the high-risk probe cocktail, but not for any individual high-risk type. [5]Tested positive for the low-risk probe cocktail, but not for any individual low-risk type.
HPV = human papillomavirus; HR = high-risk; ICC = invasive cervical cancer; LR = low-risk.

(Hologic, Marlborough, MA) for HPV testing and liquid-based cytology (LBC).

In parallel, formalin-fixed tumor biopsies were retrieved from women presenting with histologically confirmed ICC between 2002 and 2008 to the Taleghani, Mahdiyeh and Shohada Hospitals, all in Tehran, Iran. After exclusion of 19 biopsies that were beta-globin negative and/or without histological evidence of tumor, 45 ICCs remained (38 squamous-cell, 5 adeno- and 2 other specified carcinomas). The median age of included women with ICC was 51 years (range: 26–84 years).

LBC and HPV testing were performed at the VU University medical center, Amsterdam, The Netherlands, according to a protocol similar to that used in previous IARC HPV Prevalence Surveys.[3] DNA was extracted from the PreservCyt sample using magnetic beads (Macherey-Nagel, Düren, Germany) on a robotic system (Hamilton Robotics, Martinsried, Germany), according to the manufacturer's

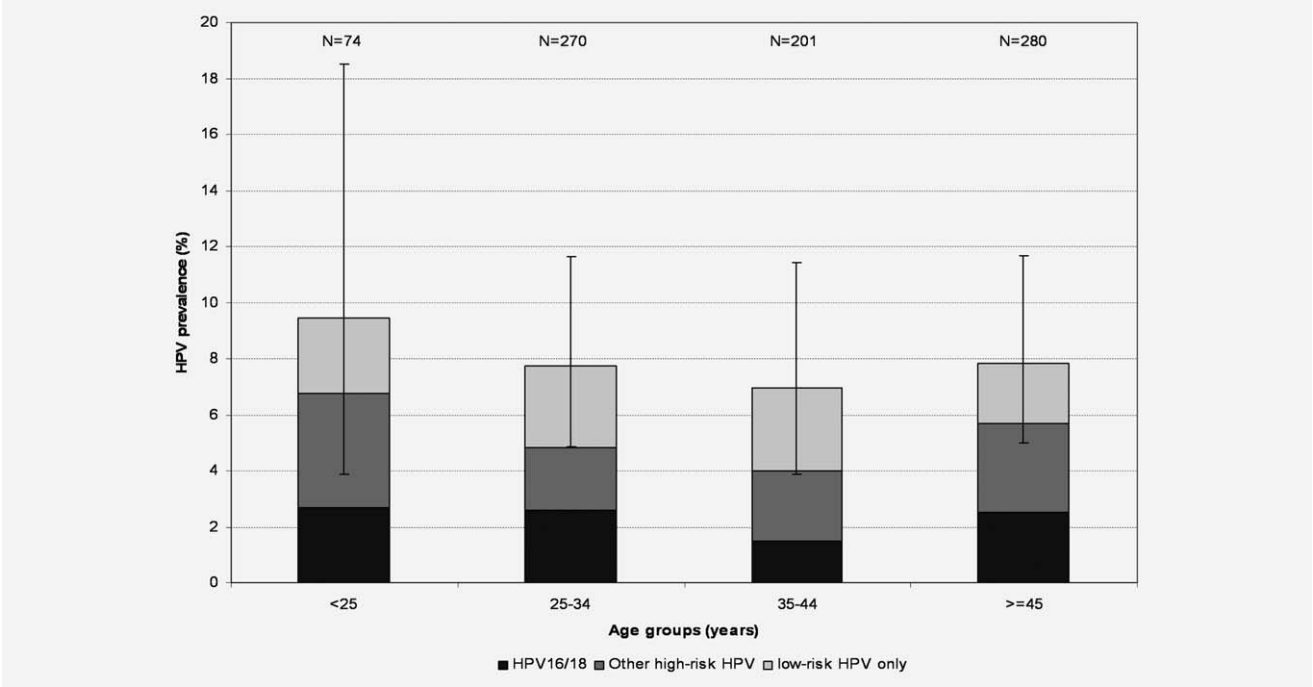

Figure 1. Age-specific prevalence of human papillomavirus (HPV) by HPV type(s) among 825 women in Iran.

instructions. For ICC biopsies, one or more 5 μM sections representing ~1 cm^2 of tissue were predigested with Proteinase K, after which DNA was extracted using magnetic beads (Macherey-Nagel, Düren, Germany). Beta-globin PCR analysis was performed first on all specimens to assess the quality of the DNA to be submitted to HPV PCR. A general primer GP5+/6+-mediated PCR was used for the detection of 44 mucosal HPV types.[4] Subsequent HPV genotyping was performed by reverse-line blot hybridization of GP5+/6+-PCR products.[5] LBC diagnosis was formulated according to CISOE-A standards and was translated into the Bethesda 2001 terminology system.[3] Five subjects were excluded due to inadequate LBC results.

Odds ratios (ORs) for HPV positivity were calculated by unconditional logistic regression adjusted for age, with OR trends assessed by considering categories as continuous variables.

Results

Among 825 women from the general population with valid liquid-based cytology and HPV results, overall HPV prevalence was 7.8% (95% confidence interval [CI]: 6.0–9.8), 5.1% (95% CI: 3.7–6.8) of high-risk HPV types (Table 1). Single and multiple HPV types accounted for 5.9 and 1.9% of HPV prevalence, respectively (not shown in table). Cytological cervical abnormalities were diagnosed in 34 (4.1%) women, of whom 35.3% were HPV-positive. They included 29 atypical squamous cells of undermined significance (10 HPV-positive), three low-grade squamous intraepithelial lesions (all HPV-negative) and two high-grade squamous intraepithelial lesions (1 HPV16-positive, 1 HPV58-positive). HPV16 was confirmed as the most common type among women with both normal (1.8%) and abnormal (8.8%) cytology. HPV16 was also the predominant HPV type in ICC (60.0%, 95% CI: 44.3–74.3), followed by HPV18 (22.2%, 95% CI: 11.2–37.1) and HPV31 (8.9%, 95% CI: 2.5–21.2) (Table 1). HPV16 and/or 18 accounted for 82.2% (95% CI: 67.9–92.0) of ICC.

Figure 1 shows the age-specific prevalence of HPV, classified hierarchically into (*i*) HPV16 or 18, (*ii*) other high-risk types and (*iii*) low-risk types only. HPV decreased from 9.5% among women aged <25 years to 7.9% in women aged =45 years, but this variation was not significant.

Table 2 shows the relationship between overall HPV positivity and various characteristics of study participants, adjusted for age. Significant risk factors for HPV positivity included being in a polygamous marriage (OR = 3.98; 95% CI: 1.04–15.29), being divorced (OR = 4.84; 95% CI: 1.24–18.93) and reporting a husband that was away from home >7 nights/month (OR = 3.62; 95% CI: 1.83–7.16) (Table 2). There were no significant associations with education level, occupation, age at sexual debut, time since sexual debut, or husbands' extramarital affairs (Table 2). Birth outside Tehran (reported by 42.2% of women), condom use (49.6%), hormonal contraceptive use (37.5%), intrauterine device use (31.8%), history of spontaneous (21.0%) or induced (12.2%) abortion, smoking (6.2%) and previous Pap smear (80.4%) were also not significantly associated with HPV positivity (data not shown). Additional adjustment for marital status, where appropriate, had no material affect on any of the above associations (data not shown).

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Table 2. ORs for HPV positivity and corresponding 95% CIs according to selected characteristics among 825 women in Iran

Characteristic	*N* women[1]	HPV-positive		OR[2]	95% CI
		N	%		
Age (years)					
<25	74	7	(9.5)	1.00	
25–34	270	21	(7.8)	0.81	(0.33–1.98)
35–44	201	14	(7.0)	0.72	(0.28–1.85)
≥45	280	22	(7.9)	0.82	(0.33–1.99)
χ^2_1 *for trend*				*0.09*	*p = 0.765*
Education level					
Illiterate[3]/Primary/Secondary	210	12	(5.7)	0.57	(0.27–1.20)
Completed school leaving certificate	375	30	(8.0)	0.85	(0.47–1.51)
Higher degree	240	22	(9.2)	1.00	
χ^2_1 *for trend*				*2.13*	*p = 0.144*
Occupation					
Housewife	670	50	(7.5)	1.00	
Employed	155	14	(9.0)	1.25	(0.67–2.34)
Marital status					
Married, husband has only 1 wife	772	57	(7.4)	1.00	
Married, husband has other wife(ves)	13	3	(23.1)	3.98	(1.04–15.29)
Divorced	11	3	(27.3)	4.84	(1.24–18.93)
Widow	28	1	(3.6)	0.48	(0.06–3.71)
Number of full-term pregnancies					
0	64	9	(14.1)	2.06	(0.90–4.72)
1–2	535	40	(7.5)	1.00	
≥3	222	15	(6.8)	0.82	(0.41–1.65)
χ^2_1 *for trend*				*2.37*	*p = 0.124*
Age at sexual debut (years)					
≤18	277	20	(7.2)	1.00	
19–22	342	27	(7.9)	1.11	(0.61–2.04)
≥23	206	17	(8.3)	1.21	(0.61–2.41)
χ^2_1 *for trend*				*0.30*	*p = 0.584*
Time since sexual debut (years)					
0–2	30	4	(13.3)	1.69	(0.43–6.63)
3–4	74	8	(10.8)	1.31	(0.65–3.84)
5–9	153	8	(5.2)	0.58	(0.22–1.53)
≥10	568	44	(7.7)	1.00	
χ^2_1 *for trend*				0.62	p = 0.432
Husband's extramarital affairs[4]					
No	693	49	(7.1)	1.00	
Yes/Maybe	93	11	(11.8)	1.80	(0.89–3.61)
Husband away from home >7 nights/month[4]					
No	719	47	(6.5)	1.00	
Yes	65	13	(20.0)	3.62	(1.83–7.16)

[1]Some figures do not add up to the total because of a few missing values. [2]Adjusted for age. [3]Only 26 illiterate. [4]Restricted to currently married women only (*N* = 786). CI = confidence interval; HPV = human papillomavirus; OR = odds ratio.

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Discussion

The present population-based study, the first carried out in Iran or the Middle East, disclosed a relatively low burden of HPV infection (7.8%) in the general female population of Tehran. HPV prevalence in the present study was much lower than that found using similar protocols in areas known to be at high cervical cancer risk in sub-Saharan Africa (*e.g.*, 51% in Guinea),[3] South America and India (14-17%),[2] but a little higher than certain very low-risk rural populations in Asia (2–4%).[2] In addition, the prevalence of high-risk HPV in Iran (5.1%) can be directly compared with GP5+/6+-based prevalence (5.6–15.7%) among women attending cervical screening in Europe and Canada.[6,7] HPV prevalence was not statistically higher in younger women, confirming the flat age-specific curve seen in other low-resource countries in Asia and Africa,[8] albeit at lower HPV prevalence.

HPV16 and 18 accounted for over 80% of ICC in Iran, confirming the high prevalence of HPV16 observed in ICC from Iran[9–12] and Western Asia in general[13] compared to other world regions. This data would suggest that the predominance of HPV16 and 18 over other high-risk types might be even greater in settings of low HPV exposure.

Major study strengths include a large population-based sample, and the use of a standardized and well-validated HPV test allowing comparisons with similar studies around the world[2,3,14–18] and with a concurrent series of ICC from the same area. The main limitation, which was nevertheless an important finding in itself, was a relatively low participation rate in older women. The principal reason for nonparticipation appeared to be a general lack of appreciation of the utility of cervical screening in the absence of symptoms. Unlike in some other Western Asian populations,[19] lack of husband's permission was not commonly cited as a reason for nonparticipation. Because HPV infection is asymptomatic, it is unlikely that participation was highly correlated to HPV positivity. Nevertheless, hesitancy to undergo gynaecological exam would need to be addressed to improve population-based cervical cancer screening efforts in Iran. Furthermore, vaginal examination was acceptable only to married women, as in similar surveys in Asia.[15,20] Nevertheless, 95% of women reported an age at sexual debut concurrent with, or soon after, age at marriage, suggesting that marriage is a good proxy of sexual debut in this population. Furthermore, participation in married women aged <25 years was relatively good (81%) perhaps suggesting increasing awareness for cervical cancer prevention in younger generations. Lastly, an HPV prevalence of 35.3% in cervical abnormalities is low,[21] highlighting problems in specificity of even gold-standard cytology in settings of low HPV prevalence.

In conclusion, the relatively low HPV prevalence in this study is consistent with the low ICC risk estimate from Tehran (4.8 cases per 100,000 women per year),[22] other regions in Iran[23–25] and neighboring countries[22] where cervical cancer is less frequently diagnosed in women than breast, ovarian endometrial and many other cancers. Furthermore, there was no evidence that HPV prevalence is increasing in young generations of urban women. Nevertheless, more than 500 cases of cervical cancer were diagnosed in Tehran between 1998 and 2001,[22] of which over 80% are estimated to be attributable to HPV16/18. These findings should be taken into account when considering the cost-effectiveness and feasibility of HPV-based vaccination and/or screening in the region.

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