RESEARCH ARTICLE

Human Papillomavirus Burden in Different Cancers in Iran: a Systematic Assessment

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Abstract

Certain types of human papillomaviruses (HPVs) are undoubtedly involved in genesis of human malignancies. HPV plays an etiological role in cervical cancer, but also in many vaginal, vulvar, anal and penile cancers, as well as head and neck cancers. In addition, a number of non-malignant diseases such as genital warts and recurrent respiratory papillomatosis are attributable to HPV. Moreover, HPV forms have detected in several other cancers including esophageal squamous cell carcinoma, lung, prostate, ovarian, breast, skin, colorectal and urinary tract cancers, but associations with etiology in these cases is controversial. The aim of this systematic assessment was to estimate the prevalence of HPV infection and HPV types in HPV-associated cancers, HPV-related non-malignant diseases and in cancers that may be associated with HPV in Iran. The present investiagtion covered 61 studies on a variety of cancers in Iranian populations. HPV prevalence was 77.5 % and 32.4% in cervical cancer and head and neck cancers, respectively. HPV was detected in 23.1%, 22.2%, 10.4%, 30.9%, 14% and 25.2% of esophageal squamous cell, lung, prostate, urinary tract cancers, breast and skin cancers, respectively. HPV16 and 18 were the most frequent HPV types in all cancers. The findings of present study imply that current HPV vaccines for cervical cancer may decrease the burden of other cancers if they are really related to HPV.

Keywords: Human papillomaviruses - prevalence - HPV types - cancer types - Iran

Asian Pac J Cancer Prev, **15 (17)**, 7029-7035

Introduction

Cancer is one of the most important mortal agents in Iran. Breast cancer, with estimated the age standardized incidence rate (ASR) 18.4, is the first common cancer and cervical cancer is the eleventh frequent cancer in Iranian women. Prostate cancer, with reported ASR 11.6, is the second most prevalent in Iranian men. Stomach, colorectum, bladder, esophagus and lung cancers are common cancers in both sex (ASR=15.6, 7.6, 7, 6.8 and 6.4per 100,000, respectively) (IARC, 2008).

Certain types of Human papillomaviruses (HPVs) are undoubtedly involved in human malignancies. One of the most important HPV-related cancers is cervical cancer that is the third most frequently cancer in women worldwide (Jemal et al., 2011; Moscicki et al., 2012). Also, HPV plays an etiological role in many vaginal, vulvar, anal, penile, as well as head and neck cancers (Gillison et al., 2012d; Moscicki et al., 2012). In addition, a number of non-malignant diseases such as genital warts and recurrent respiratory papillomatosis are attributable to HPV, particularly HPV6 and 11 (Chelimo et al., 2013; Gillison et al., 2012c). Moreover, HPV detected in several other cancers including esophageal squamous cell carcinoma (Syrjanen, 2002b; Tornesello et al., 2009), lung (Rezazadeh et al., 2009b; Munoz et al., 2012), prostate (Lin et al., 2011), ovarian (Rosa et al., 2013), breast (Simoes et al., 2012), skin (Iftner et al., 2003), colorectal (Burnett-Hartman et al., 2008; Lorenzon et al., 2011) and urinary tract cancers (Li et al., 2011), but association of HPV to these cancers is controversial.

Infection by specific types of HPV, particularly HPV16 and 18, is responsible for development of HPV-related cancers. It is identified that most HPV-related cancers and HPV weekly related cancers are associated to infections by high-risk types including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73 (Munoz et al., 2003; Cogliano et al., 2005; Munoz et al., 2006; Bouvard et al., 2009; Doorbar et al., 2012).

In the HPV-associated cancers commonly several years after the initial infection, tumors progress in the epithelia. Persistent infection with expression of some viral genes, particularly E6 and E7 is needed for development of invasive cancer. However, most HPV infections have a benign outcome because nearly half of them clear within 6 months and up to 2 years the majority of cases clear from infection, but those that persist can progress to cancer (Rodriguez et al., 2010; Moscicki et al., 2012).

The aim of this systematic review is to estimate the prevalence of HPV infection and HPV types in HPV-

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Table 1. List of Studies on HPV-related Cancers (Cervical Cancer and Head & Neck Cancers) and Healthy Subjects in Iranian Population

Samples	"Province (Sampling time)"	Year	"Mean or median age (y) (Range)"	No.	"HPV pos N (%)"	"Detection method (Primers) "	Typing-method	References
Cervix								
ICC	Gilan	2002	-	39	29 (74.3)	PCR (GPs)[a]	ISH [b]	(Hamkar et al., 2004)
	Golestan	2002	-	43	31 (72.1)	PCR (GPs)	ISH	(Hamkar et al., 2004)
	Mazandaran	2002		42	33 (78.6)	PCR (GPs)	ISH & Sequencing	(Hamkar et al., 2002)
	Tehran	2002	-	69	59 (85.5)	ISH	TSP[c] (HPV16,18,33)	(Mortazavi et al., 2002)
	Fars	2003	49.1	101	88 (87.1)	-	-	(Farjadian et al., 2003)
	Tehran	2006	52.5 (32-73)	64	38 (59.4)	TSP PCR	TSP (HPV16,18)	(Maleknejad et al., 2006)
	Tehran (2005-2006)	2006	35.3	7	7 (100)	PCR (GPs)	TSP (HPV6,11,16,18,31,33)	(Ghaffari et al., 2006)
	"East Azarbaijan (2000-2006)"	2007	51.1 (29-79)	74	47 (63.5)	PCR (GPs)	Type specific multiplex	(Esmaeili et al., 2008)
	Tehran (1999-2005)	2007	52.16 (30-75)	37	32 (86.5)	PCR	Hybridization	(Yarandi et al., 2007)
	"West Azarbaijan (1999-2005)"	2007	51.8 (31-83)	18	10 (55.5)	PCR	TSP (HPV16,18)	(Omrani et al., 2007)
	Yazd	2007	47.2 (23-86)	40	30 (75.0)	PCR (GPs)	Sequencing	(Mahmoodi et al., 2007)
	Tehran	2008	46.5 (25-68)	70	34 (48.6)	PCR Kit	Typing PCR Kit (Sacace)	(Eslami et al., 2008b)
	Tehran (2003-2007)	2011	48 (28-72)	87	72 (82.7)	Real-time (GPs)	Sequencing	(Shahsiah et al., 2011)
	Tehran (2002-2008)	2011	51(26-84)	45	45 (100)	PCR (GPs)	Reverse-line blot hybridization	(Khodakarami et al., 2012)
	Isfahan (2007-2009)	2011	52 (29-73)	47	45 (95.7)	PCR (GPs)	-	(Allameh et al., 2011)
	Isfahan (2006-2010)	2011	-	12	12 (100)	PCR (GPs)	Real-time	(Heidarpour et al., 2011)
	Mazandaran (2009-2011)	2013	52.6	67	56 (83.6)	PCR	HPV Genotype-Eph kit (AmpliSens)	(Haghshenas et al., 2013)
HSIL	Tehran (2005-2006)	2006	35.3	7	5 (71.4)	PCR (GPs)	TSP (6,11,16,18,31,33)	(Ghaffari et al., 2006)
	"East Azarbaijan (2000-2006)"	2007	51.1 (29-79)	34	28 (82.3)	PCR (GPs)	Type specific multiplex	(Esmaeili et al., 2008)
	Tehran (1999-2005)	2007	39.80 (26-52)	40	15 (37.5)	PCR	Hybridization	(Yarandi et al., 2007)
	"West Azarbaijan (1999-2005)"	2007	51.8 (31-83)	1	0 (0.0)	PCR	TSP (HPV16,18)	(Omrani et al., 2007)
	Tehran (2002-2008)	2011	(18-59)	2	2 (100)	PCR (GPs)	Reverse-line blot hybridization	(Khodakarami et al., 2012)
	Isfahan (2007-2009)	2011	52 (29-73)	29	27 (93.1)	PCR (GPs)	-	(Allameh et al., 2011)
	Isfahan (2006-2010)	2011	-	12	12 (100)	PCR (GPs)	Real-time	(Heidarpour et al., 2011)
	Mazandaran (2009-2011)	2013	52.6	12	8 (66.7)	PCR	HPVGenotype-Eph kit (AmpliSens)	(Allameh et al., 2011)
	Mazandaran (2008-2009)	2013	26.19	11	2 (18.2)	PCR	-	(Sharbatdaran et al., 2013)
LSIL	Tehran (2005-2006)	2006	35.3	12	7 (58.3)	PCR (GPs)	TSP (HPV6,11,16,18,31,33)	(Ghaffari et al., 2006)
	"East Azarbaijan (2000-2006)"	2007	51.1 (29–79)	23	9 (39.1)	PCR (GPs)	Type specific multiplex	(Esmaeili et al., 2008)
	Ormia (1999-2005)	2007	51.8 (31-83)	16	3 (18.7)	PCR	TSP (HPV16,18)	(Omrani et al., 2007)
	Tehran (2002-2008)	2011	(18-59)	3	0 (0.0)	PCR (GPs)	Reverse-line blot hybridization	(Khodakarami et al., 2012)
	Isfahan (2007-2009)	2011	52 (29-73)	39	36 (92.3)	PCR (GPs)	-	(Allameh et al., 2011)
	Isfahan (2006-2010)	2011	-	12	12 (100)	PCR (GPs)	Real-time	(Heidarpour et al., 2011)
	Mazandaran (2009-2011)	2013	52.6	19	14 (73.7)	PCR	HPV Genotype-Eph kit (AmpliSens)	(Allameh et al., 2011)
	Mazandaran (2008-2009)	2013	29.31	2	1 (50.0)	PCR	-	(Sharbatdaran et al., 2013)
ASCUS	Gilan	2002	-	8	5 (62.5)	PCR (GPs)	ISH	(Hamkar et al., 2004)
	Golestan	2002	-	6	4 (66.7)	PCR (GPs)	ISH	(Hamkar et al., 2004)
	Mazandaran	2002		14	9 (64.3)	PCR (GPs)	ISH & Sequencing	(Hamkar et al., 2002)
	Tehran (2005-2006)	2006	35.3	31	18 (58.1)	PCR (GPs)	TSP (HPV6,11,16,18,31,33)	(Ghaffari et al., 2006)
	Isfahan (2007-2009)	2011	52 (29-73)	15	10 (66.7)	PCR (GPs)	-	(Allameh et al., 2011)
	Mazandaran (2008-2009)	2013	29.31	17	0 (0.0)	PCR	-	(Sharbatdaran et al., 2013)
Normal	Gilan	2002	-	34	3 (8.8)	PCR (GPs)	ISH	(Hamkar et al., 2004)
	Golestan	2002	-	38	2 (5.3)	PCR (GPs)	ISH	(Hamkar et al., 2004)
	Mazandaran	2002		44	4 (9.1)	PCR (GPs)	ISH & Sequencing	(Hamkar et al., 2002)
	Tehran (2005-2006)	2006	33	77	10 (13)	PCR (GPs)	TSP (HPV6,11,16,18,31,33)	(Ghaffari et al., 2006)
	Tehran (2003-2005)	2008	(15-55)	597	31 (5.2)	PCR (GPs)	Sequencing	(Jamali Zavarei et al., 2008)
	Fars (July to Dec 2008)	2010	35.2 (20-72)	402	22 (5.5)	PCR	TSP (HPV16,18)	(Safaei et al., 2010)
	Bushehr (2008-2009)	2010	-	200	11 (5.5)	PCR (GPs)	Sequencing	(Zandi et al., 2010)
	Golestan	2011	37.54 (15-75)	226	41 (18.1)	PCR (GPs)	TSP (HPV16,18)	(Moradi et al., 2011)
	Tehran (2002-2008)	2011	(18-59)	791	52 (6.6)	PCR (GPs)	Reverse-line blot hybridization	(Khodakarami et al., 2012)
	Isfahan (2009-2010)	2012	(18-60)	180	46 (25.5)	PCR (GPs)	TSP (HPV6,11,16,18)	(Allameh et al., 2013)
	Bushehr (2009-2010)	2012	35.96	799	5 (0.62)	PCR	INNO-LiPA	(Eghbali et al., 2012)
	Mazandaran (2008-2009)	2013	26.19	60	0 (0.0)	PCR	-	(Sharbatdaran et al., 2013)
Head & neck	Sistan & Balochestan	2005	56.6 (35-80)	51	11 (21.6)	PCR (MYs) d	TSP (HPV6,11,16,18,31,33)	(Sargolzaie et al., 2005)
Oral cavity & oropharyngeal	Kerman (1995-2003)	2006	51 (27-74)	15	9 (60.0)	PCR (MYs)	TSP (HPV16,18)	(Zarei et al., 2007)
	Tehran	2010	44.37	24	15 (62.5)	Nested-PCR (MYs + GPs)	EIA	(Haratian et al., 2010)
	Tehran (2001-2008)	2011	57.88 (22-84)	94	25 (26.6)	PCR	HPV16,18 typing by kit	(Seraj et al., 2011)
	East Azarbaijan	2011	68.9 (48-85)	30	6 (20.0)	PCR (MYs)	-	(Halimi & Morshedi, 2011b)
	East Azarbaijan	2012	39.71 (27-50)	14	8 (57.1)	Nested-PCR (MYs and GPs)"	Sequencing	(Asvadi Kermani et al., 2012)
Oral lesions	Kerman (1995-2003)	2006	40.5 (4-67)	45	7 (15.5)	PCR (MYs)	TSP (HPV16,18)	(Zarei et al., 2007)
	Isfahan	2009	49.55 (22-84)	29	9 (31.0)	PCR of HPV18	PCR of HPV18	(Razavi et al., 2009)
	Khorasan Razavi	2011	-	20	0 (0.0)	PCR	TSP (HPV16,18,31,33)	(Saghravanian et al., 2011)
Saliva or oral mucosa of healthy subjects								
	Sistan & Balochestan	2005	30.7	28	1 (3.6)	PCR (MYs)	TSP (HPV6,11,16,18,31,33)	(Sargolzaie et al., 2005)
	Isfahan	2009	48.5 (29-70)	14	1 (7.1)	PCR of HPV18	PCR of HPV18	(Razavi et al., 2009)
	Tehran	2009	64.4	20	5 (25.0)	PCR (GPs)	TSP (HPV6,11,16,18,31,33)	(SahebJamee et al., 2009)
	Khorasan Razavi	2011	-	18	0 (0.0)	PCR	TSP (HPV16,18,31,33)	(Saghravanian et al., 2011)
	East Azarbaijan	2013	31.6 (16-61)	114	7 (6.1)	Nested-PCR (MYs + GPs)	Sequencing	(Seifi et al., 2013)

*[a]GPs: GP5±/GP6±, [b]ISH: In situ hybridization, [c]TSP:Type specific primers, [d]MYs: MY09/MY11

associated cancers, HPV-related non-malignant diseases and cancers may be associated with HPV in Iranian population.

Materials and Methods

A systematic review of the published studies up to November 2013 was carried out to assess the prevalence and HPV types in variety of cancers that are associated with HPV (anogenital cancers as well as head and neck cancers) or may be associated with HPV. Data were obtained by searches of PubMed, Current Contents, Scopus and national databases including IranMedex, SID, Magiran with the following search terms: ''human papillomavirus (HPV)'', ''cancer/neoplasms'', ''epidemiology'', ''prevalence'', and "Iran".

The following information were obtained from each included article: first author, year of publication, journal name, study period, sample size, age, gender, city, type of cancer, HPV detection methods, HPV prevalence, HPV genotyping methods and HPV types.

After exclusion of some studies due to duplication or irrelevant data, 61 studies were included in this study.

Results

Present systematic review was included 61 studies on variety of cancers that strongly or weekly associated with HPV. Tables 1 and 2 summarize the studies on HPV-related cancers and cancers may be associated with HPV in Iranian population, respectively. The prevalence of HPV16 and 18 types in different kind of cancers were shown in Figure 1.

HPV associated-cancers

Anogenital cancers. HPV prevalence data only were available for cervical cancer, but not for the other kind of anogenital cancers including vulva, vagina, penil and anal. Crude HPV prevalence was 77.5%, 66.9%, 65.1%, 50.5% and 6.6% among ICC, HSIL, LSIL, ASCUS and normal cases in Iran (Table 3). HPV16 was the most prevalent HPV type for all five histological types, followed by HPV18, 6/11, 31 and 33 types. Also HPV45, 58, 59, 68 and 73 types were detected in a minority of subjects.

Table 2. List of Studies on HPV May be Associated-cancers and Corresponding Controls in Iranian Population

Cancer type	"Province (sampling time)"	Year	HPV positive Cancer	Control	"Method (Primers)"	Typing-method	References
ESCCa	Golestan (1997-98)	2002	42/85	-	PCR (GPs)[b]	Sequencing	(Moradi et al., 2002)
	Tehran (1996-2001)	2005	14/38	5/38	PCR (MYs)[c]	TSP d (HPV16,18)	(Farhadi et al., 2005)
	Tehran	2007	33/140	-	PCR (GPs)	Sequencing	(Far et al., 2007)
	"Mazandaran (2001-2008)"	2011	15/40	5/40	AmpliSense PCR Kit	"AmpliSense FRT PCR Kit"	(Emadeian et al., 2011)
	Fars (1982-2002)	2012	0/92	0/20	PCR	-	(Noori et al., 2012)
	Tehran (1991-2005)	2012	8/93	-	PCR (SPF10)	INNO-LiPA	(Abdirad et al., 2012)
	Mazandaran (2004-2011)	2012	49/177	-	Real-time PCR (MYs)	"AmpliSense FRT PCR Kit"	(Yahyapour et al., 2012)
	Tehran	2013	0/30	-	PCR (GPs)	-	(Haeri et al., 2013)
Lung cancer	Mazandaran (1998-2004)	2007	33/141	8/92	"Nested-PCR (MY and GP)"	Sequencing	(Nadji et al., 2007)
	-	2004	18-Aug	-	"Semi-nested PCR for HPV-16 & 18"	TSP (HPV16,18)	(Shafaghi et al., 2004)
	"East Azarbaijan (2009-2011)"	2011	30-Mar	-	PCR (MYs)	-	(Halimi & Morshedi, 2011)
	"East Azarbaijan 2006-2009)" (MY and GP)"	2013 Sequencing	9/50	-	"Nested-PCR		(Jafari et al., 2013)
Prostate cancer	Tehran	2011	13/104	8/104	"Nested-PCR (MYs and GPs)"	Sequencing	(Aghakhani et al., 2011)
	Isfahan (2001-2006)	2011	30-Mar	1/90	IHC e	-	(Mokhtari et al., 2011)
	Gilan	2012	3/68	0/85	PCR (MYs)	-	(Salehi & Hadavi, 2012)
	Tehran	2013	29-May	8/167	"Nested-PCR (MY and GP)"	-	(Ghasemian et al., 2013)
Urinary tract-cancers	Tehran (1999-2002)	2005	21/59	20-01	PCR	RFLP	(Barghi et al., 2005)
	Fars (2003-2006)	2012	7/49	0/16	Nested-PCR	Sequencing	(Salehipour et al., 2012)
	Tehran	2008	51/147	3/39	"PCR Kit (Sacace)"	"Typing PCR Kit (Sacace)"	(Eslami et al., 2008a)
Breast cancer	Golestan	2009	0/231	-	"Nested-PCR (MY and GP)"	-	(Moradi et al., 2009)
	-	2011	20/67	-	-	-	(Ghaffari et al., 2011)
	Mazandaran (2002-2009)	2012	16/79	1/59	PCR (GPs, CP & FAP)	Sequencing	(Sigaroodi et al., 2012)
Skin cancer	Mazandaran	2007	35/136	1/139	"Nested-PCR (MY and GP)"	Sequencing	(Shahmahmoudi et al., 2007)
	Tehran	2012	18/60	15/60	PCR (MYs)	INNO-LiPA	(Shayanfar et al., 2013)
	Isfahan	2005	13/66	2/66	-	-	(Mokhtari & Bayat, 2005)
Conjunctiva SCC f	Tehran (2000-2006)	2011	46/50	0/50	"Nested-PCR (MY and GP)"	TSP (HPV16,18)	(Asadi-Amoli et al., 2011)

*[a]ESCC: Esophagus squamous cell carcinoma, [b] GPs: GP5+/GP6+, [c]MYs: MY09/MY11, [d]TSP:Type specific primers, [e]IHC: Immunohistochemistry,t [f] SCC: squamous cell carcinoma

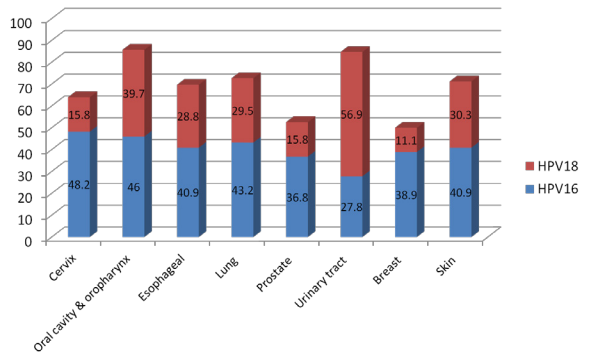

Figure 1. Prevalence of HPV16 and 18 Types in a Variety of Cancers

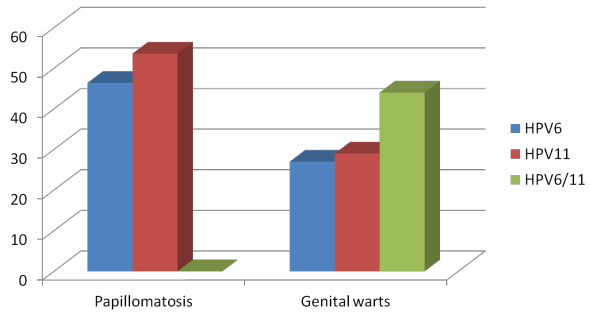

Figure 1. Prevalence of HPV 11, 16 and 18 Types in Non- Cancer Lesions

Head and neck cancers. The crude HPV prevalence 32.4% was estimated in patients with Oral cavity and oropharyngeal cancers. Also, HPV was detected in 17% and 7.2% of oral lesions and Saliva and/or oral mucosa of healthy subjects, respectively (Table 3). The most common HPV types were HPV16 and 18, followed by 6, 11 and 31.

Cancers may be associated with HPV

Esophagus squamous cell carcinoma: The overall HPV prevalence in esophageal cancer and control groups was 23.1% and 10.2%, respectively. According to HPV types, the most common type was HPV16 (40.9%) in cases. The other high-risk types were HPV18, 31, 33, 45 and 52. In contrast, in control group the prominent type was HPV18 (70%) followed by HPV16 (30%).

Lung cancer: HPV positivity in lung cancer and corresponding control groups estimated 22.2% and 8.7%, respectively. The two most frequent types were HPV16 and 18 in cases, followed by 6/11 and 31, but HPV6/11 were prominent in control group.

Prostate cancer: The crude HPV prevalence was 10.4% versus 3.8% in prostate cancer cases and benign prostatic hyperplasia subjects, respectively. Regarding to HPV types, detection of HPV16 and 18 in cases were almost equal to controls.

Urinary tract cancers: Frequency of HPV estimated 30.9% and 5.3% in urinary tract cancer and control groups, respectively. The most frequent type was HPV18, followed by HPV16 in case and control groups. However, in case group other types including HPV6, 31, 33 and 52 detected in few samples.

Breast cancer: The overall HPV prevalence in breast cancer cases and control subjects was 14% and 1.1%, respectively. The most prevalent HPV type was HPV16 in breast cancer patients, followed by HPV6, 11 and 18. In few samples the other HPV types including 15, 23, 31, 33 and 124 detected. In control group, the only one HPV detected was HPV124.

Skin cancers: HPV positivity in non-melanoma skin cancers (squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]) and control groups obtained 25.2% and 6.8%, respectively. According to histological stratification, HPV detected in 22.7% and 29.3% of SCC and BCC cases, respectively. Regarding to HPV types in skin cancer patients, HPV16 and 18 were more prevalent. The other types detected were HPV6, 11, 56. In control group, HPV types did not determine.

Conjunctiva squamous cell carcinoma: HPV was detected in 92% of conjunctiva cancer, but not among control group. All samples were negative for HPV16, 18, 31 and 33.

Table 3. Overall HPV and Type-specific HPV prevalence in Variety of Cancers and Controls in Iranian Population

Cancer types	No. of cases	HPV Positive n (%)	HPV types		
			High-risk	Intermediate or-Low-risk	Undetermined
HPV associated-cancers and controls					
Cervical cancer					
ICC	862	668 (77.5)	618	27	23
HSIL	148	99 (66.9)[a]	101	8	0
LSIL	126	82 (65.1)	70	6	6
ASCUS	91	46 (50.5)	32	9	5
Normal cervical cytology	3448	227 (6.6)	162	30	35
Head & neck cancers					
Oral cavity and-oropharyngeal cancers	228	74 (32.4)	63	4	7
Oral lesions	94	16 (17)	11	5	0
Saliva or oral mucosa-of healthy subjects	194	14 (7.2)	11	3	0
HPV weekly associated-cancers and controls					
Esophageal squamous-cell carcinoma	695	161 (23.1)[a]	118	25	35
Normal endoscopy tissue	98	10 (10.2)	10	0	0
Lung cancer	239	53 (22.2)	43	7	3
Controls	92	8 (8.7)	3	5	0
Prostate cancer	231	24 (10.4)	10	3	11
Benign prostate hyperplasia	446	17 (3.8)	5	3	9
Urinary tract cancers	255	79 (30.9)[a]	78	4	0
Benign lesions	75	4 (5.3)	4	0	0
Breast cancer	427	60 (14)[a]	36	26	1
Benign lesions	88	1 (1.1)	0	1	0
Skin cancer (SCC & BCC)[b]	262	66 (25.2)[a]	48	12	17
Benign lesions	265	18 (6.8)	1	0	17
Conjunctiva squamous-cell carcinoma	50	46 (92)	0	0	46[c]
Normal conjunctiva	50	0 (0.0)	0	0	0
HPV-associated non-malignant diseases					
Recurrent respiratory-papillomatosis	29	28 (96.5)	0	28	0
Genital warts	165	100 (60.4)	0	100	0

[*a]coinfection cases reported; [b]Squamous cell carcinoma (SCC) =163, Basal cell carcinoma (BCC) =99 cases; [c]types of all samples was not HPV16,18,31,33 , but the other types did not determine

HPV-related non-malignant diseases

There are few reports about HPV prevalence and type distribution in genital warts (GW) (Nassiri et al., 2009; Jamshidi et al., 2012) and recurrent respiratory papillomatosis (RRP) (Izadi et al., 2012) in Iran. In these studies, HPV detected in 60.4% and 96.5% of GW and RRP cases, respectively. Nearly all HPV positive cases were infected with HPV6 and 11. In genital warts group, many subjects were coinfected with HPV6/11 (44%).

Discussion

This systematic review obtained from 61 published studies estimated the prevalence of HPV infection and HPV types in HPV-associated cancers, cancers may be associated with HPV and HPV-related non-malignant diseases in Iranian population. Therefore, present study allowed us to make the inclusive estimates of HPV prevalence and HPV types in different kind of cancers in Iran.

In most studies on ICC in Iran, HPV prevalence was less than 100% prevalence that might be attributable to low sensitivity of techniques used to detect HPV DNA. The overall HPV prevalence of HSIL and LSIL were 66.9% and 65.1%, respectively. HPV prevalence was diverse among HSIL and LSIL Iranian subjects that likely are result of small sample size and using different methods to detection of HPV. The six most common HPV types were HPV16, 18, 6/11, 31 and 33 in all groups. The most frequent HPV type was HPV16 followed by HPV18 in all five different histology. It is estimated that 70.1% of ICC are caused by HPV16 or 18 worldwide (Castellsague et al., 2007).

In present study HPV detected in 44.4% of patients with head and neck cancers. The most common HPV types were HPV16 and 18. It is demonstrated that HPV infection is causally related to head and neck cancers (Kreimer et al., 2005; Strati et al., 2006; Gillison et al., 2012b; Jung et al., 2010). A strong association between HPV16 and oropharyngeal cancer has been demonstrated in frequent case-control studies (Kreimer et al., 2005; Sudhoff et al., 2011). Moreover, a small fraction of head and neck cancers may be caused by further HPV types such as HPV18, 31, 33, 35 (Gillison et al., 2012a).

In all HPV weekly associated-cancers investigated in this study HPV detected in a number of cancer cases and control subjects. However, the HPV was more prevalent in cases versus controls. HPV16 and 18 were most frequent HPV types in all cancers ranging from 50% to 84.7%. These findings are consistent to some epidemiological studies that had been reported HPV detection in variety of cancers (Syrjanen, 2002a; 2002b; Iftner et al., 2003; Rezazadeh et al., 2009a; Tornesello et al., 2009; Li et al., 2011; Lin et al., 2011; Munoz et al., 2012; Simoes et al., 2012). However, detection of HPV DNA in these cancers by PCR alone is inadequate to verify causality. Therefore, to confirm the casually role of HPV in these kind of cancers, it is mandatory to investigate the biological activities of HPV such as E6/E7 expression or integration in these precancerous and cancerous lesions. Moreover, experimental models are needed to investigate the initiation and maintenance processes of tumorgenesis in these cancers. If the association of HPV with these cancers proves, it will be good news for prevention of these malignancies as current HPV vaccines will reduce dramatically the incidence of them.

In conclusion, pooled data of epidemiological studies in Iran suggest that HPV may play an important role in progression of cancers of the esophagus, skin, breast, lung, prostate and urinary tract. However, these findings should be verified by precise investigation of HPV transformational activity in these cancers. In another aspect, findings of present study imply that current HPV vaccines for cervical cancer may decline the burden of other cancers if they will really relate to HPV.

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