

## MINI-REVIEW

# Epidemiological Features of Human Papillomavirus (HPV) Infection among Women Living in Mainland China

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### Abstract

Cancer of the cervix is the third most common cancer in women worldwide, more than 85% of the cases occurring in developing countries such as China. In China, since a national cancer registry is already set up but with geographically limited data generated, the burden of cervical cancer is believed to be underestimated. High-risk human papillomavirus (HR-HPV) prevalence among women attending routine cervical cancer screening programs has been shown to correlate well with cervical cancer incidence rates based on independently obtained HPV prevalence data as well as findings for the worldwide cervical cancer burden. Therefore, reviewing data on HR-HPV prevalence in population-based screening studies and hospital-based case studies will be important in the context of better understanding the cervical cancer burden and for the evaluation of the potential impact of HPV vaccination in the country. With the advent of prophylactic vaccines, significant progress is likely to be made in cervical cancer prevention. This article reviews available data on the HPV epidemiology over a 12-year time period (2001-2012) in mainland China under different epidemiological aspects: by age group of study population, by ethnicity, by geographic area, as well as time period. The authors also review the potential acceptability of HPV vaccination among Chinese women.

**Keywords:** Human papillomavirus (HPV) infection - cervical cancer - Chinese women

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### Introduction

Cancer of the cervix is the third most common cancer in women worldwide, with an estimated 529,000 new cases and 274,000 deaths occurring in 2008 (Ferlay et al., 2010). More than 85% of the cases occur in developing countries such as China. A previous review has demonstrated the unbalanced disease burden of cervical cancer regarding age group, ethnicity and area of residence (rural or urban) in China (Li et al., 2011a). In China, since a national cancer registry is already set up but with geographically limited data generated, the disease burden of cervical cancer is believed to be underestimated.

With the causal relation between human papillomavirus (HPV) and cervical cancer being firmly established (Nobbenhuis et al., 1999; Bosch et al., 2002), high-risk human papillomavirus (HR-HPV) prevalence has been shown to correlate well with cervical cancer incidence rates based on the independently obtained HPV prevalence data among women attending routine cervical cancer screening programs (Bruni et al., 2010) and data on the worldwide cervical cancer burden (Arbyn et al., 2011).

Therefore, reviewing data on HR-HPV prevalence will be important in the context of better understanding the cervical cancer burden in the country. In recent years, significant progress has been made in cervical cancer prevention especially with the availability of prophylactic vaccines. HPV vaccination holds a promising future for cervical cancer prevention especially for countries with limited access to screening.

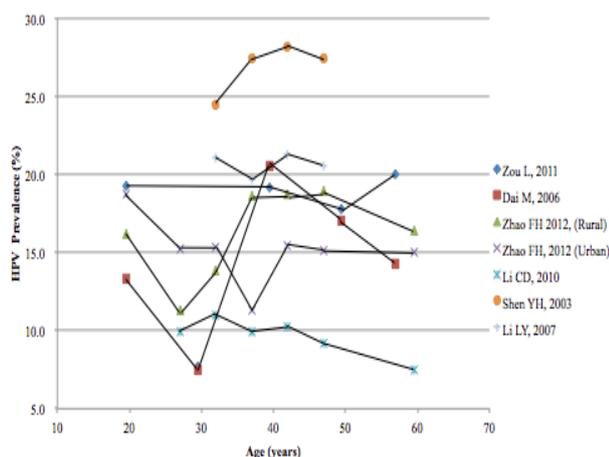
In China, phase III clinical trials of the prophylactic vaccines are ongoing. Before the vaccines were commercially available in China, much needs to be understood about the potential benefit when HPV vaccines are administered in Chinese women. The authors reviewed several multi-centre, hospital-/population-based studies published over a 12-year period (2001-2012) including the first population-based HPV study published in China (Zhao et al., 2001) as well as the most recent HPV pooled analysis (Zhao et al., 2012b). The present article aims to report on important additional evidence regarding HPV prevalence and type distribution in women attending cervical cancer screening and in women diagnosed with cervical cancer or precancerous lesions in China,

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**Table 1. HPV Prevalence among Women Participating in Population-based Cervical Screening Studies**

Author/Pub year	Study year	Location	Number (N)	Age Range (yrs)	Lab assays	Target HPV types	Overall Prevalence (%)	Prevalence Range (%)
(Belinson et al., 2001)	1999	Xiangyuan	1,997	35-45	HC2	13 HR-HPV*	18.2	-
(Zhao et al., 2006)	2001-2002	Yangcheng and Xiangyuan	8,798	35-50	HC2	13 HR-HPV*	23.6	-
(Shen et al., 2003)	2001-2002	Xiangyuan and Yangcheng Shanxi	9,683	30-50	HC2	13 HR-HPV*	27.5	24.5-28.2
(Zou et al., 2011)	2004	Yangcheng	745	15-59	HC2	13 HR-HPV*	16	7.7-20.0
(Li et al., 2007)	2004	Xiushui Jiangxi	2,432	30-49	HC2	13 HR-HPV*	18.5	19.7-21.3
(Li et al., 2006)	2004-2005	Shenyang	685	15-59	GP5+/6+ mediated PCR	HR-HPV* & 30 LR-HPV*	16.8	8.7-19.4
(Dai et al., 2006)	2004-2005	Yangcheng	662	15-59	GP5+/6+ mediated PCR	HR-HPV* & 30 LR-HPV**	14.8	7.5-20.5
(Wu et al., 2007)	2004-2005	Shenzhen	1,027	15-59	GP5+/6+ mediated PCR	HR-HPV* & 30 LR-HPV**	16.6	13.2-24.4
(Zhao et al., 2012b)	1999-2008	Rural areas	29,579	15-59	HC2	13 HR-HPV*	18	11.3-18.6
		Urban areas					15.2	11.3-18.7
		Overall					17.7	-
(Li et al., 2010)	2006-2009	Beijing	6,185	25-54	HC2	13 HR-HPV*	9.9	7.5-11.0
(Hu et al., 2011)	2009	Jiangsu	316	18-25	HC2	13 HR-HPV*	17.1	-

\*HR-HPV, high-risk human papillomavirus; \*\*LR-HPV, low-risk human papillomavirus



**Figure 1. HPV Prevalence among Women Participating in Population-based Cervical Screening Studies, by Age** (Shen et al., 2003; Dai et al., 2006; Li et al., 2007; Li et al., 2010; Zou et al., 2011; Zhao et al., 2012b)

by study population, geographic area and time period. The authors also review evidence regarding the level of awareness about HPV and the acceptability of HPV vaccination among Chinese women, which is thought to be an important element in the prevention of HPV related diseases such as cervical cancer.

## HPV Epidemiology

### *HPV prevalence and type distribution in different populations*

**HPV prevalence and type distribution in women attending screening:** An overall average HR-HPV prevalence of 17.7% was reported recently based on a pooled analysis of 17 population-based screening studies conducted between 1999 and 2008 in mainland China using Hybrid Capture 2 (HC2, Qiagen) (Zhao et al., 2012b). Table 1 listed the HPV prevalence among women participating in population-based cervical screening

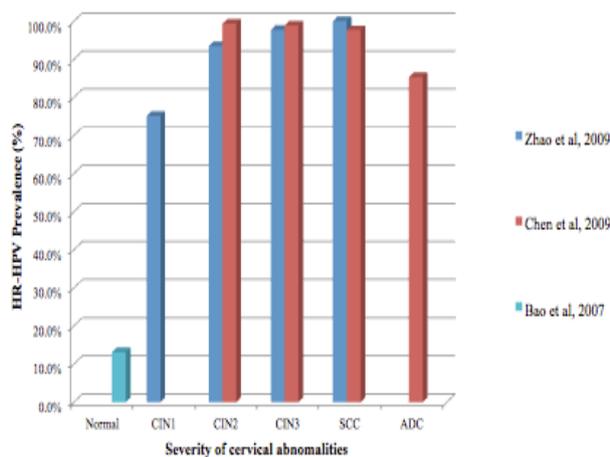
studies by using HC2 or polymerase chain reaction (PCR) as the detecting method, including the pooled analysis.

Figure 1 shows the HPV prevalence of women attending population-based screening, by age group. Studies using GP5+/6+ mediated PCR lab assays to detect 14 HR-HPV and 30 low risk HPV (LR-HPV) suggest that among women aged 15-59 years, the prevalence of any HPV-type showed a first peak at age 15-24 years from 13.3% to 15.0%, to then decline to less than 10.0% at age 25-29 years, to then increase again to form a second peak in women at age 35-54 years from 17.0% to 24.4% (Li et al., 2006; Dai et al., 2006; Wu et al., 2007). A similar age pattern was observed for HR-HPV prevalence in studies using HC2. The HR-HPV prevalence presented two peaks, one at age 15-24 years (16.2% to 19.3%) and the other in women aged 35-49 years (15.2% to 28.2%), respectively (Shen et al., 2003; Zhao et al., 2006; Li et al., 2007; Li et al., 2010; Zou et al., 2011; Hu et al., 2011). Conversely, for LR-HPV prevalence, no significant age-specific trend was observed (Zhao et al., 2009b).

The “two peak” pattern pertained to both rural and urban women. The crude HR-HPV prevalence was seen to peak among urban women aged 15-24 years (18.7%) and among women older than 40 years of age (16.0%). Among rural women, it peaked at age 15-24 years (16.2%) and 35-39 years (18.6%) (Zhao et al., 2012b). This pattern differs from that observed in women from Western countries, among whom, HPV prevalence peaked only at their mid-twenties, then steadily decline as age increases (Moscicki et al., 2006; Stanley, 2010; Grant et al., 2011; Wheeler et al., 2012).

The first peak in China may due to the fact that younger women are more sexually active and more likely to have multiple partners, especially in urban areas (Zhao et al., 2012c). Reasons for the second peak in Chinese women are not well understood; viral persistent infection may be one of the explanations (Castle et al., 2005) or reactivation of a latent HPV infection (Li et al., 2005).

Type-specific HPV prevalence also showed an age



**Figure 2. HR-HPV Prevalence Reported in a Meta-analysis (Bao et al., 2007), a Multi-centre Population-based Screening Study (Zhao et al., 2009a), and a Multi-centre Hospital-based Study (Chen et al., 2009) Conducted in China.** \*ICC: Invasive Cervical Cancer; SCC: Squamous Cell Carcinoma; ADC: Adenocarcinoma; CIN: Cervical Intraepithelial Neoplasia

trend in a population-based multi-centre study using a PCR-based assay to detect 37 HPV types (Linear Array, Roche) (Smith et al., 2012). The prevalence of HPV16 reported in this study peaked among women aged 30-34 years (4.2%) and 45-49 years (3.8%), while the prevalence of HPV18 (1.3%) peaked at age 40-44 years (Smith et al., 2012).

In China, there are 56 ethnic groups (Ma, 2012), with Han representing the vast majority (91% of the total population). HPV prevalence among Han women participating in population-based screening studies varied from 6.7% in Beijing to 29.6% in Yangcheng County Shanxi province (Zhao et al., 2001; Shen et al., 2003; Dai et al., 2006; Wu et al., 2006; Li et al., 2007; Zhao et al., 2009b; Zou et al., 2011). Interestingly, other ethnic groups presented HR-HPV positivities of less than 10%: 6.9% and 7.3% in Uyghur women (Mayineur et al., 2011), 7.6% in Maonan women (Guizhou province) (Wei et al., 2010), and 9.1% in Tibetan women (Jin et al., 2009). Genetic variation, cultural diversity, religious beliefs and different lifestyle are likely to contribute to the observed differences.

Women with human immunodeficiency virus (HIV) infection are more likely to be HPV positive due to their immunosuppression (Palefsky and Holly, 2003; Strickler et al., 2005). In mainland China, approximately 15,000 women were reported to have an HIV infection or Acquired Immune Deficiency Syndrome (AIDS) (Wang and Ni, 2008), accounting for 1/3 of 47,982 HIV/AIDS cases reported in 2007 in China. Zhang et al reported an HPV prevalence of 49.4% (41/83) among women with HIV/AIDS in Yunnan province, China, which is significantly higher than that of the general population (Zhang et al., 2012).

It is well known that the prime mode of transmission of HPV is sexual activity. Gupta et al reported that male partners of women with invasive cervical cancer (ICC) were more likely to be HPV positive (Nicolau et al.,

2005; Gupta et al., 2006). High HPV positivity in females increases the risk of developing condylomata acuminata (CA), as well as penile and anal cancers for the male partners (Castellsagué et al., 2004). Few studies have evaluated the concordance of HPV infection among couples in China. One population-based HPV prevalence study was conducted among 400 Uyghur couples in Xinjiang province, reporting an overall HPV prevalence of 14.3% and 8.0% in women and their husbands, respectively (Ablimit et al., 2011).

**HPV prevalence and type distribution in women with abnormal cervical cytology:** Data on the HPV prevalence and type distribution in women with cervical lesions are critical for China's future evaluation of the cost-effectiveness of prophylactic HPV vaccination and of HPV-based screening guidelines. As observed in published reports, HPV prevalence in women with abnormal cytology from China varies between studies. In the cytologically confirmed abnormal samples, HPV prevalence varied from 26.4% to 54.6% in women with atypical squamous cells of undetermined significance (ASCUS), 42.4% to 56.9% in women with low-grade squamous intraepithelial lesions (LSIL), and from 47.8% to 83.3% in women with high-grade squamous intraepithelial lesions (HSIL) (Sun et al., 2010; Li et al., 2011b; Li et al., 2011c; Hou et al., 2012), respectively. After adjusting for confounding factors (geographic area, classification of cervical disease status and type of specimen for HPV DNA testing), a meta-analysis showed that the adjusted overall HPV prevalence was 66.2% in HSIL and 61.3% in LSIL (Bao et al., 2008), respectively. In HSIL samples, the predominant HPV types were HPV16 (35.4%), HPV58 (14.5%), HPV52 (12.3%), HPV18 (9.2%) and HPV33 (8.0%); in LSIL samples, HPV16 (21.1%), HPV58 (18.5%), HPV52 (11.3%), HPV18 (11.1%) and HPV33 (7.2%) were the most commonly detected types (Bao et al., 2008).

**HPV prevalence and type distribution in women with abnormal histology:** Worldwide, oncogenic HPV types 16 and 18 are attributable for approximately 70% of ICC cases (Munoz et al., 2003). In China, variations in HPV prevalence of ICC cases between studies are observed due to differences in study methodology and laboratory testing protocols (Peng et al., 1991; Lo et al., 2002; Smith et al., 2007). A nation-wide, multi-center hospital-based study using the highly sensitive SPF 10 LiPA25 for HPV DNA detection indicated that HPV prevalence was 97.6% in squamous cell carcinoma (SCC) and 85.3% in adenocarcinoma (ADC). HPV16 (76.7%) and HPV18 (8.0%) were the most common types in SCC, followed by HPV31, HPV52 and HPV58 (Chen et al., 2009).

Recently, a pooled analysis including 30,371 women from 17 cross-sectional, population-based studies in various parts of China showed that HR-HPV prevalence was 11.2% in women with normal histology, 79.7% in cervical intraepithelial neoplasia grade 1 (CIN1), 95.0% in cervical intraepithelial neoplasia grade 2 (CIN2), 97.4% in cervical intraepithelial neoplasia grade 3 (CIN3), and 98.0% in SCC and ADC (Zhao et al., 2010). Figure 2 demonstrates that HPV prevalence is positively related

**Table 2. HPV Prevalence and Type Distribution in Urban and Rural Women in China**

Living area	Author/Pub year	Study year	Location	N	Age Range (yrs)	Lab-assays	HPV prevalence (%)					HPV genotyping (%)						
							overall	CIN1	CIN2	CIN3	ICC	HPV16	HPV52	HPV58	HPV42	HPVj9710		
Urban	(Li et al., 2006)	2004-2005	Shenyang	685	15-59	GP5+/6+ mediated PCR	16.8	89.7*	-	-	-	-	HPV16 (3.4)	HPV52 (2.5)	HPV58 (1.9)	HPV42 (1.5)	HPVj9710 (1.2)	
	(Wu et al., 2007)	2004-2005	Shenzhen	1,027	15-59	GP5+/6+ mediated PCR	16.6	68.2*	-	-	-	-	HPV16 (2.5)	HPV52 (2.0)	HPV58 (1.6)	HPV31 (1.5)	HPV39 (1.5)	
	(Zhao et al., 2009b)	2006-2008	Beijing	5,552	25-54	PCR (MY09/11 primer)	6.7	44.4*	-	-	-	-	HPV16 (2.6)	HPV58 (1.0)	HPV33 (0.8)	HPV43 (0.7)	HPV56 (0.7)	
	(Li et al., 2010)	2006-2009	Beijing	6,185	25-54	HC2	9.9	39.9	88.6**	-	-	-	-	-	-	-	-	-
	(Wu et al., 2010)	2008-2009	Fujian	2,338	20-70	PCR (MY09/11 primer)	22.5	70.5	90.2***	94.8	-	-	HPV52 (23.1)	HPV16 (21.3)	HPV18 (11.6)	HPV33 (11.2)	HPV53 (9.3)	
Rural	(Zhao et al., 2001)	1999	Xiangyuan	1,997	35-45	HC2	20.8	61.4	95.3	100	100	-	-	-	-	-	-	
	(Shen et al., 2003)	2001-2002	Xiangyuan and Yangcheng	9,683	30-50	HC2	27.5	-	-	-	-	-	-	-	-	-	-	
	(Zou et al., 2011)	2004	Yangcheng	745	15-59	HC2	16	-	-	-	-	-	-	-	-	-	-	
	(Li et al., 2007)	2004	Xiushui Jiangxi	2,432	30-49	HC2	18.5	-	-	-	-	-	-	-	-	-	-	
	(Wu et al., 2006)	2000-2004	Jiangxi and Guangzhou	1,010	18-84	HC2	-	68.8	80.3	90.2	89.9	-	-	-	-	-	-	
	(Dai et al., 2006)	2004-2005	Yangcheng	662	15-59	GP5+/6+ mediated PCR	14.8	46.2	68.8	91.7	100	HPV16 (5.7)	HPV58 (3.2)	HPV52 (1.2)	HPV42 (1.1)	HPV33 (1.2)		

\*HPV prevalence in cervical abnormalities (including CIN1, CIN2, CIN3 and ICC); \*\*HPV prevalence in women with  $\geq$  CIN2; \*\*\*HPV prevalence in CIN2/3

**Table 3. HPV Prevalence and Type Distribution in Seven Geographic Areas in China**

Geographic areas	Author/Pub year	Study year	Location	Number (N)	Age Range (yrs)	Lab-assays	HPV prevalence (%)								
							overall	normal cytology/histology	cervicitis	Cytological abnormality			Histological abnormality		
										ASCUS	LSIL	H SIL+	CIN1	CIN2+	
Northeast China	(Li et al., 2006)	2004-2005	Shenyang	685	15-59	GP5+/6+ mediated PCR	16.8	-	-	-	-	-	-	-	89.7*
	(Sun et al., 2010)	2007-2009		4945	-	PCR	-	21.8	35.7	54.6	-	-	-	-	67.4*
North China	(Li et al., 2010)	2006-2009	Beijing	6,185	25-54	HC2	9.9	-	-	-	-	-	-	-	39.9 88.6
Northwest China	(Chen et al., 2011)	2009-2010	Xinjiang	2,519	18-64	PCR	19.7	9.2	38.7	-	-	-	-	-	56.6 96.4
	(Zhou et al., 2011)	2009-2010	Gansu	638	19-80	PCR	-	-	-	-	67.6	93.9	-	-	-
Central China	(Shen et al., 2003)	2001-2002	Xiangyuan and Yangcheng Shanxi	9,683	30-50	HC2	27.5	-	-	-	-	-	-	-	-
	(Dai et al., 2006)	2004-2005	Yangcheng	662	15-59	GP5+/6+ mediated PCR	14.8	-	-	-	-	-	-	-	46.2 79.3
	(Zou et al., 2011)	2004	Yangcheng	745	15-59	HC2	16	-	-	-	-	-	-	-	-
Southwest China	(Li et al., 2011b)	2007-2009	Chengdu	207	-	PCR (MY09/11 primer)	-	-	-	-	-	-	74.9	-	-
East China	(Wu et al., 2010)	2008-2009	Fujian	2,338	20-70	PCR (MY09/11 primer)	22.5	-	-	-	-	-	-	-	70.5 92.4
South China	(Li et al., 2012)	2010	Chaozhou Guangdong	13750	35-59	PCR	7.2	-	-	-	-	-	-	-	-

\*HPV prevalence in cervical abnormalities (including CIN1, CIN2, CIN3 and ICC)

to the severity of cervical abnormalities. It is lower in women with normal cervical histology (13.1%) than in women with CIN1 (75.0%), or in women with CIN2 and/or CIN3 (93.4%-99.3%), or in women with SCC or ADC (85.3%-100%). It also shows that HPV DNA is more likely to be present in SCC than in ADC ( Bao et al., 2007; Chen et al., 2009; Zhao et al., 2009a)..

#### *HPV prevalence and type distribution among women from population-based screening studies and hospital-based studies in different geographic areas*

**HPV prevalence and type distribution in urban and rural Chinese women:** When women from population-based screening studies and hospital-based studies in mainland China were classified as living in either rural or urban areas, HPV prevalence showed a similar pattern but different rates (Table 2). In rural women, the HPV prevalence was somewhat higher than that in urban women. A pooled-analysis of 17 population-based reported a crude HR-HPV prevalence of 18.0% and 15.2% in rural and urban women, respectively (Zhao et al., 2012b). Six studies conducted in rural areas reported a HPV prevalence of 14.8% to 29.6% depending on the targeted age group and the HPV DNA detection method used ( Zhao et al., 2001; Shen et al., 2003; Dai et al., 2006; Wu et al., 2006; Li et al., 2007; Zou et al., 2011). However, in five studies conducted in urban areas, HPV prevalence varied from 6.7% in Beijing to 22.5% in Fuzhou, Fujian province (Li et al., 2006; Wu et al., 2007; Zhao et al., 2009b; Li et al., 2010; Wu et al., 2010).

The most commonly used method for detection of HPV DNA was different between urban (GP5+/6+ mediated PCR) and rural (HC2) area. The sensitivity of HC2 assay was higher than that of the PCR detection (Kulmala et al., 2004; Schiffman et al., 2005). Moreover, the procedure of the HC2 assay is standardized and can be easily controlled, whereas PCR contains several steps and is difficult to standardized (Kulmala et al., 2004). Another potential bias was that most sites for rural studies were located in high risk area in China, such as Yangcheng, Xiangyuan, so the figures for rural could be probably overestimated.

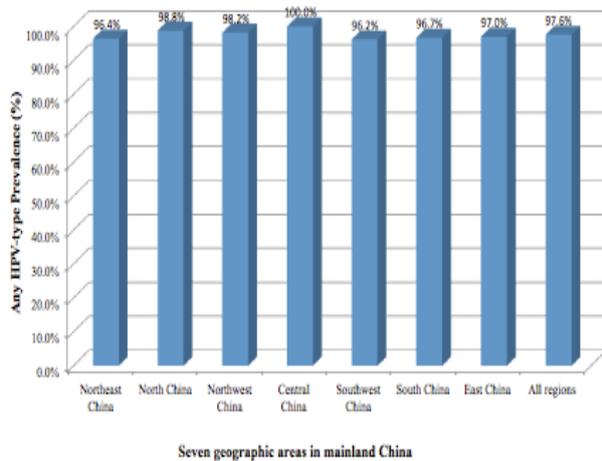
Although differences in HPV prevalence were observed between rural and urban areas, the predominant HPV types do not significantly differ. Among all, HPV16, 52 and 58 were the most commonly detected HPV types in the population-based study when GP5+/6+ -based PCR assay was used for HPV typing (Dai et al., 2006; Li et al., 2006; Wu et al., 2007).

**HPV prevalence and type distribution in women from population-based screening studies and hospital-based studies in seven geographic areas:** Evidence on HPV type distribution varies greatly across geographic regions of China. Traditionally, China is regarded as consisting of seven distinct geographic regions: Northeast, North, Northwest, Central, Southwest, South, and East China. This section reports on HPV prevalence and type distribution in women from population-based screening studies and hospital-based studies in each of the seven regions (Table 3).

**Table 4. HPV Prevalence in Women from Population-based Screening Studies and Hospital-based Studies in Different Time Period**

Author/Pub year	Study year	Location	Number (N)	Age Range (yrs)	Lab-assays	Participants Source	HPV prevalence (%)		
							overall	CIN1	CIN2+
(Zhao et al., 2001)	1999	Xiangyuan	1,997	35-45	HC2	Population-based	20.8	61.4	97.7
(Shen et al., 2003)	2001-2002	Xiangyuan and Yangcheng Shanxi	9,683	30-50	HC2	Population-based	27.5	-	-
(Zhao et al., 2006)	2001-2002	Yangcheng and Xiangyuan	8,798	35-50	HC2	Population-based	23.6	-	-
(Wu et al., 2006)	2000-2004	Jiangxi and Guangzhou	1,010	18-84	HC2	Hospital-based	-	68.8	88.5
(Zou et al., 2011)	2004	Yangcheng	745	15-59	HC2	Population-based	16.0	-	-
(Li et al., 2007)	2004	Xiushui Jiangxi	2,432	30-49	HC2	Population-based	18.5	-	-
(Li et al., 2006)	2004-2005	Shenyang	685	15-59	GP5+/6+ mediated PCR	Population-based	16.8	89.7*	
(Dai et al., 2006)	2004-2005	Yangcheng	662	15-59	GP5+/6+ mediated PCR	Population-based	14.8	46.2	79.3
(Wu et al., 2007)	2004-2005	Shenzhen	1,027	15-59	GP5+/6+ mediated PCR	Population-based	16.6	68.2*	
(Zhao et al., 2012b)	1999-2006	Shanxi, Beijing, Xinjiang, Henan, Shanghai	13,004	16-54	HC2	Population-based	14.7	80.4	96.6
(Zhao et al., 2009b)	2006-2008	Beijing	5,552	25-54	PCR (MY09/11 primer)	Population-based	6.7	44.4*	
(Li et al., 2010)	2006-2009	Beijing	6,185	25-54	HC2	Population-based	9.9	39.9	88.6
(Hou et al., 2012)	2006-2009	Beijing	533	-	PCR (MY09/11 primer)	Hospital-based	-	33.7	50.7
(Wu et al., 2010)	2008-2009	Fujian	2,338	20-70	PCR (MY09/11 primer)	Population-based	22.5	70.5	92.4
(Hu et al., 2011)	2009	Jiangsu	316	18-25	HC2	Population-based	17.1	77.8	90

\*HPV prevalence in cervical abnormalities (including CIN1, CIN2, CIN3 and ICC)



**Figure 3. HPV-type Prevalence among Women with  $\geq$ CIN2 in Seven Geographic Areas in Mainland China (Chen et al., 2009)**

**Northeast China:** A population-based screening study in Shenyang reported an overall HPV prevalence of 16.8% among women aged 15~59 years old (Li et al., 2006). In Shenyang, a hospital-based study among 4,780 women with cervical disease and 165 women with normal cytology reported that the HPV prevalence was 21.8% in women with no obvious disease, 35.7% in cervicitis, 54.6% in ASCUS, 64.1% in CIN and 83.4% in cervical cancer. In this study, using HPV GenoArray test kit (HybriBio, Hong Kong) for HPV DNA detection, HPV16 (19.6%) was the most prevalent genotype, followed by HPV58 (8.4%), HPV52 (6.4%), HPV33 (4.6%) and HPV53 (3.2%) (Sun et al., 2010).

**North China:** A population-based screening study using HC2 assay among women aged 25-54 years in Beijing found that the HR-HPV prevalence was 9.9% overall, 39.9% in women with CIN1, and 88.6% in women with  $\geq$  CIN2. PCR with the PGMY09/11 primer was used for HPV typing. The most commonly detected HPV types

were HPV16 (26.5%), HPV58 (8.8%), HPV33 (7.8%) and HPV56 (5.3%) in women with cervical lesions (Li et al., 2010).

**Northwest China:** Xinjiang and Gansu are two important regions in northwest China. A population-based screening study conducted among women visiting 3 clinics aged 18-64 years in Xinjiang including Han, Uygur and Hazak showed an overall HPV prevalence of 19.7%, with 9.2% in normal tissues, 38.7% in cervicitis, 56.6% in CIN1, 78.0% in CIN2, 100% in CIN3 and 100% in ICC. Among all targeted HPV types, HPV16 (30.7%), HPV58 (12.5%), HPV18 (5.9%), HPV52 (5.7%) and HPV31 (4.2%) were the five most important types (Chen et al., 2011). In Gansu, the HPV prevalence is reported to be as high as that in Xinjiang in abnormal tissues (67.6% in LSIL, 90.9% in HSIL and 98.7% in SCC) with HPV16 (88.2%), HPV18 (7.9%) and HPV58 (5.3%) as the common types in SCC (Zhou et al., 2011).

**Central China:** Population-based studies conducted in Yangcheng county, Shanxi Province, between 2001 and 2005 showed that the HPV prevalence varied from 14.8% by using GP5+/6+ mediated PCR to 29.6% by using HC2 (Shen et al., 2003, Dai et al., 2006, Zou et al., 2011). Dai et al reported that the predominant HPV types were HPV16, 58, 52, 33 and 18 by using GP5+/6+ mediated PCR (Dai et al., 2006).

**Southwest China:** A hospital-based study was carried out among 144 women with cervical cancer and 63 with HSIL in Chengdu. This study reported an HPV prevalence of 61.9% in HSIL and 80.6% in ICC by using PCR detection with MY09/11 primers (HybriBio) to detect 21 HPVtypes. Among all targeted HPV types, HPV16 (34.9%), 58 (17.5%), 52 (3.2%) and 18 (1.6%) were the predominant HPV types in HSIL samples. In ICC, HPV16 (34.9%), 58 (8.3%), 18 (4.9%) and 52 (2.8%) remained the most important (Li et al., 2011b).

**East China:** A population-based screening study in Fujian reported an HPV prevalence of 22.5% overall, with 19.4% in normal women, 70.5% in CIN1, 90.2% in CIN2/3, 94.3% in SCC and 100% in a very limited sample of nine ADC cases among women aged 20-70 years. The PCR assay with MY09/11 primer (Chaozhou Hybribio Biotechnology Corp. China) was employed for HPV DNA detection. The prevalent types were HPV52 (23.1%), 16 (21.3%) and 18 (11.6%) among women with HPV infection. The most common types in SCC and ADC were HPV16 (42.7%), 18 (20.8%) and 33 (12.5%) (Wu et al., 2010).

**South China:** A population-based study in Chaozhou, Guangdong province reported an overall HPV prevalence of 7.2% among 13,750 women aged 35-59 years. The most commonly detected HPV types were HPV52 (27.5%), HPV16 (14.5%), HPV58 (10.8%), HPV68 (8.3%) and HPV33 (6.8%) (Li et al., 2012).

**China Nationwide:** A hospital-based, multi-center large scale type distribution study in histologically confirmed cervical lesions using highly sensitive, state-of-the-art PCR methods (SPF10 LiPA 25 version 1 assay) in 7 geographical areas of China showed that HPV was highly prevalent among women with high-grade precancerous lesions and cervical cancer regardless of where they live (Figure 3). Same as worldwide, HPV16 (76.7%) and HPV18 (7.8%) were the most common types in all regions. The importance of other HPV types varied by region. HPV58 and HPV52 were more prevalent in the South and Southwest compared to other regions among women with precancerous lesions and cervical cancer (Chen et al., 2009).

#### *HPV prevalence in women from population-based screening studies and hospital-based studies in different time periods*

Table 4 presents the results of multi-centre, hospital-/population-based studies conducted over the last decade (1999-2009), showing an overall crude HPV prevalence of 20.8% in 1999, 27.5% in 2001-2002, 14.8% - 16.8% in 2004-2005, and 6.7% - 22.5% in 2006-2009 depending on the targeted population and the DNA detection method used (Zhao et al., 2001; Shen et al., 2003; Dai et al., 2006; Li et al., 2006; Zhao et al., 2006; Wu et al., 2007; Zhao et al., 2009b; Li et al., 2010; Wu et al., 2010; Zhao et al., 2012a). When considering studies conducted in Shanxi Province between 1999 and 2005, a declining trend was observed from 27.5% in 2001-2002 (Shen et al., 2003) to 14.8% in 2004-2005 (Shen et al., 2003; Dai et al., 2006; Zhao et al., 2006; Zou et al., 2011). Apart from the impact of time, HPV prevalence is highly dependant on the targeted population, location, study protocol and lab methodology.

In a recent meta-analysis, after adjusting for histological diagnosis of the tumor, source of specimen and type of PCR primers used, the HPV prevalence in ICC showed an increasing trend over different time periods in China. The adjusted HPV prevalence was 64.3% before the year 2000, then increased to 85.0% from 2000 to 2003,

to further increase to 86.7% from 2004 to 2006 (Bao et al., 2007).

### **Knowledge of HPV-related Disease, Attitudes and Acceptability of HPV Vaccination**

With prophylactic HPV vaccines being licensed in many developed and developing countries, the era of comprehensive cervical cancer prevention is coming. In China, phase III clinical trials are ongoing to evaluate the efficacy of the vaccines in Chinese women. Lack of knowledge about and negative attitude towards HPV and HPV vaccination were reported to be a major potential obstacle to be expected during the time of introduction of HPV vaccination (Hu et al., 2011). In general, awareness of HPV was low (15.5%) among Chinese women, but when women were defined as living in rural or urban areas, urban women were twice as likely to have heard of HPV (21.6%) compared to those living in rural areas (9.3%) (Li et al., 2009). In Beijing, a typical metropolitan city in China, 38.2% of women aged older than 40 years reported to be aware of the relationship between HPV and cervical cancer (Fu et al., 2010). By contrast, in the rural areas, where cervical cancer remains a critical public health problem, HPV awareness was extremely low. In Xiangyuan, a county with a high disease burden due to cervical cancer, only 5.9% of women reported that they had ever heard of HPV (Song, 2007). In the southern Xinjiang autonomous region, none of the women reported that they had heard about HPV (Ablimit et al., 2009).

In a recent multicenter survey, researchers interviewed 11,852 women from the general population aged 15-59 years from seven urban and 14 rural areas of China, as well as 763 government officials and 760 healthcare providers. HPV awareness among urban and rural healthcare providers was 96% and 80%, respectively, and was therefore higher than that among government officials (44%), urban women (34%) and rural women (16%). Less people reported to have heard of HPV vaccination in government officials (33%) and the general population (23%). Approximately 80% of government officials and medical personnel were willing to vaccinate themselves and their daughters (Zhao et al., 2012d).

Apart from safety, efficacy and cost of the vaccines, HPV awareness and knowledge are directly related to the acceptance of HPV vaccination (Hu, 2011). In order to ensure a high level of acceptance of vaccination in order to prevent cervical cancer especially in the rural areas, education and HPV awareness campaigns represent an urgent concern. For both rural and urban women, recommendations from doctors or nurses in favor of getting vaccinated and educational lectures carried out in hospitals played an important role in helping women decide to get vaccinated (Song, 2007; Li et al., 2009). Therefore, educating doctors and nurses on HPV and HPV vaccination is a critical initial step of such a campaign.

### **Conclusions**

In conclusion, invasive cervical cancer and precancerous lesions are important public health concerns

in China. In cervical cancer, HPV 16 and 18 consistently represent the most commonly detected types across China. HPV 58 and 52 are found to be more prevalent in women with cervical cancer and precancerous lesion from Southern and coastal regions of mainland China. Cervical cancer is a malignancy that can be prevented by vaccination especially in countries and regions where cervical cancer screening is not universally available or accepted, as is the case in China. Factors essential to the successful implementation of HPV vaccination in China include a widespread public health campaign about HPV and HPV vaccination, government endorsement of vaccination programs with commitment of resources, affordable vaccines, and the establishment of a health care infrastructure to ensure efficient vaccine delivery especially in the rural areas of China.

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