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Population-based Human Papillomavirus 16,18, 6 and 11 DNA Positivity and Seropositivity in Chinese Women

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Abstract

To optimize HPV vaccination implementation at the population-level in China, data are needed on age-specific HPV 16, 18, 6 and 11 prevalence. This cross-sectional, population-based study evaluated the age- and type-specific HPV 16, 18, 6 and 11 prevalence of DNA and serum antibodies among women in China. From July 2006 to April 2007, 17 to 54-year-old women from three rural provinces (Xinjiang, Shanxi, and Henan) and two cities (Beijing and Shanghai) provided cervical exfoliated cells for HPV DNA and liquid-based cervical cytology (SurePath). High and low-risk HPV types were detected with HC-II (Qiagen), with genotyping of HPV-positive samples using Linear Array (Roche). HPV 16, 18, 6, and 11 serum antibodies were detected using a Luminex-based, competitive immunoassay (Merck and Co). A total of 4,206 women with DNA and serum antibody results were included. HPV 16 DNA prevalence peaked in women aged 30–34 (4.2%) and 45–49 years (3.8%), while HPV 18 DNA prevalence peaked at ages 40–44 years (1.3%). Most women were dually DNA and serum antibody negative: HPV 16 (92.2%), 18 (97.2%), HPV 16 & 18 (90.2%), 6 (92.0%), 11 (96.6%), 6 & 11(89.9%), and HPV 16, 18, 6, & 11 (82.5%). Future national HPV vaccination programs in China should target younger

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women due to increased exposure to HPV types 16, 18, 6 and 11 with age. Cumulative exposure of HPV may be underreported in this population as cross-sectional data do not accurately reflect exposure to HPV infections over time.

Keywords

HPV prevalence; HPV DNA; HPV antibodies; China

Introduction

Human papillomavirus (HPV) types 16 or 18 infection are causally attributed to approximately 70% of cervical cancer worldwide,[1,2] whereas infection by HPV types 6 or 11 account for approximately 90% of genital warts.[3] Two prophylactic HPV vaccines, a bivalent HPV 16/18 and a quadrivalent HPV 16/18/6/11 vaccine, have been developed[4,5] and are licensed in several countries worldwide for cervical cancer prevention[1,6,7] Vaccine clinical trial data have demonstrated safety and efficacy for prevention of cervical intra-epithelial lesions and persistent infection attributable to HPV types included in these prophylactic vaccines.[8–12]

Clinical trials data have shown that HPV vaccination will be most beneficial for cervical cancer prevention if provided to “naïve women” aged 9 to 26 years who are negative both to cervical HPV infection (as measured by HPV DNA) and to serum antibodies (indicating past HPV infection) of oncogenic types 16 and 18.[4,5,13,14] Women with current HPV 16 or 18 DNA were not shown to derive benefit against the HPV vaccine type for which they were infected.[15] Among women with evidence of previous exposure to infection with a specific HPV vaccine type (seropositive/DNA negative for that type), available vaccine efficacy data suggest a potential protective effect.[16,17] Women positive to both HPV DNA infection and serum antibodies to a specific HPV vaccine type were not shown to benefit from vaccination against that specific HPV type.[8,11]

Data on the age-specific prevalence of HPV DNA infection and HPV 16, 18, 6 and 11 serostatus are useful to guide prophylactic HPV vaccination programs at the population-level. Although age-specific data are available on HPV 16/18/6/11 DNA among women from several countries,[18–20] few data are available on the simultaneous prevalence of both DNA status and serostatus to HPV types 16, 18, 6 and 11 within the same population worldwide. In addition, very little is known about the prevalence of HPV 6, 11, 16 and 18 in urban and rural regions of China.

We report here on HPV 16, 18, 6 and 11 prevalence of both DNA and serum antibodies among over four thousand women aged 15 to 54 years from three rural and two urban regions of China. These data provide useful information for guiding HPV vaccine policy and implementation programs in China.

Methods

Study subjects

A cross-sectional, population-based study of 4,215 women was conducted in three rural provinces (Xinjiang, Shanxi, and Henan) and two urban areas (Beijing and Shanghai) of China from July 2006 to April 2007, as previously described.[21] Women aged 15 to 54 were eligible to participate. Exclusion criteria consisted of current pregnancy, being less than 3 months post-partum, having self-reported HIV-seropositivity, or a history of either hysterectomy or treatment for cervical cancer. Names, dates of birth, and addresses of resident women in these provinces were obtained from national census data. Participants were recruited from the target population via booklets, notices placed on community billboards, television announcements, and household visits by village doctors. Eligible women who were interested in participating underwent informed consent. For women under 18 years of age, parental consent was also obtained. A trained female interviewer conducted a structured interview with each participant to obtain information on socio-demographic, sexual, reproductive and behavioral factors.

Sample collection

Participating women consented to undergo a physician-conducted pelvic examination, where cervical exfoliated cells were collected and placed in a 10 cc vial of CytoRich for cytology screening by liquid-based cytology (SurePath, Franklin City, NJ) and in a separate 2cc vial of STM for HPV DNA testing by HC-II (Qiagen, Gaithersburg, MD). Women with positive HC-II HPV DNA test results or a cytological diagnosis of ASC-US or higher were referred for colposcopic examination. Colposcopy was conducted according to the Preventive Oncology International protocol of directed and random biopsies (minimum all 4 quadrants) and an endocervical curettage.[22] Women who reported having no history of vaginal sexual intercourse did not undergo pelvic examination or cervical sample collection for liquid-based cytology. A 9 ml blood sample was also collected from all consenting study participants for serum antibody testing.

HPV DNA testing

Cervical exfoliated samples were tested for HPV DNA using a Hybrid Capture II assay (HC II, Digene) according to manufacturer's instructions. Both high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and low-risk types (6, 11, 42, 43, 44) were tested by HC II. Cervical samples testing positive by HC II, a 3.4% random sample of women whose specimens tested negative by HC II, and women diagnosed with ≥ CIN2 were genotyped by Linear Array (Roche) PCR-based assay.[23] Linear Array provides testing results for a total of 37 different HPV types that include: HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39, and CP6108.[24]

Serum antibody detection

Serum samples were shipped to Merck Research Laboratory (MRL) to conduct type-specific serological testing using a competitive, multiplexed Luminex assay for individual HPV

types 16, 18, 6, and 11. This work was conducted without knowledge or access to the HPV laboratory results. The Luminex assay determines the type and concentration of anti-HPV antibodies in the serum by measuring fluorescence.[25,26] Phycoerythrin-labeled, neutralizing, monoclonal antibodies compete with serum antibodies elicited by infection or immunization to bind to the HPV type-specific, neutralizing, epitopes present on virus-like particles (VLPs).[25] The concentration of immunogenically produced anti-HPV antibodies is inversely proportional to the amount of fluorescence measured and reported in arbitrary milli-Merck Units per milliliter (mMU/mL).[25,26]

Data analysis

Among the 4,215 sexually active women enrolled in the study, nine women had missing HPV serology results; of these nine, six women also had missing HPV DNA results. Thereafter, a total of 4,206 women with HPV serology and HPV DNA data were included in subsequent data analyses. HPV antibody levels and the presence of HPV DNA were examined for trends, and the association between HPV DNA and serology positivity was assessed via the McNemar test. The data were analyzed using SAS 9.1.3 (SAS Institute, Cary, NC).

Results

In 4,206 participating women, the mean age was 37.5 years (range 17 to 54). One third of women had elementary or lower education (32.2%), while most were married (94.7%), non-smokers (96.8%), non-drinkers (76.1%), and had a history of contraception use (88.1%) (data not shown). Most women reported sexual debut before 25 years of age (79.8%) and a single lifetime sexual partner (75.2%). The number of women from each study site ranged from 771 women (18.3%) in Shanghai to 884 women (21.0%) in Shanxi Province; overall, 37.2% (1563) of participants were from urban settings and 62.8% (2642) from rural areas (data not shown). In Xinjiang, participants were Uyghur minority women; the remainder was Han Chinese, the majority ethnic group. Overall prevalence for HPV 16, 18, 6, and/or 11 serum antibodies was 19.6% and ranged from 15.7% in Henan Province to 28.7% in Shanghai, while the overall prevalence of HPV 16, 18, 6 and/or 11 DNA was 4.0%, with a range of 3.0% in Xinjiang to 5.4% in Shanxi Province (data not shown).

Of note, HPV 16 DNA prevalence was significantly higher in CIN2+ (69.1%) compared to DNA prevalence of HPV 18 (8.0%), 6 (0.0%), and 11 (2.9%). For women diagnosed with HSIL or more severe (HSIL+), HPV 16 DNA prevalence was significantly higher (66.7%) compared to that of HPV 18 (3.2%), 6 (9.0%), or 11 (1.6%). Similar trends were found for HPV seroprevalence: HPV 16 seropositivity was significantly higher for both CIN2+ (69.1%) and HSIL+ (42.9%) compared to those of HPV 18 (4.4%; 3.2%), HPV 6 (14.7%; 11.1%), or HPV 11 (7.4%; 12.7%), respectively (data not shown).

HPV DNA Prevalence

Very few women were DNA positive for HPV 16 (2.9%), 18 (0.8%), 6 (0.02%), or 11 (0.3%) (Table 1). Rural women had higher DNA positivity for HPV 16 (3.1%) as compared to urban women (2.4%) but had a similar prevalence of DNA positivity for HPV 18 (both at

0.8%) and HPV 6 (both at 0.0%) (Figure 1). Almost all women (96.4%) were DNA negative for HPV types 16 or 18 (Figure 2). When stratified by age, HPV 16 DNA prevalence peaked at ages 30–34 (4.2%) and 45–49 years (3.8%) before declining at ages 50–54 (2.2%), while HPV 18 DNA prevalence peaked at ages 40–44 years (1.3%) (Figure 2). Of note, HPV 16 DNA was more prevalent than HPV 18 DNA in all age-groups (Figure 2). Comparatively, only 0.3% of women were DNA-positive for the non-carcinogenic HPV types tested, with HPV 11 (0.3%) more prevalent than HPV 6 (0.0%) (Table 2). Rural women had slightly lower HPV 11 DNA positivity (0.3%) than urban women (0.4%) (Figure 1).

HPV Seroprevalence

Overall, 15.8% of women were HPV seropositive for HPV 16, 18, 6 and/or 11 (Table 2). Fewer than eight percent of participants (7.8%) were seropositive to HPV 16 (6.3%) or HPV 18 (2.1%) (Table 2), with 0.6% seropositive for both HPV 16 and 18. Urban women had significantly higher HPV 16 (7.7%) and 18 (3.8%) seropositivity compared to those of rural women (5.4% and 1.2%, respectively) (Figure 1). When stratified by age, HPV 16 seroprevalence peaked in women aged 35–39 years (7.4%) and 45–49 years (7.0%), while HPV 18 seroprevalence peaked at 3.9% both in women aged 40–44 and 45–49 years (Figure 2). HPV 16 seroprevalence was more common than HPV 18 seroprevalence in all age groups (Figure 2). For non-carcinogenic HPV types, more women were seropositive for HPV 6 (8.0%) than HPV 11 (3.2%) (Table 1), with the seropositivity for HPV 11 significantly higher in urban women (4.7%) than among rural women (2.3%) (Figure 1.

Age-stratified HPV DNA/seroprevalence

When stratified by age, the prevalence of women positive for HPV 16 or 18 DNA or antibodies increased until age 30–34 years (11.5%) and then leveled off to 11.0% for 40–44 and 45–49 year-old women (Figure 2), Of note, HPV 16 DNA or antibody prevalence increased with age, peaking in women aged 30 to 34 years (9.1%) and was significantly higher across age than HPV 18 DNA or antibody prevalence (Figure 2).

Concordant HPV DNA and seroprevalence

Overall, 2.1% of participating women were dually DNA positive/seropositive for any of the four HPV types (16, 18, 6, or 11), while 82.5% were dually DNA negative/sero-negative for all four HPV types (Table 2). Of the two carcinogenic HPV types tested (HPV 16 and 18), most women were dual negative for both serum antibodies and DNA HPV types 16 (92.2%), 18 (97.2%), and 16 or 18 (90.2%) (Table 2). Only 1.6% of women were sero-positive and DNA-positive for HPV 16 (1.3%), 18 (0.2%), or 16 and 18 (0.02%) (Figure 3). For non-carcinogenic types HPV 6 and 11, most women were dually HPV DNA and antibody negative for HPV 6 (92.0%), 11 (96.6%), and 6 or 11 (89.9%) (Table 2). Only 0.1% of women were DNA and sero-positive for either HPV 6 (0.0%) or 11 (0.1%) (Figure 3). Of note, the percentage of HPV DNA-positive women who were positive for HPV antibodies of the same type were 45% for HPV 16, 20% for HPV 18, 43% for HPV 11, and 0% for HPV 6.

Discussion

This study contributes to the limited pool of data on the prevalence of HPV DNA and antibodies within the same female population and the prevalence of HPV worldwide. Within a sample of over four thousand Chinese women of reproductive age, few women were both sero- and DNA-positive to any of the four HPV types tested (2.1%), with HPV 16 being the most common type. Overall, HPV 16 DNA (2.9%) was more prevalent in our study population than HPV 18 DNA prevalence (0.8%). Nearly fourteen percent of participating women were HPV seropositive, indicating previous exposure to at least one of the four HPV types, with HPV 16 and 18 seropositivity being less common than HPV 6 and 11.

Our observed HPV 16 seroprevalence (6.3%) was comparable to that observed in a populations of similar age in South Korea,[27] but significantly less than that in Mongolia.[28] Our observed HPV 18 seroprevalence was lower than previously observed in these same populations.[27,28] Differences in seroprevalence may be secondary to variations in HPV serological assays employed, population characteristics, or the burden of cervical disease. We found HPV 16 seroprevalence to be higher than HPV 18 seroprevalence in China, consistent with worldwide findings presented in a recent meta-analysis.[1] Our observed overall HPV 16 and/or 18 seroprevalence (7.8%) was similar to that in population-based survey of women in multiple Asian countries (7%)[29], albeit lower than that in a recent global review (~18%).[30] Considering that over two-thirds of this study population reported having one lifetime sexual partner and that relatively lower rates of other sexually transmitted infections have been found in China,[31] it is not surprising that reported HPV seroprevalence is lower in China than in other countries in Asia.

The age-trend of HPV antibody positivity varied by HPV type, with HPV 16 seroprevalence highest at 35–39 years of age and HPV 18 seroprevalence highest at 40–49 years of age. Our HPV 16 findings support prior literature reporting lower HPV seroprevalence in women in their late forties,[31–35] possibly characteristic of a cohort effect due to lower exposure rates of HPV infection or waning immunity over time.[36] Of note, our age-specific HPV 16 seroprevalence and HPV 18 seroprevalence generally increased with age until their peaks, in contrast with data from other low-resource countries such as Mongolia,[28] Thailand,[34] and Costa Rica,[35] that found that age-specific HPV 16 seroprevalence and HPV 18 seroprevalence remained relatively constant across age. Interestingly, our HPV 16 and 18 seroprevalence curves were more consistent with those observed in women from the United States.[37]

Among women surveyed, the DNA or seroprevalence of oncogenic HPV types 16 or 18 (9.9%) was slightly lower than that of non-oncogenic HPV types 6 or 11 (10.1%), consistent with other cross-sectional studies.[29,37] Our HPV 6 seroprevalence (8.0%) was higher than those previously reported from women of similar age from mainland China study[38] (2.0%),

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albeit lower than population-based studies from Taiwan (31%)[39] and Japan (19–25%).[40] Of note, although only a small percentage of our study population were DNA-positive for HPV 6 (0.02%) or 11 (0.2%), HPV 6 is the most seroprevalent HPV type in our study and elsewhere.[37] We thus speculate a high probability of cumulative exposure to HPV 6 in China, which has been shown to account for between fifty and sixty percent of genital warts cases in China.[41]

Significantly, combined HPV 16, 18, 6 and 11 DNA and serological prevalence increased with increasing age in our study population. The relatively low sensitivity of HPV serological assays, however, limits our ability to determine cumulative HPV exposure over women's lifetime.[45] Cumulative exposure of HPV may thus be underreported in this population as our cross-sectional data does not accurately reflect exposure to HPV infections over time.

In terms of concordant HPV DNA and sero-prevalence, very few women were positive for HPV DNA and antibodies of the same type (HPV 16: 1.3%, HPV 18: 0.2%, HPV 6: 0%, and HPV 11: 0.1%), consistent with most studies[4,42], but not all.[43] Rates of HPV antibody and DNA detection were not positively correlated in our Chinese sample, similar to research in South Africa[44] and another study in China[38]. For example, HPV 6 seroprevalence was relatively high (8.0%), while HPV 6 DNA prevalence was low (0.02%). Within this sample of Chinese women, the percentage of HPV DNA positive women who were also seropositive for the same HPV type ranged notably, from 45% for HPV 16 to 0% for HPV 6. We believe this wide range of DNA and antibody concordance by type occurred because no women in our study population were HPV 6 DNA positive, thus resulting in no participants observed who were concordantly HPV 6 DNA positive and seropositive. Our observed rate of HPV 16 DNA and HPV 16 antibody concordance (45%) is slightly higher than that observed in a recent IARC meta-analysis (40%) of 7,074 women worldwide.[30] Our observation of HPV 18 DNA and antibody concordance of 21% is consistent to that observed in the IARC meta-analysis (23%).[30]

There were several strengths to this study. First, both the DNA and serology test used in this study are well validated and standardized tests that were used to support similar studies in the United States, United Kingdom, South Korea, Australia as well as the phase III studies to support the approval of the quadrivalent vaccine.[23,24] Second, in addition to the large sample size, which covered both rural and urban areas within five study sites throughout China, the wide age range of participants (15–54 years) also allowed for presentation of results stratified by age groups. Among study limitations, data obtained from the five geographic sites might not be representative of China, considering the country's large population and that participants were recruited via advertisements. We believe, however, that our large sample size allows for a fair estimate of HPV DNA and seroprevalence among women in China. Another potential study weakness is that participating women were recruited via advertisement instead of random sampling, potentially causing selection bias in our study; albeit this limitation is again likely minimized by the relatively large sample size.

Data presented from this study, the largest conducted on HPV-DNA and antibody prevalence for types 16, 18, 6 and 11 in China, should have significant implications for

vaccination programs in China. Already approved for commercial use in many countries, Gardasil (HPV 6, 11, 16, and 18; Merck and Co., USA) and Cervarix (HPV 16 and 18; GlaxoSmithKline, Belgium) will soon be submitted to the Chinese State Food and Drug Administration for commercial use in China. These prophylactic vaccinations have been shown to be most beneficial if provided to young women who are HPV DNA/sero-negative for included vaccine HPV types,[4,5,13,14] but do not provide benefit to HPV DNA-positive women for the specific HPV vaccine type(s) by which they were infected.[15] Our data, collected from a study population of over 4000 women, found that most Chinese women aged 15–24 years were dually negative for HPV 16 or 18 DNA (96.9%), and HPV 16 or 18 antibodies (94.8%), though HPV 16 or 18 prevalence (DNA or serology) sharply increased in 30–34 year-old women (11.5%). These results suggest that younger women should receive prophylactic HPV vaccination to optimize benefits of primary cervical cancer prevention in China.

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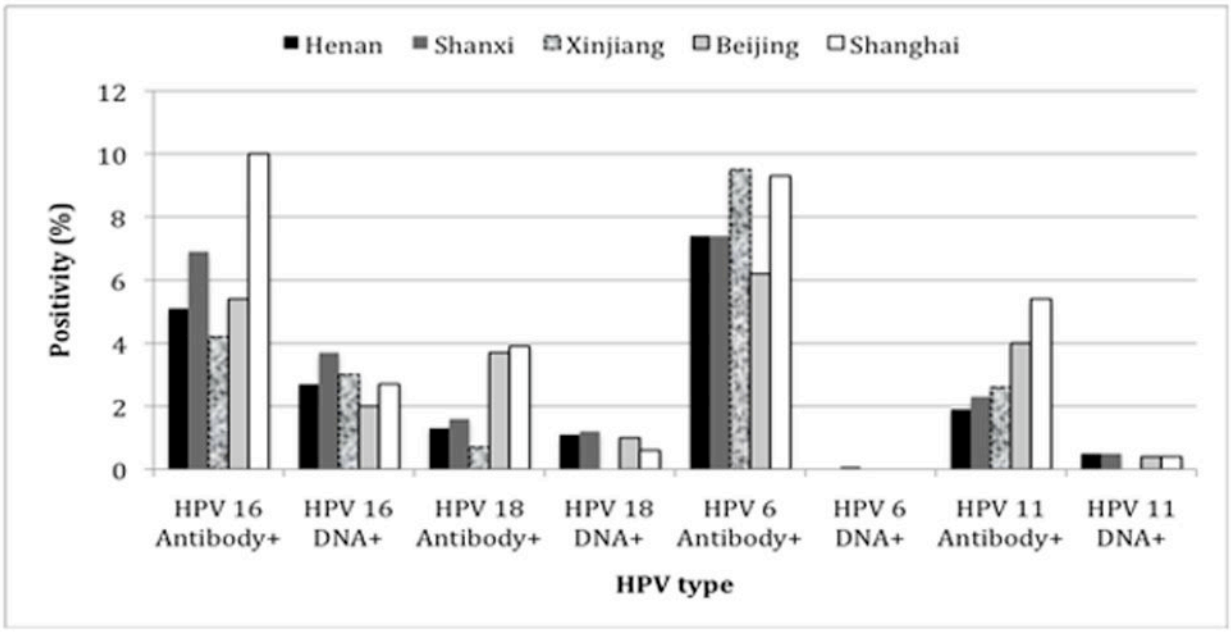

Figure 1.

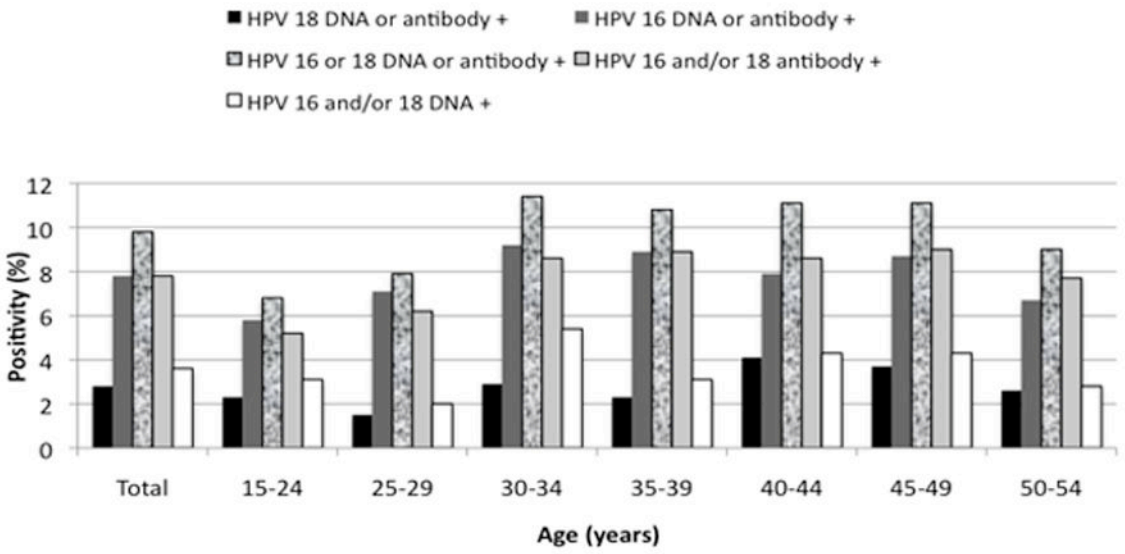

Figure 2.

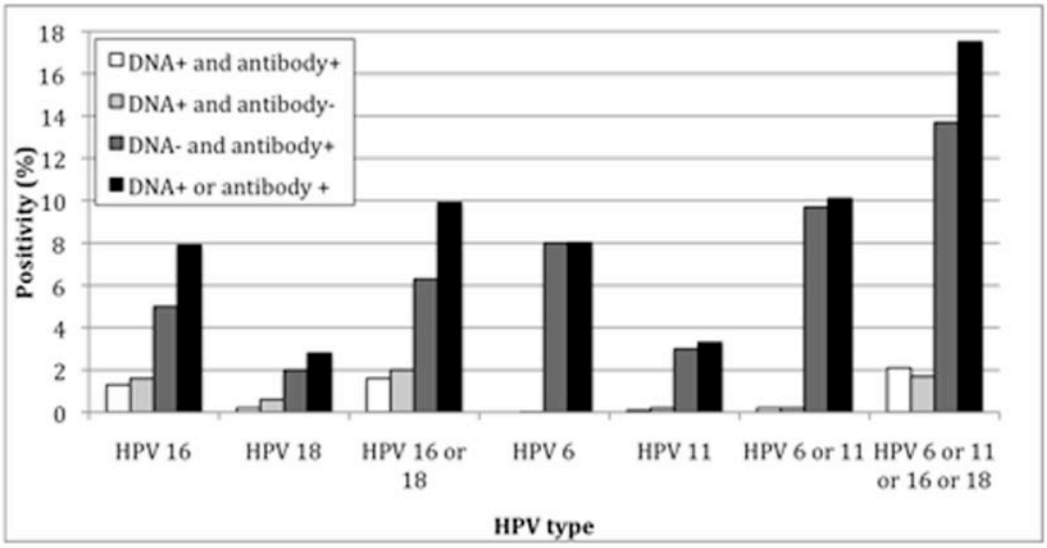

Figure 3.

Table 1

Overall Concordance of HPV DNA and Antibody Positivity in 4,206 Chinese women, stratified by HPV type 16, 18, 6, and 11

% of Women (# of Women)			HPV DNA		
			16		
			Positive	Negative	Total
		Positive	1.3%(54)	5.0%(209)	6.3%(263)
	16	Negative	1.6%(66)	92.2%(3,877)	93.7%(3,943)
		Total	2.9%(120)	97.1%(4,086)	4,206
			18		
			Positive	Negative	Total
		Positive	0.2%(7)	2.0%(83)	2.1%(90)
	18	Negative	0.6%(27)	97.2%(4,089)	97.9%(4,116)
		Total	0.8%(34)	99.2%(4,172)	4,206
HPV Serology			6		
			Positive	Negative	Total
		Positive	0.0%(0)	8.0%(335)	8.0%(335)
	6	Negative	0.02%(1)	92.0%(3,870)	92.0%(3,871)
		Total	0.02%(1)	99.98%(4,205)	4,206
			11		
			Positive	Negative	Total
		Positive	0.1%(6)	3.0%(128)	3.2%(134)
	11	Negative	0.2%(8)	96.6%(4,064)	96.8%(4,072)
		Total	0.3%(14)	99.7%(4,192)	4206

Table 2

Overall Prevalence of HPV DNA and/or antibodies, stratified by HPV Type 16, 18, 11, or 6 in 4,206 Chinese women

	DNA+ and antibody+ (%)	DNA+ and antibody− (%)	DNA− and antibody+ (%)	DNA+ or antibody+ (%)	DNA− and antibody− (%)
HPV 16	1.3	1.6	5.0	7.8	92.2
HPV 18	0.2	0.6	2.0	2.8	97.2
HPV 16 or 18	1.6	2.0	6.3	9.8	90.2
HPV 6	0.0	0.0	8.0	8.0	92.0
HPV 11	0.1	0.2	3.0	3.3	96.6
HPV 6 or 11	0.1	0.2	9.7	10.1	89.9
HPV 6 or 11 or 16 or 18	2.1	1.7	13.7	17.5	82.5