RESEARCH COMMUNICATION

Cervical Human Papilloma Virus Infection among the General Female Population in Vietnam: A Situation Analysis

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Abstract

Human papilloma virus (HPV) is the necessary cause of cervical cancer. This survey used a sample of 1,500 married women aged 15-69 to examine the prevalence of HPV infection and HPV specific types in Vietnam as well as risk factors of HPV infection. Results indicated that the prevalence of HPV infection in Hanoi and HCM was 6.13 and 8.27. The proportion of multiple HPV infection was also higher in HCM than in Hanoi (35.5% vs. 17.4%). Risk factors having significant associations with general HPV infection were early age at first sexual intercourse, number of life time sexual partners and period of use of oral contraceptives. Future implementation of HPV vaccine campaigns in Vietnam should consider the fact that HPV type 58 is common among both Hanoi and HCM populations, which none of the currently available vaccines target.

Keywords: Cervical cancer - human papilloma virus - Vietnam

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Introduction

Cervical cancer is the second most common cancer among women worldwide (after breast cancer), accounting for 11.7% of the total cancer burden (Parkin et al., 2001). In Vietnam, the incidence rate of cervical cancer is 17.3 per 100,000 women and accounts approximately for 6000 new cases and 2500 deaths per year (Pham et al., 2001). Human Papilloma virus (HPV) is one of the cause of cervical cancer. Infections with low-risk types, such as HPV types 6 and 11, can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent respiratory papillomatosis. High-risk HPV types can cause cervical, anal, and other genital cancers. High-risk HPV types are detected in 99% of cervical cancers, and worldwide approximately 70% of cervical cancers are due to HPV types 16 and 18 (Walboomers et al., 1999).

A highly efficacious prophylactic vaccines against HPV types 6, 11, 16, and 18 was licensed in June 2006 and recommended for routine use in females aged 11 to 12 years in the United States (Villa et al., 2005). Some health organizations in Vietnam are considering the possibility of offering HPV vaccine to Vietnamese women with the hope to reduce the burden of cervical cancer in Vietnam.

In order to implement the vaccine campaign successfully, representative and updated data on type-specific prevalence of HPV in Vietnam is critical. Unlike other countries where data on HPV infection is updated regularly, in Vietnam only one study on HPV infection situation done 10 years ago had been published (Pham et al., 2003).

Thus, we conducted a large scale survey on two big cities in the North and the South of Vietnam to collect information on (1) prevalence of HPV cervical infection (2) distribution of HPV specific type and (3) risk factors of HPV cervical infection.

Materials and Methods

Study population and enrollment

The survey was done in Hoan Kiem district of Hanoi (capital city in the North) and Tan Binh district of Ho Chi Minh (a city in the South). Those chosen districts in Hanoi and HCM were similar to other districts in Hanoi and HCM provinces. With the anticipated prevalence of HPV as 10%, the estimated sample size for this survey is 1700 (with the relative precision of 15%, estimated non-respondent rate of 10%). The selection criteria were women (1) not pregnant (2) had not undergone a hysterectomy or conization and (3) not mental impaired.

In each city, 850 eligible women were randomly selected from the study areas. These women were explained about the objectives of the study as well as obtained a written consent form for their participation in this study. The response rate of our study was 88.2% (750 women participated in the study in each city).

Procedure to collect/process information and specimen

Information and specimen collection was done through the following steps. First, a personal interview was done to collect information on socio-demographic variables, obstetric/gynecologic history, and sexual lifestyle. After

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interviewing, each participant was scheduled for a pelvic examination carried out by a gynaecologist. Samples of exfoliated cells from the ectocervix were collected with 2 wooden Ayre spatulas and from the endocervix with a cytobrush. Samples of exfoliated cells were sent to the laboratory of Vietnam National Obstetrics and Gynecology Hospital for Pap smear test and to the laboratory of Vietnam National Institute of Dermatology for HPV test on the same day of the sample collections.

The HPV genogyping protocol includes 4 steps. The first step is to receive and treat samples using cotton swab and storage solution. The second step is to extract DNA HPV using DNA extraction kit based on phenol/chloroform. The third step is to use the real-time PCR kit (Light Power iVA HPV PCR Kit) to detect HPV DNA using TaqMan probe. Step 4, genotype by reverse dot blot, was applied for all the HPV postive samples detected in step 3 using the LightPower iVAHPV Genotype RDB Kit. This kit allows the detection of 24 Human Papllomavirus genotype by reverse dot blot (i.e., Low-risk: 6, 11, 42, 43, 61, 70, 71, 81 and High-risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82).

Ethics Approval

The study protocol was submitted to the Hanoi school of Public Health IRB, registered with U.S. Dept. of Health and Human Services - IORG number 0003239, FWA number FWA00009326. The protocol was reviewed and cleared by this ethical committee (Ethical Approval Number 013/2010/YTCC-HD3).

Results

HPV prevalence and distribution of HPV specific types

The prevalence of HPV infection and the distribution of specific types of HPV among Ho Chi Minh (HCM) and Hanoi populations were presented in Table 1. The prevalence of HPV infection in HCM is higher than that in Hanoi (8.27% vs. 6.13%). In addition, the distribution of HPV types in HCM city is much more diversified compared to the distribution of HPV types in Hanoi. Of 62 HPV positive cases in HCM city, only 40 cases (64.5%) were infected with a single HPV type and 22 cases (35.5%) were infected with multiple HPV types, one HPV positive case in HCM was detected with 6 types of HPV. In Hanoi, 38 cases (82.6%) were infected with a single HPV type, only one case was detected with 3 types of HPV. The proportion of multiple HPV infection of women aged less than 30 is 40% while that is around 20% among women aged 30 and over.

Total of 18 types of HPV were detected in this study (Figure 1). The most popular types were HPV 18 and HPV 16, accounting for 40.74% and 22.22% of the positive cases, respectively. The five most common HPV types among Hanoi population were HPV 16 (overall prevalence 1.73%), HPV 18 (overall prevalence 1.47%), HPV 58 (overall prevalence 1.2%), HPV 81 (overall prevalence 0.80%) and HPV (overall prevalence 0.53%). The five most common HPV types among HCM population were HPV 18 (4.4%), HPV 11 (2.13%), HPV 16 (1.47%), HPV 58 (0.93%) and HPV 70 (0.80%).

Table 1. Distribution of Specific Types of HPV Detected in Hanoi and HCM

Ho Chi Minh				Hanoi			
HPV Type	n	% of Positive	% of All	HPV Type	n	% of Positive	% of All
HPV (-)	698		91.7	HPV (-)	704		93.9
HPV (+)	62	100	8.27	HPV (+)	46	100	6.13
Type 18	20	32.3	2.67	Type 18	10	21.7	0.67
Type 11	6	9.68	0.80	Type 16	8	17.4	0.53
Type 81	4	6.45	0.53	Type 58	7	15.2	0.47
Type 16	3	4.84	0.40	Type 45	4	8.70	0.27
Type 58	2	3.23	0.27	Type 35	1	2.17	0.07
Type 71	2	3.23	0.27	Type 42	1	2.17	0.07
Type 52	1	1.61	0.13	Type 51	1	2.17	0.07
Type 61	1	1.61	0.13	Type 52	1	2.17	0.07
Type 70	1	1.61	0.13	Type 53	1	2.17	0.07
Type 11,18	3	4.84	0.40	Type 59	2	4.35	0.13
Type 11,59	2	3.23	0.27	Type 81	2	4.35	0.13
Type 11,35	1	1.61	0.13	Type 11, 16	1	2.17	0.07
Type 11,52	1	1.61	0.13	Type 16, 81	2	4.35	0.13
Type 11,70	1	1.61	0.13	Type 16, 58	1	2.17	0.07
Type 16, 18	1	1.61	0.13	Type 33, 53	1	2.17	0.07
Type 18,35	1	1.61	0.13	Type 33, 54	1	2.17	0.07
Type 18,58	1	1.61	0.13	Type 70, 81	1	2.17	0.07
Type 18,81	1	1.61	0.13	Type 16,18,81	1	2.17	0.07
Type 52,53	1	1.61	0.13				
Type 16,18,58	2	3.23	0.27				
Type 11,16,18	1	1.61	0.13				
Type 16,59,70	1	1.61	0.13				
Type 16,18 ,68	1	1.61	0.13				
Type 35,58,70	1	1.61	0.13				
Type 52, 59,70	1	1.61	0.13				
Type 11,16,18,51	1	1.61	0.13				
Type 16,18,35,58,70,81	1	1.61	0.13				

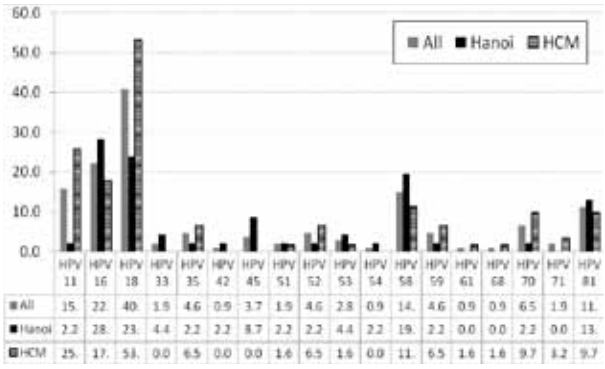

Figure 1. Distribution of Specific HPV Types by Study Location

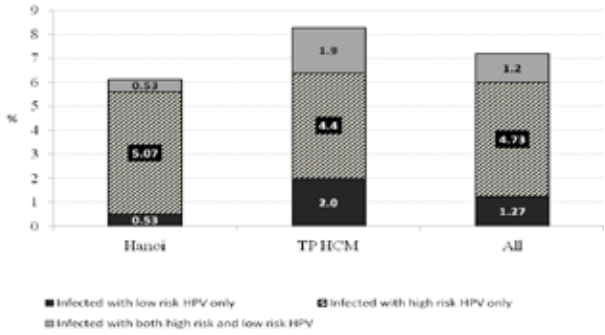

Figure 2. Distribution of HPV Low Risk and High Risk Types

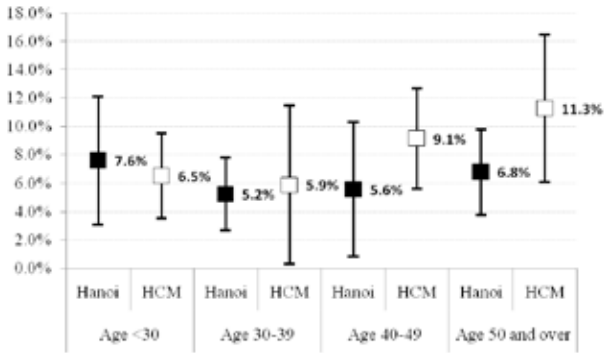

Figure 3. Distribution of HPV Positive by Age Group

Figure 2 shows the distribution of HPV low risk and high risk groups among Hanoi and HCM populations. HPV types considered low risk in this study include HPV type 6, 11, 42, 43, 70, 71 and 81. As presented in Figure 2, the overall prevalence of high risk HPV infection is 6% (both infected with high risk HPV only and with combination of high and low risk HPV). Although the prevalence of HPV positive of HCM is higher than that of Hanoi, the proportion of positive cases in HCM city infected with high risk HPV types was much lower than that in Hanoi (75.8% vs. 91.3%).

The prevalence of HPV positive by age groups was presented in Figure 3. It was observed that the distribution of HPV positive by age group was different between Hanoi and HCM population. In Hanoi sample, the prevalence was highest among the youngest age group while in HCM sample, the prevalence was highest among the oldest age group. However, it should be noted that due to the small sample size in some age/city stratification, the 95% confidence interval for the estimated prevalence was quite large, thus a clear age pattern was not observed.

Table 2. Descriptive Analysis for Risk Factors of HPV Infection Examined in this Study

Variable		n	%
Age Group	<30	222	14.8
	30-39	514	34.3
	40-49	554	36.9
	>=50	210	14.0
Highest	Primary	98	6.5
Education	Secondary	463	30.9
Attained	High School	586	39.1
	Higher than High School	353	23.5
Occupation	Government officers	294	19.6
	Workers/Handicraft	202	13.5
	Small Trade	348	23.2
	Un-employed/House-Wife/ Retired	518	34.5
	Other	138	9.2
Marital Status	Live with Husband	1342	89.5
	Separated/Divorced	85	5.7
	Widower	45	3.0
Time of	None	1,205	80.3
Using Oral	<1 year	176	11.7
Contraceptives	2 years	45	3.0
	>2 years	74	4.9
Smoking	No	1,469	97.9
	Yes	31	2.1
Age at Menarche	<=13	207	13.8
	>13	1,293	86.2
Age at first	<=18	25	1.67
Pregnancy	>18	1,475	98.3
Parity	0	60	4.00
	1-2	1,205	80.3
	>2	235	15.8
Sponaneous	No	1,166	87.7
Abortion	Yes	334	22.3
Induce Abortion	No	821	54.7
	Yes	679	45.3
History of STDs	No	1,483	98.9
	Yes	17	1.13
Life time Sexual	1	1,421	94.7
Partners	>=2	79	5.3
Age at first	<=18	66	4.40
Intercourse	>18	1,434	95.6

Pap smear abnormal and HPV positive

Of 1500 women participated in this study, 50 women (3.33%) had abnormal Pap smear results. Specifically, 44 women had ASCUS PAP smear results (ASCUS stands for Atypical Cells of Undetermined Significance, and basically means there were mild cellular changes and the cause is unknown). Pap smear test showed a finding of LSIL (low grade squamous intraepithelial lesion) in 2 women and a finding of HSIL (high grade squamous intraepithelial lesion) in 4 women. Four women with Pap smear showing a finding of Ascus and 2 women with Pap smear showing a finding of HSIL had HPV positive.

Risk factors for HPV and high risk HPV infection

This study considered the following variables as potential risk factors for HPV and high risk HPV infection: some selected demographic factors (i.e., age, occupation, education, and marital status), some obstetrical & gynecological histories (i.e., age at menarche, age at first pregnancy, parity, spontaneous abortion, induced abortion, and history of STDs) and some sexual behavior

Table 3. Multiple Logistic Regression Models for HPV Infection and High Risk HPV Infection

	Model for General HPV infection		Model for High risk HPV infection	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Age group (vs. <30)	0.26		0.20	
30-39	0.64	1.17 (0.61; 2.27)	0.75	1.12 (0.55; 2.29)
40-49	0.94	1.03 (0.52; 2.04)	0.79	0.91 (0.43; 1.92)
>=50	0.12	1.90 (0.85; 4.26)	0.14	1.94 (0.81; 4.65)
Occupation (vs. Government officers)	0.22		0.17	
Workers/handicraft	0.24	1.69 (0.71; 4.03)	0.37	1.54 (0.60; 3.97)
Small trade	0.92	1.04 (0.45; 2.44)	0.93	0.96 (0.38; 2.42)
Unemployment/Housewife/Retired	0.81	0.90 (0.40; 2.05)	0.42	0.69 (0.28; 1.71)
Other	0.36	0.62 (0.23; 1.71)	0.38	0.61 (0.20; 1.84)
Education (vs. Primary school)	0.44		0.30	
Secondary	0.58	1.27 (0.54; 3.02)	0.09	2.98 (0.85;10.5)
High school	0.81	0.89 (0.36; 2.20)	0.24	2.18 (0.60; 7.95)
Higher than high school	0.54	1.42 (0.47; 4.26)	0.25	2.37 (0.54; 10.4)
Marital status (vs. Living with husband)	0.77		0.19	
Separated/Divorced	0.85	1.08 (0.48; 2.46)	0.09	0.28 (0.06; 1.20)
Widower	0.50	0.60 (0.13; 2.66)	0.51	0.61 (0.14; 2.72)
Smoking vs. Non-smoking	0.67	1.32 (0.37; 4.75)	0.34	1.86 (0.51; 6.72)
Age at menarche (<=13 vs. >13)	0.94	0.98 (0.53; 1.79)	0.66	0.86 (0.44; 1.68)
Parity (vs. having 1-2 children)	0.59		0.60	
0 children	0.54	0.69 (0.21; 2;26)	0.41	0.55 (0.13; 2.30)
>2 children	0.43	1.23 (0.74; 2.04)	0.59	1.17 (0.67; 2.05)
History of STD (Yes vs. No)	0.79	0.75 (0.09; 6.17)	0.95	0.93 (0.11; 7.96)
History of spontaneous abortions (Yes vs. No)	0.18	0.70 (0.41; 1.19)	0.68	0.89 (0.51; 1.56)
History of induced abortions (Yes vs. No)	0.86	0.96 (0.62; 1.49)	0.93	1.02 (0.63; 1.65)
Age at first pregnancy (<=18 vs. >18)	0.09	0.24 (0.04; 1.25)	0.13	0.27 (0.05; 1.47)
Number of life time sexual partners (>=2 vs. 1)	<0.001	3.23 (1.64; 6.35)	<0.001	3.83 (1.88; 7.83)
Age at first intercourse (<=18 vs. >18)	<0.001	4.00 (1.83; 8.76)	<0.001	4.20 (1.77; 9.96)
Year of using oral contraceptives (vs. Never)	0.11		0.47	
<1 year	0.88	1.05 (0.55; 2.01)	0.67	0.85 (0.41; 1.78)
1- 2 years	0.32	0.36 (0.05; 2.67)	0.33	0.36 (0.05; 2.75)
>2 years	0.03	2.25 (1.09; 4.62)	0.28	1.61 (0.69; 3.79)
City (HCM vs. Ha Noi)	0.20	1.37 (0.85; 2.21)	0.66	1.12 (0.67; 1.88)

factors (i.e., age at first intercourse, number of life time sexual partners, and time of using oral contraceptives) and smoking. Table 2 presents the distribution of these potential risk factors.

Table 3 shows the multiple logistic models for the probability of infected with general HPV and the probability of infected with high risk HPV types. Although the prevalence of general HPV infection in HCM sample is higher than that in Hanoi (8.27% vs. 6.13%), multivariable models does not show a significant difference in the probability of infected with general HPV among these two samples (OR=1.37, p=0.2). Similarly, the probability of infected with high risk HPV types was not significantly different between Hanoi and HCM (OR=1.12, p=0.66).

Of 15 variables examined in the multivariate model, only 3 variables showed significant associations with the probability of infected with general HPV. These were number of life time sexual partners, age at first intercourse, and years of using oral contraceptives. Specifically, the odds of having general HPV positive among women who had first sexual intercourse before 18 is 4.00 times higher than that among women who had first sexual intercourse after 18 (p <0.001). Women who had more than 1 life time sexual partners is at higher risk of infected with general HPV compared to women who had only 1 sexual life time partner (OR=3.23, p<0.001). Compared to women never used oral contraceptives, women used that for less than 2 years had no significantly higher risk, however, women used that for two years or more were at 2.25 times higher risk of infected with general HPV.

The multivariate logistics model for infected with high risk HPV revealed only two significant associations (i.e., association between outcome with number of life time sexual partners and with age at first intercourse). The risk of infected with high risk HPV types among women had more than 1 life time sexual partners was 3.83 times higher that among women had only 1 life time sexual partner. Having first sexual intercourse before 18 increased the odds of infected with high risk HPV 4.20 times compared to having first intercourse after 18. Unlike in the model for infected with general HPV, time of using oral contraceptives did not show a significant association with the probability of infection with high risk HPV.

Discussion

A previous study compared an urban setting in HCM and semi-urban setting in Hanoi around 10 years ago showed that HPV prevalence in HCM was 5 fold higher than that in Hanoi (Pham et al., 2003). Our study showed that HPV infection prevalence in Hanoi was still lower than that in HCM, however, the gap in HPV prevalence between these cities decreased significantly over time. Huynh et al. conducted a study about war and cervical cancer and observed that the higher rate of cervical cancer in Southern Vietnam could be attributed to the ground

combat militarization of South Vietnam during the time 1955-1975 (Huynh et al., 2004). Their hypothesis was the war in the South of Vietnam made most men attending military to experience multiple pre- and postnuptial partners, including commercial sex workers, who may serve as important reservoirs of HPV and thus increase the HPV prevalence of their partners in the Southern of Vietnam and then cervical cancer. This hypothesis can be applied in our study to explain for the reducing difference in HPV prevalence between Hanoi (the North of Vietnam) and HCM the South of Vietnam). Just by examining the HPV prevalence across different age groups, it can be observed that the difference in HPV prevalence between these two cities much higher among older age group (among age 50 and over, HPV prevalence in HCM city was almost 2 fold higher than that in Hanoi)); among younger age group (women less than 30 years old), perhaps the impact of combat militarization of women's partners was over, the HPV proportion in Hanoi is even higher than that in HCM.

A broad spectrum of H PV types was reported in this study with the most popular types of HPV 16 and 18; this finding was similar with previous studies in Vietnam and other countries (Giuliano et al., 2001; Pham et al., 2003; Dunne et al., 2007). Currently, some health organizations are considering two types of HPV vaccines licensed by the FDA (i.e., Cervarix made by GlaxoSmithKline and Gardasil made by Merck) (Food and Drug Administration (FDA)). Cervarix protects against only HPV types 16 and 18 while the vaccine Gardasil also protects against HPV types 6 and 11. Thus, for HCM population, vaccine Gardasil may be more suitable because the proportion of HPV 11 among HPV positive in HCM sample is quite high (25%). It should be noted that none of the currently available vaccines can protect against the HPV type 58 (i.e., high risk) while 11% and 19% HPV positive cases in HCM and Hanoi were infected with this type. Other studies also reported that HPV58 was among the most common types found in cervical cancer specimens in China, Thailand, and the Philippines (Clifford et al., 2003). The results of higher multiple HPV infections among women aged less than 30 compared to that among other age groups were consistent with previous literature (Clifford et al., 2003; Pham et al., 2003).

In this study, we examined a broad range of potential risk factors for HPV infection, these potential risk factors came from the literature review of risk factors for both cervical cancer and HPV infection (Giuliano et al., 1999; Sellors et al., 2003; Cooper et al., 2007; Bosch, 2008) because the literature on risk factors for HPV infection was quite scatter. Controlling for broad range of potential risk factors including some selected demographic factors, obstetrical & gynecological histories, sexual behavior factors and smoking helped to minimize the risk of confounding effects, thus our study may have less type 1 errors compared to previous studies controlling for less potential risk factors. Our finding about the positive associations between HPV infection and number of life time sexual partners and early first sexual intercourse were consistent with previous studies (Giuliano et al., 1999; 2001; Lazcano-Ponce et al., 2001; Pham et al., 2003). More important, it was observed the associations between these two risk factors with HPV high risk infections were stronger. Other studies have reported that using oral contraceptives was consistent risk factor for cervical carcinoma rather than for HPV infection. However, our results indicated that women using oral contraceptives for more than 2 year was at higher risk of HPV infection compared to women never using oral contraceptives.

The findings of this study came from two urban district of Hanoi and HCM city and therefore, caution must be taken in generalizing these findings to all Vietnam population, especially to rural population. However, all the prevalence/association yielded from this study should provide a representative estimation of Hanoi and HCM city because we had followed a very strict protocol to avoid biases such as women were randomly chosen in the same way in the 2 areas, all clinical examination and specimen collections were done by qualified gynecologists, and all the samples were examined in parallel in the same laboratory. The detection of HPV positive using real time PCR method and the genotyping of HPV type using reverse dot blot method in this study also provided more precise results compared to the Hybrid Capture Tube Method applied in previous studies (Giuliano et al., 2001).

Collectively, the results from this study suggest that: (1) the difference in HPV prevalence between the North and the South of Vietnam reduced over time (2) the distribution of HPV types was more diversified in HCM than Hanoi and (3) risk factors of general HPV and high risk HPV infections were number of sexual partners and early age at first sexual intercourse.

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