Prevalence of Human Papillomavirus in Women with Abnormal Cervical Smears from Sarawak, Malaysia

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ABSTRACT

Introduction

Cervical cancer is common cancer and ranked in fourth place in both incidence and mortality worldwide. It is 3rd most common female cancer in Malaysia with a lifetime risk of 1 in 116. Infection with high-risk oncogenic human papillomavirus (HPV) is recognized as one of the substantial risk factors for the development of cervical cancers.

Methods

It was a cross-sectional study conducted to determine the prevalence of HPV infection and its subtypes among women with various degrees of abnormal smears, who were seen in the colposcopy clinic of Sarawak General Hospital within six months' period from January to June 2018. We recruited 56 participants. There were 23 each for an atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) and 10 high- grade squamous intraepithelial lesion (HSIL). DNA was extracted, and HPV genotypes were determined via polymerase chain reaction (PCR) using two primer pairs MY09/MY11 and GP5+/GP6+.

Results

The age ranged from 23 to 56 years, with a mean age of 42.96 years. HPV was detected in 20 out of 56 (35.7%). There were 6 high-risk oncogenic HPVs (18, 51, 52, 56, 58, 68) detected in participants and the most prevalent subtypes were 18, 52, and 58 (20% each). Four low-risk HPVs detected were 6, 53, 70, and 84. There was a significant association between the severity of cervical lesions and HPV positivity ($P < 0.004$). HSIL had the highest positive predictive value to have HPV infection as 70% compared to 43.4% of LSIL and 9.3% of ASC-US.

Conclusion

Distribution of HPV subtypes from women with abnormal smears from Sarawak indicated a high prevalence of HPV 18, 52, and 58. We also identified HPV 70, which has never been reported in West Malaysia. These findings could contribute valuable information for HPV vaccination strategies, particularly for Sarawakian women.

Keywords

Prevalence, human papillomavirus, abnormal cervical smears, cervical cancer

Introduction

Cervical cancer is common cancer and ranked in fourth place in both incidence (6.6%) and mortality (7.5%) according to GLOBOSCAN estimates [1]. Almost 80% of cases occur in developing countries [2]. Globally it was estimated that more than 500,000 new cases with 300,000 deaths from cervical cancer in the year 2018[1]. It is 3rd most common female cancer in Malaysia, and according to the National Cancer Registry of Malaysia (2016), Sarawak ranked as the highest age-standardized incidence rate for cervical cancer at 12.1 per 100,000 women [3].

There are known risk factors such as early intercourse, sexual promiscuity, immunosuppression, sexually transmitted diseases, and smoking. However, above all, infection with human papillomavirus (HPV) plays the most crucial role in the development of cervical cancer.

HPV is a small, highly conserved, non-enveloped double-stranded DNA virus that belongs to the Papillomaviridae family [4]. To date, more than 200 HPV subtypes have been identified [5]. It can be classified into mucosal or cutaneous, and the former being known as an important aetiological agent for the development of cervical cancers. Mucosal-infecting HPV is subdivided into high- and low-risk groups. There were at least 15 HPV subtypes identified as high-risk oncogenic HPVs which include subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 [6].

The HPV infection is asymptomatic in the majority of women, and most cases resolve within two years [7]. Some studies reported that infection spontaneously resolves in 50-90% of HPV-positive women in one year [8,9]. Nonetheless, 10-15% of all HPV-infected women may have persistent infection [7] and consecutively, increased risk of cancers, and other benign diseases. Among 15 high-risk oncogenic HPVs, type 16 and 18 were most prevalent types associated with 70-80% of cervical and anal cancers, and 40-50% of vulvar and oropharyngeal cancers [10, 11]. It is pertinent to note that HPV infection can be transmitted through intimate skin to skin contact without having penetrative intercourse, and once infected, there is a lifetime risk of infection up to 85% [10].

The prevalence of HPV infection and the distribution of subtypes varied in a wide range across the region and population [12]. In Southeast Asia, estimated HPV prevalence was reported as 14% [13]. The prevalence increases with increased severity of cervical lesions. A systematic review reported the prevalence of high-risk HPV 16 and 18 in cytology of Malaysian women with cervical cancer as 88.7% [4]. However, most of the data contributed were from West Malaysia, and there are currently no published data on the prevalence of HPV subtypes among women with abnormal smears in Sarawak.

The objectives of our study were: a) to determine the proportion of HPV infection among women with various degrees of abnormal smears who were seen in Sarawak General Hospital; b) to identify the common HPV subtypes seen in abnormal cervical smears in Sarawak. The incorporation of HPV tests in the management supported the effectiveness of already implemented guidelines on abnormal smears management in a resource-limited area like Sarawak. At the same time, identifying the common subtype would help to introduce the respective vaccination program to become more cost-effective and improve the efficacy of the vaccine.

MATERIALS AND METHODS

Study design

It was a cross-sectional study involving all sexually active women with abnormal pap smears, who attended the colposcopy clinic of Sarawak General Hospital within six months period from 1st January to 31st June 2018. Pregnant women and those who have had prior HPV vaccination were excluded from the study. Ethical clearance was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR-17-1952-36173) as well as UNIMAS Medical Ethics Committee [UNIMAS/NC-21.02Jld.3(17)]. A patient information leaflet was provided to all participants. Informed consent was taken along with their sociodemographic data, medical and sexual history.

Cervical samples

All the samples were taken by convenience sampling method. Cervical liquid-based cytology was obtained as follows; the cervix was scraped 360 degrees (both endocervix and ectocervix) of each participant by a single gynecologist (MSY) using sterile Cervex-Brush (Rovers Medical Devices, Lekstraat, Netherlands). Then the Cervex-Brush was preserved in BD Surepath Medium in the collection vial and stored at 4 °C. The samples were sent in the cold chain to the Medical Microbiology Laboratory, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak on a twice-weekly basis.

Molecular detection of the HPV genome

The cervical cells were dislodged and resuspended in the BD Surepath medium via vortexing in 3 short bursts of 10 seconds each. Two mL of the cell suspension (10% of the total volume) was pelleted by centrifugation at 3000 x g for 30 mins at 4 °C. The supernatant was carefully discarded by aspiration, and cells resuspended in sterile phosphate-buffered saline (PBS). The viral nucleic acid was extracted from the cell suspension using the High Pure Viral Nucleic Acid Kit (Roche) according to the manufacturer's instruction.

In our study, we used two different pairs of oligonucleotides primers to detect HPV DNA: MY09/MY11, followed by GP5+/GP6+. Polymerase chain reactions (PCR) were carried out separately for each oligonucleotide primer as previously described by Venceslau et al [14]. Primer set amplifying human ß-globin gene was included as an internal control. Amplicons were resolved in 2 % (w/v) agarose gel prepared in TBE buffer, excised, and sequenced using the BigDyeâ Terminator chemistry (Applied Biosystems). We used a short PCR fragment to amplify the 65bp fragments of the HPV genes. Then the amplified products were analyzed by electrophoresis in a 3% agarose gel containing ethidium bromide and photographed. HPV was typed by direct DNA sequencing (ABI prism 377 DNA sequencer). Results were interpreted as positive when one of the primers testings detected the viral DNA.

Statistical Analyses

We used to chi-square test to assess the association between demographics, cervical pathology, and HPV infection.

RESULTS

We recruited a total of 56 women in this study. The age ranged from 23 to 56 years, with a mean age of 42.96 years. Table 1 showed the demographic data of participants. HPV was detected in 20 out of 56 (35.7%). There were 6 high-risk oncogenic HPVs (18, 51, 52, 56, 58, 68) detected in participants and the most prevalent subtypes detected were 18, 52, and 58 (20% each). Four low-risk HPVs detected were 6, 53, 70, and 84.

The frequency distribution of cytology lesions within the HPV positive and negative groups were shown in Table 2. Among participants, 15% of the atypical squamous cell of undetermined significance (ASC-US), 50% of low-grade intraepithelial lesions (LSIL), and 35% of high-grade intraepithelial lesions (HSIL) were HPV positive. In contrast, 8.3% of HSIL, 36% of LSIL, and 55% of ASC-US were negative. There was a significant association between the severity of cervical lesions and HPV positivity ($P < 0.004$). HSIL had the highest positive predictive value to have HPV infection as 70% compared to 43.4% of LSIL and 9.3% of ASC-US.

There was no significant difference in HPV prevalence among age and ethnic groups [Table 2]. Subtype 18 was more commonly seen in high-grade squamous intraepithelial lesions (HSIL). The distribution of HPV subtypes was presented in table 3. Among all participants, 11 did not require any interventions. A large loop excision of the transformation zone (LLETZ) was performed in 11, and cervical biopsy in 34. The intervention measures were done according to the Sarawak General Hospital guideline for abnormal cervical smears. The follow-ups planned as scheduled as six-monthly, yearly, and returned to the routine call.

Discussion

Sarawak is the largest of 13 states in Malaysia with six major ethnic groups; Iban, Chinese, Malay, Bidayuh, Melanau and Orang Ulu, and more than 40 sub-ethnic groups. Although it has a relatively low population density compared to West Malaysia, it ranked at the highest incidence rate for cervical cancer nationwide. This study was the first HPV study among multi-ethnic women with abnormal cervical smears in Sarawak.

In our study, the overall HPV prevalence in women with abnormal cervical smears was 35.7% with high-risk HPV prevalence of 26.7%. There was no significant difference between age and ethnicity. A few studies had described the HPV prevalence in Malaysian women with abnormal cervical smears over the last decade. Sharifah and colleagues reported in 2009 that the prevalence of HPV in 38 abnormal cervical smears was 95%, and the most prevalent genotypes were HPV 16 and 52. The smears used in their study were collected from cytological archives, and approximately one-third was cancer cases [15]. Another study conducted in the North Eastern coastal part of West Malaysia revealed a 3% HPV prevalence for the general population, but 61.5% in abnormal pap smears [16]. A study conducted in Singapore and Southern Malaysia reported that 39.7% in women with abnormal cytology [17]. Chong and colleagues presented that the overall prevalence of 46.7% among 180 women in Selangor, but their study included only five abnormal smears, all of which were positive for HPV [18].

Globally many studies have reported the prevalence of HPV and its subtypes, which varies widely across the different geographical regions and populations [12, 13]. This variables rate is due to different methods used for HPV detection (hybrid/PCR) and typing (primers), types of the studied materials (smears/frozen materials), anatomical localization, and population [14]. In our study, we

used PCR to achieve a molecular diagnosis of HPV infection. PCR is the most commonly used technique as it can detect small fragments of DNA [19]. Two different pairs of primers (MY09/MY11 and GP5+/GP6+) can identify a wide range of HPVs and are most frequently used in clinical studies [18, 20].

Most of the studies from West Malaysia reported the different distribution of HPV subtypes. The most prevalent subtypes were 16,18, 52, 58 [15-18, 21, 22]. In this study, the most frequent types detected were 18, 52, and 58, while we did not identify 16 in our participants. The HPV genotyping kit we used in this study had a wide range of detection for different HPV genotypes. Besides 6 high-risk oncogenic HPVs (18, 51, 52, 56, 58, 68), additional 4 low-risk HPVs (6, 53, 70 and 84) were detected in present work. Interestingly, none of the previous studies conducted in West Malaysia has reported the presence of HPV 70.

Recently a paper published from the neighbour state, Sabah, reported that 9.6% of HPV prevalence, which included the majority of normal smears and a few abnormal smears, with the most prevalent type detected in abnormal smears was 58 [23]. They also observed the prevalence of HPV 70 (16.7%) in participants from Sabah. These findings suggest that HPV 58 is the subtype frequently associated with abnormal smears in East Malaysia, and HPV 70 is relatively prevalent among women in this region compare to West Malaysia. One meta-analysis reported that HPV 58 attributed to cervical intraepithelial neoplasia and cervical cancer in East Asia nearly four times higher than other continents [24]. A prospective study conducted in Taiwan noted that the long-term risk of invasive cervical cancers was higher for subtype 58 compared to other non-HPV 16 subtypes [25].

There was one HIV positive participant, and she was found to be HPV negative, which was probably due to the practice of barrier contraceptive method. There was no case of multiple infections detected. There were 4 participants as a first time screening. Their first pap smear was done and straightaway to be seen in the colposcopic clinic, which suggested that the uptake of cervical screening programs by the public was low. According to the Ministry of Health Malaysia Annual Report 2017, cervical screening coverage was only 26.3%, although it aimed for 40% of all sexually active women between 20 – 65 years [26].

We noted that there was a significant association between the severity of cervical lesions and HPV positivity ($P < 0.004$). HSIL had the highest positive predictive value to be HPV positive as 70% compared to 43.4% of LSIL and 9.3% of ASC-US. This finding supports that the prevalence increases with increased severity of cervical lesions as reported by other studies [4, 27].

The HPV infection is preventable by prophylactic vaccination, which was proved to be effective and safe. Currently, there are two types available in Malaysia. The bivalent vaccine protects high-risk oncogenic HPV 16 and 18, which account for 70% of cervical cancers, and the quadrivalent vaccine that targets additional subtypes 6 and 11, which causes 90% of genital warts [28, 29]. In Malaysia, the vaccine was approved in 2007, and the national program on HPV immunization was launched in 2010 [30]. In late 2014, nonavalent (9-valent) vaccine was approved in US, which extends the coverage to additional 5 high-risk oncogenic HPVs 31, 33, 45, 52 and 58 [31]. However, more comprehensive data on cost-effectiveness, affordability, and feasibility are still needed for resource-limited settings.

We studied the prevalence of HPV among women with abnormal cervical smear for the first time in Sarawak. The sample size was relatively small, which may limit the statistical significance. The study included only participants with abnormal smears, so that the result may not be generalizable

to the whole Sarawakian community. However, it may act as a stepping stone for future studies as it described HPV subtypes associated with abnormal cervical smears. Further studies with larger sample size and extensive coverage of other areas of Sarawak will help better understanding of HPV prevalence and distribution in the state. The identification of HPV subtypes in the local community may assist in implementing the appropriate strategies for cervical cancer prevention. Understanding the distribution of HPV subtypes is crucial to determine the most suitable HPV vaccines against the infection and cost-effective approach for the prevention of cervical cancer.

Conclusion

Distribution of HPV subtypes from women with abnormal smears from Sarawak indicated a high prevalence of HPV 18, 52, and 58. We also identified HPV 70, which has never been reported in West Malaysia. These findings could contribute valuable information for HPV vaccination strategies, particularly for Sarawakian young women.

Table1. Socio-Demographic characteristics of participants (n= 56)

Characteristics	Number	Percent
Age (years)	23 – 68 Mean - 42.96	
Ethnicity		
Malay	20	35.70
Chinese	11	19.65
Bidayuh	14	25.00
Iban	11	19.65
Marital status		
Single	1	1.8
Married	53	94.6
Divorced	2	3.6
Duration of relationship		
<10 years	16	28.6
>10 years	40	71.4
Parity		
No child	3	5.4
1 child	7	12.5
2-5 children	43	76.8
> 5 children	3	5.4
Education		
<Secondary	23	41.1
Secondary	26	46.4
Degree	7	12.5
Sexually transmitted infection		
Yes	1	1.8
No	55	98.2
Contraception		
No	22	39.3
COCP	14	25.0
Injection & BTL	19	33.9
Barrier	1	1.8
No. of pap smear done before		
Never	4	7.1
1-2 times	31	55.4
>2 times	21	37.5
Intervention done		
No	15	26.8
Biopsy	29	51.8
LLETZ	12	21.4
HPV result		
Negative	36	64.3
Positive	20	35.7

Table 2. Prevalence of HPV among study participants

Status	Prevalence		Total (56)	p-value
	HPV(+)	HPV (-)		
Age (years)				
<30	1	5	6	
30-49	17	20	37	0.083
≥50	2	11	13	
Ethnicity				
Malay	6	14	20	
Chinese	3	8	11	0.5078
Bidayuh	5	9	14	
Iban	6	5	11	
Cervical lesions				
ASC-US	3 (15%)	20 (55%)	23	
LSIL	10 (50%)	13 (36%)	23	0.004355
HSIL	7 (35%)	3 (8.3%)	10	

Table 3. Distribution of HPV subtypes in 20 abnormal cervical smears

Lesions	HPV Subtypes										Total
	6	18	51	52	53	56	58	68	70	84	
ASC-US	-	1	-	-	-	-	2	-	-	-	3
LSIL	1	-	1	2	1	1	2	1	1	-	10
HSIL	-	3	-	2	-	-	-		1	1	7
Total	1	4	1	4	1	1	4	1	2	1	20

ASC-US – Atypical squamous cell of undetermined significance

HSIL – High- grade squamous intraepithelial lesion

LSIL – Low-grade squamous intraepithelial lesion

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Declaration

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