ORIGINAL ARTICLE

Factors Associated with Presence of Human Papillomavirus Infection among Women: Findings from New Cervical Cancer Screening in Kelantan, Malaysia

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ABSTRACT

Introduction: Human papillomavirus (HPV) infection is known to cause cervical cancer worldwide. Recently, Malaysia introduced HPV DNA detection testing for cervical cancer screening program. However, knowledge regarding factors for HPV infection among women still limited. Thus, this study aimed to determine the prevalence and factors associated with HPV infection among women in Kelantan, a north-eastern state of Malaysia. **Methods:** This study used secondary data extracted from HPV DNA test registry book and HPV DNA laboratory request forms. Data on all Malaysian women aged 30 to 49 years old in 2019 reported in registry book were included. Simple random sampling was applied. All information from book and forms were collected using proforma and analysed using SPSS. The outcomes were categorised into HPV infection and non-HPV infection. The parameters related to factors associated with HPV infection were determined using multivariable logistic analysis. **Results:** The prevalence of HPV infection among women attending the new cervical screening was 8.4% (95% CI 6.4%, 10.3%). Those aged between 30 and 39 years old (AdjOR 2.09; 95% CI 1.16, 3.78, p=0.014), had 5 or more parities (AdjOR 2.82; 95% CI 1.58, 5.06, p<0.001) and hormonal contraception users (AdjOR 7.48; 95% CI 4.07, 13.76, p<0.001) were significantly associated with HPV infection. **Conclusion:** Overall, the prevalence of HPV infection from this study is comparable to the local and international studies. Age, number of parities and hormonal contraception users influence the HPV infection. This finding could help in designing more targeted screening for cervical cancer.
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Keywords: Factor associated, Human papillomavirus (HPV), HPV DNA test, HPV screening, Cervical cancer screening

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INTRODUCTION

Cervical cancer continues to be a significant public health issue for women around the globe. Recent update of worldwide cancer burden by International Agency for Research on Cancer (IARC) stating that, cancer cases have increased to 19.3 million, and cancer deaths climbed to 10 million by 2020. In addition, the incidence of cervical cancer, which is known to be preventable, has also increased, accounting for approximately 604,127 cases, or 6.5% of cancer incidence in females (1). Meanwhile, cervical cancer incidence in Malaysia accounted for approximately 7.2% in 2018 and it also considered as the third most common malignancy among females and the second most common cancer among 15 to 44 years old (2).

Formerly, pap smears were used as primary screening for cervical cancer prevention. Then, the HPV DNA test was introduced to overcome the shortcomings from pap smear. Previous reports had suggested its superiority compared to a pap smear. In addition, the test is more sensitive and far more capable of detecting precursor lesions (3). Thus, testing for HPV DNA is now recommended, given that HPV-based screening offers more than 60% protection against invasive cervical carcinomas (3).

The IARC has demonstrated that HPV infection is crucial in the development of cervical cancer (4). HPV potentially associated with cervical cancer are high-risk types that can be identified as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. However, HPV types 16 and 18 are the most carcinogenic and cause approximately 70% of all cervical cancer cases globally (5-7). Furthermore, persistent infection may be predisposed to development of precancerous lesions in which later progresses into invasive carcinoma if

the precancerous lesion is not discovered and treated earlier (8). In Malaysia, retrospective evidence showed that 88.7% of invasive cervical cancer cases were due to high-risk type of HPV infection (8).

Ministry of Health (MOH) began new cervical cancer screening by incorporating the HPV DNA test as primary screening in 2019 and pioneered it in four states, including Kelantan. This screening is targeted at those aged 30 to 49 years, consistent with the World Health Organization (WHO) recommendation that screening begins at the age of 30 years. Additionally, those under the age of 30 are not recommended for HPV DNA tests since the infection was transient and most likely to resolve within two years. Consequently, this test may subject them to unnecessary procedures.

Since HPV infection is one of the most common sexually transmitted infection worldwide, numerous studies have reported association between sexual behaviour and lifestyles with HPV infection. Women with high lifetime sexual partners, younger age of sexual intercourse and smoking were associated with higher risk of HPV infection (9-11). However, the HPV infection can also be contributed by other factors as well such as sociodemographic and reproductive characteristics of the women. Among them are characteristic related to lower socioeconomic status, area of residency, low educational level, high parity and contraceptive use (12-14). To date, research regarding HPV infection is relatively scarce in Malaysia. In addition, since HPV DNA testing still a new screening program in Malaysia, this study aimed to determine the prevalence of HPV infection and association between sociodemographic and reproductive characteristics with HPV infection among women attending to the cervical cancer screening in Kelantan.

MATERIALS AND METHODS

Study Area and design

The study area was in Kelantan, a northeast state of peninsular Malaysia which consist of 10 districts, with total population of 1.90 million in 2019 (15).

This study was a cross sectional study conducted based on state-wide secondary data review involving data from new cervical cancer screening program in Kelantan for year 2019. Considering this is pioneered program from Ministry of Health (MOH), it was implemented in all government health clinics and hospitals in Kelantan. Therefore, screening conducted at private health facilities were not included in this study. All women attended the screening were registered in the Registry Book which was managed at district level and regularly monitored by Maternal and Child Health Unit, Kelantan State Health Department in Microsoft Excel format. Since this program just started, the only completed data until the period of this study was for year 2019. Data of all registered Malaysian women aged 30 to 49 years old in 2019 reported in the Registry Book of HPV DNA test were included in this study. However, those with an unsatisfactory result of the HPV DNA test and missing important study variables were excluded.

Sample Size Determination

The sample size for determination of prevalence of HPV infection in Kelantan was calculated based on single proportion formula, n= (Z/d)2 p (1- p), where Z value based on 95% CI is 1.96, d (precision) is set at 0.05 and p based on previous prevalence 0.47 (16). Meanwhile, for determination of factors associated with HPV infection, sample size was calculated based on two proportion formula using Power and Sample Size (PS) Software version 3.1.6. The following parameters and values were used; P0 is proportion of non-exposed among HPV infection from previous study (17), whereby P1 is estimated proportion of exposed among HPV infection and m (number of non-exposed per exposed women among HPV infection). Considering 80% power of study, significance level of 5%, and after adjustment with 10% missing data, final sample size needed was 789. As the list of registered women attending screening in 2019 were 5174, the RAND function in Microsoft Excel were used to generate random number on list of registered women. Then the number arranged according to sequence 1 to 1000 and first 1 to 789 were selected as required.

Research Tools and Data Collection

The information required as following: 1) sociodemographic factors; date of birth, age, ethnicity and locality; 2) reproductive characteristics; the number of parities, contraception status and types, data of last childbirth and menopausal status; and 3) outcome; the result of HPV DNA test. The information was extracted from the Registry Book of HPV DNA Test and HPV DNA test request forms. The Registry Book was prepared in Microsoft Excel file. Data collection done using proforma then were entered into Microsoft Excel 365. It was conducted from January to May 2021 by a single researcher.

Statistical Analysis

Analysis was performed using IBM SPSS Software version 26. Data were explored for any missing values and errors. Categorical variables were summarized in frequency (n) and percentage (%). Numerical variables were described in mean and standard deviation (SD) for normally distributed data whereas for skewed data, the variables described as median and interquartile range (IQR). For sociodemographic factors, age was categorised into 30 to 39 years and 40 to 49 years, ethnicity was divided into Malay and non-Malay, and locality was categorised into rural and urban areas (18). Contraception considered in this study included contraceptive pills, injections, implants, intrauterine devices (IUD) and tubal ligation. Contraceptive pills (including combined or progestogen-

only pills), injections (Depo-Provera), and implants (Implanon) were regarded as hormonal methods, while bilateral tubal ligation approach was considered as non-hormonal. The outcome of interest in this study was HPV infection. HPV infection is referred as a laboratory-confirmed infection from any HPV DNA genotype. Prevalence of HPV infection estimates (with 95% CIs) was described using percentages, while the association between variables and HPV infection was evaluated using simple and multiple logistic regression analysis. Simple logistic regression was used to obtain preliminary variables associated with HPV infection presented by crude odds ratio (OR) and 95% confidence interval (CI). Variables selected in multiple logistic regression were variables with p<0.25 or that were clinically significant. Subsequently, the preliminary main effect model was obtained by comparing the models using forward likelihood ratio (LR) and backward LR. Multicollinearity and plausible two-way interaction were examined. The model fitness was assessed by Hosmer-Lemeshow test, classification table and area under receiver operating characteristics (ROC) curve. The final model was presented with an adjusted odds ratio (AdjOR) and 95% CI, Wald statistics, and p-value. A two-tailed P value of <0.05 was considered statistically significant.

Ethical Approval

The study was conducted based on principles outlined in the Declaration of Helsinki. Ethical approval was granted from the Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/20110591) and Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia, [NMRR-20-2542-57249 (IIR)].

RESULTS

Characteristics of women attending new cervical cancer screening in Kelantan

Based on calculated sample size, we analysed 789 of the women attended new cervical cancer screening in 2019. The mean age of attendee was 38.82 (5.44) years old. The attendees were predominantly Malays (98.6%), and only 1.4% of the women were categorised as non-Malays, which consisted of five Chinese, an Iban, a Kadazan and four Siamese. The detailed characteristics are described in Table I.

Prevalence of HPV infection and genotype distribution

This study discovered an overall prevalence of HPV infection of about 8.4% (95% CI 6.4%, 10.3%). The genotypes identified from this study were divided into HPV types 16/18 and HPV types non 16/18. The prevalence of HPV types 16/18 was 4.8% (95% CI 3.3%, 6.3%), while the prevalence of HPV types other than 16/18 was 3.5% (95% CI 2.2%, 4.8%). Among those tested positive for HPV, majority were possessed HPV types 16/18 (38/66, 57.6%).

Table I: Sociodemographic and reproductive characteristics of women attending new cervical cancer screening in Kelantan in 2019 (n=789)

Variables		n	%
Age (year)		38.8 (5.44)[a]	
	40 – 49	344	43.6
	30 – 39	445	56.4
Ethnicity			
	Non-Malay[b]	11	1.4
	Malay	778	98.6
Locality			
	Urban	60	7.6
	Rural	729	92.4
Parity		3.06 (1.80)[a]	
	Less than 5	633	80.2
	5 and more	156	19.8
Contraception used			
	None	511	64.8
	Hormonal	244	30.9
	Non-Hormonal	34	4.3
Menopausal status			
	Not menopause	779	98.7
	Menopause	10	1.3
Duration of last childbirth		3.00 (6.30)[c]	
	<6 months	162	20.5
	6-12 months	142	18.0
	>12 months	485	61.5

[a]Mean (SD),
[b]Chinese, Iban, Kadazan, Siamese,
[c]Median (IQR)

Factors associated with HPV infection in Kelantan

According to univariable analysis (Table II), variables with a p-value of <0.25 were age, number of parities, contraception used, menopausal status and duration of childbirth. There were three factors, namely age (p=0.013), number of parities (p=0.001) and hormonal contraception used (p<0.001), that were significantly associated with HPV infection.

The binary multivariable analysis identified three variables significantly associated with HPV infection (Table III). Women in the age group of 30 –39 years old were associated with a higher risk of HPV infection (AdjOR=2.09, 95% CI 1.16, 3.78) after being adjusted for number of parities and contraception used. Women who had five or more parities were 2.82 times more likely to have an HPV infection than those who had children less than five, adjusted for age and contraception used (AdjOR=2.82, 95% CI 1.58, 5.06). Additionally, women who used hormonal contraception had 7.48 times the risk of having HPV infection compared to those who did not use contraception (AdjOR=7.48, 95% CI 4.07, 13.76) after adjusting for age and number of parities.

Table II: Simple logistic regression for factors associated with presence of HPV infection among women attending new cervical cancer screening in Kelantan (n=789)

Variables	HPV Positives (n=66)		HPV negatives (n= 723)		Crude OR (95% CI)	Wald statistic (df)	*p*-value
	n	%	n	%			
Age (year)		37.86 (4.85)[a]		38.91 (5.48)[a]			
40 -49	19	28.8	325	45.0	1		
30 -39	47	71.2	398	55.0	2.02 (1.16, 3.51)	6.22 (1)	0.013
Ethnicity							
Non-Malay[b]	1	1.5	10	1.4	1		
Malay	65	98.5	713	98.6	0.91 (0.12, 7.23)	0.11 (1)	0.930
Locality							
Urban	4	6.1	56	7.7	1		
Rural	62	93.9	667	92.3	1.30 (0.46, 3.71)	0.24 (1)	0.622
Parity		3.58 (1.75)[a]		3.02 (1.80)[a]			
Less than 5	42	63.6	591	81.7	1		
5 and more	24	36.4	132	18.3	2.56 (1.50, 4.37)	11.81 (1)	0.001
Contraception used							
None	16	24.2	495	68.5	1		
Hormonal method	47	71.2	197	27.2	7.38 (4.09, 13.33)	43.97 (1)	<0.001
Non-hormonal method	3	4.5	31	4.3	2.99 (0.83, 10.83)	2.80 (1)	0.095
Menopausal status							
Not menopause	64	97.0	715	98.9	1		
Menopause	2	3.0	8	1.1	2.79 (0.58, 13.43)	1.64 (1)	0.200
Duration of last childbirth (months)		4.00 (7.30)[c]		3.00 (6.30)[c]			
<6 months	9	9 13.6	153	21.2	1		
6 – 12 months	13	19.7	129	17.8	1.71 (0.71, 4.14)	1.43 (1)	0.231
>12 months	44	66.7	441	61.9	1.70 (0.81, 3.56)	1.96 (1)	0.162

[a]Mean(SD)
[b]Chinese, Iban, Kadazan, Siamese
[c]Median(IQR)

Table III: Multiple logistic regression of factors associated with presence of HPV infection among women attending the new cervical screening in Kelantan, 2019 (n=789)

Variables	Adjusted regression coefficient (b)	Adjusted OR (95% CI)	Wald statistic (df)	*p*-value
Age (year)				
40 -49	0	1		
30 -39	0.74	2.09 (1.16, 3.78)	6.00 (1)	0.014
Parity				
Less than 5	0	1		
5 and more	1.04	2.82 (1.58, 5.06)	12.25 (1)	<0.001
Contraception used				
None	0	1		
Hormonal method	2.01	7.48 (4.07, 13.76)	41.87 (1)	<0.001
Non-hormonal method	1.14	3.11 (0.83, 11.60)	2.55 (1)	0.091

Forward LR Multiple Logistic Regression was applied.
Multicollinearity and important interaction terms were checked and not found.
Model is fit with Hosmer-Lemeshow test p=0.894, classification table=91.6% and area under ROC curve=79.2%

On the other hand, women who used non-hormonal contraception such as IUDs were not shown to be statistically significant in our study (p=0.091). Other factors, such as menopausal status and duration of childbirth, did not have a significant association with HPV infection.

DISCUSSION

HPV infection can be considered as precursor for developing cervical cancer. The worldwide prevalence of HPV infection among women ranged from 5.4% to 46.7% (5,19,20). Present study showed that the overall prevalence of HPV infection among women aged 30 to 49 years attending new cervical cancer screening in Kelantan was 8.4% (95% CI 6.4%, 10.3%). This magnitude is consistent with other research conducted in Malaysia which reported prevalence of 7.2% and 9.6%, respectively. The consistency between these studies might be due to a similar platform for detecting HPV infection, which used target amplification (PCR technique) to detect HPV DNA (21,22). However, comparing to similar studies in Malaysia, our findings had lower prevalence due to disparity in study population

which involved broader range of age and either hospital-based or population -based. Besides, women who attended hospital mostly having gynaecological problems, thus the prevalence of HPV among them would be higher (16).

Since PCR technique in current study only amplify and perform genotyping for HPV 16 and 18, thus, only these two genotypes are discussed. Identifying the type is critical because the risk of progression varies greatly by HPV type. HPV types 16/18 have higher likelihood to be more persistent infection after two years and above and this condition lead to higher risk for developing high-grade of CIN (11). Therefore, the presence of these two genotypes, either single or combined, was already adequate to risk stratify for further necessary procedures or therapeutic measures. Early identification of these genotypes is also vital since there is an available treatment for preinvasive lesions with a good prognosis with 100% of five-year survival rate (23). Besides, HPV types 16 and 18 are the most prevalent high-risk types and frequently associated with high-grade CIN lesions (9,21,22,23). We noted a similar finding in our study, which showed that the prevalence of HPV type 16/18 among women attending new cervical cancer screening in Kelantan was measured at 4.8% (95% CI 3.3%, 6.3%), while the prevalence of HPV type non 16/18 was slightly lower at 3.5% (95% CI 2.2%, 4.8%). The prevalence of HPV type 16/18 measured in this study was somewhat higher when compared to the worldwide prevalence of HPV type 16/18, which ranges from 2.5% to 4.4% (5).
Regarding the factors associated with HPV infection, age groups were the only significant sociodemographic factors whereas parity and hormonal contraception used were the reproductive factors that had significant association with HPV infection. Age-related HPV infection observed in the study mainly affected women aged between 30 and 39 years, reflecting about 71.2%. Similar findings also reported in previous evidence (24,25). Furthermore, mean age of current study is corresponded to the optimal age group for the effective cervical cancer screening intervention. However, global trend demonstrated age-specific prevalence was seen among <25 years old and declined with increasing age (5). Meanwhile, a study conducted by Li et al (26) showed that age-specific prevalence has a "two peaks" pattern whereby the first peak occurs among the age group of 15 to 24 years and the second peak occurred among the age group of 35 to 39 years. However, since our study did not include women less than 30 years old, we could not establish the other peak in the younger age group. Even though our finding somewhat different from global pattern, this reflects the most at-risk age groups that need to be consider when planning for screening strategies.

Besides, current study established women aged 30 to 39 years old have 2.09 times more likely to be infected with HPV as compared to age group 40 to 49 years old. This finding was in line with previous studies, in which suggested HPV infection at that particular age could be related with sexual behaviour (27,28). Nevertheless, we could not establish this relationship, as we did not assess any information regarding sexual behaviour. Even so, marriage and divorce trend can be the proxy for this information. Polygamous marriage reported to have higher risk of HPV infection (27,29). Kelantan was reported to have highest proportion of polygamous marriage which contributed about 79% (30) and has the third-highest divorce cases among spouses less than 39 years old which mainly due to extramarital affairs or issues with polygamous marriage (28). Thus, these conditions, may reflect the risk of women especially in Kelantan for contracting with HPV infection which may be the possible explanation for current findings.

Another factor associated with HPV infection was the number of parity. In present study, the percentage of women having five or more parities was higher (36.4%) among those with HPV positives than those with HPV negatives (18.3%). Similarly, this finding also supported with previous studies (31,32). Furthermore, in multivariable analysis, parity showed a significant association with HPV infection, whereby having five and more parities indicated risk of HPV infection 2.82 times higher compared to those with less than five parities ($p < 0.001$). This finding comparable with another study carried out in Tanzania, which showed that having five or more parities has a 3.2-fold increase in risk for HPV infection compared to less parity (33). Higher parities can be considered as increased number of deliveries and women who had multiple deliveries had 5.4-fold increased risk for HPV infection (9). A possible explanation for this finding is, those with more parities may have higher levels of oestrogen and progesterone and experienced a higher frequency of delivery-related cervical trauma. These led to eversion of the transformation zone into ectocervix, which predisposes one to HPV infection (34,35). Nonetheless, previous studies oppose the above finding by demonstrated none or less parities have higher risk than multiparity for HPV infection (36). However, number of parity still an important information during cervical cancer screening, since increasing number of parities was associated with a higher risk of cervical cancer (37,38).

The role of contraception use in relation to cervical cancer has been extensively studied (39,40). Longer duration used of oral contraception led to 1.90 times increased risk of developing invasive cervical cancer which seen in previous study (41). Even though current study did not relate the duration, we managed to establish an association between the use and non-use of contraception and HPV infection which supported by previous evidence (42,43). Majority of women with HPV infection used hormonal contraception (71.2%), followed by 24.2% of non-contraception users and 4.5% non-hormonal contraception users.

Furthermore, multivariable analysis showed hormonal contraception was significantly associated with HPV infection. Women who used hormonal contraception in the current year have developed 7.48 times higher odds of developing HPV infection (AdjOR=7.48, 95% CI, 4.07, 13.76) compared to women not using any contraception as the reference group. This finding was supported by previous studies (14,40,42-44). A plausible mechanism for this association can be due to the use of hormonal contraception-induced cervical changes called cervical ectopy. The changes occur through the interaction of exogenous hormones with the hormonal receptor present in cervical tissue which can potentially increase the risk of HPV infection (41,45). Besides, contraception users tend to have higher sexual activity, subsequently increase likelihood of HPV transmission and HPV infection (45,46). On the other hand, there is no association between non-hormonal contraception used and HPV infection from current study. Besides, previous study had reported that used of non-hormonal method such as IUD has protective association with HPV infection by producing immune mediators that would clear the infection (47).

However, the present study did not show any significant association between menopausal status (p = 0.200), ethnicity (p=0.930) and locality (p= 0.622). These findings were similar with previous reports (22,48,49). Even though menopausal status reported not significant in current study, menopausal women have higher risk of HPV infection since menstrual flow in non-menopause women play as anti-HPV infection. Furthermore, our study sample for menopause women was relatively small (n=10), thus the finding should be interpreted with caution. Kelantan has a predominantly 98.6% Malay population (15). Thus, this proportion explained the disproportionate distribution among Malay and non-Malay ethnicities in this study. Even though the study findings showed no significant association between locality and HPV infection, we discovered a higher percentage (93.9%) of HPV infection among those living in rural than their urban counterparts. Thus, screening for cervical cancer should still be emphasised among women living in rural areas since they may have a lack of awareness and knowledge of HPV infection and cervical cancer (38,50,57).

This study has some limitations. The use of secondary data led to the absence of other important associations of HPV infection and typical risk factors that have been proven in previous literature, such as sexual behaviour, lifestyle factors and other reproductive factors like age of menarche. Some of the variables were small in number, thus limiting the model estimation. Besides, the population involved in this study was reported to composed majority of Malay ethnic. As such, the findings may not necessarily represent Malaysian population and thus, generalization should be done with caution. Despite the limitations, with a relatively large sample size, this study can be used to represent the status of women's health among the Kelantan population. Therefore, we believe the study findings will be helpful for policymakers in considering future strategies for cervical cancer prevention measures in Malaysia. Nevertheless, future research should emphasise other factors that may have an impact on HPV infection among women, such as socioeconomic status, educational level and sexual behaviour of the women and partners, to enhance the cervical cancer screening program. The proper identification of these factors along with subsequent strategic planning to boost up the screening uptake, will prepare Malaysia to totally eliminate cervical cancer by 2030.

CONCLUSION

Overall prevalence of HPV infection found from this study was 8.4% which was comparable to both international and local prevalence (5.4% to 46.7%). Thus, this showed that screening for cervical cancer through HPV DNA tests provides a potentially beneficial impact in the form of increasing women's participation in early cervical cancer screening. Additionally, the significant factors identified can be useful in reaching the target group for cervical cancer screening and subsequently increasing screening coverage. Moreover, the findings also can help in better plan for future education, increase engagement and improve resource allocation to improve outcomes in cervical cancer prevention.

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