FACTORS ASSOCIATED WITH PRESENCE OF HUMAN PAPILLOMAVIRUS INFECTION AMONG WOMEN ATTENDING NEW CERVICAL CANCER SCREENING PROGRAM IN KELANTAN IN 2019

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by

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LIST OF SYMBOLS

α	Alpha
β	Beta
=	Equal
<	Less than
>	More than
%	Percentage

LIST OF ABBREVIATIONS

AdjOR	Adjusted Odds Ratio
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
Crude OR	Crude Odds Ratio
DNA	Deoxyribonucleic acid
DOSM	Department of Statistics Malaysia
GCO/GLOBOCAN	Global Cancer Observatory
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
IQR	Interquartile Range
IUD	Intrauterine device
MOH	Ministry of Health
ROC	Receiver Operating characteristics
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

FAKTOR YANG BERKAITAN JANGKITAN *HUMAN PAPILLOMAVIRUS* DALAM KALANGAN WANITA YANG MENJALANI PROGRAM SARINGAN KANSER SERVIKS YANG BAHARU PADA TAHUN 2019

ABSTRAK

Latar Belakang: Jangkitan *Human Papillomavirus* (HPV) sememangnya diketahui boleh menyebabkan kanser serviks. Mutakhir ini, Malaysia telah memperkenalkan ujian pengesanan DNA HPV dalam saringan untuk program kanser serviks. Walau bagaimanapun, masih banyak jurang pengetahuan tentang faktor yang berkait dengan jangkitan HPV dalam kalangan wanita yang masih perlu diterokai.

Objektif: Tujuan kajian ini adalah untuk mengkaji prevalens dan faktor yang mempunyai hubungan dengan jangkitan HPV dalam kalangan wanita yang menghadiri program saringan baru kanser serviks di Kelantan pada tahun 2019.

Metodologi: Satu kajian hirisan lintang telah dijalankan antara bulan Januari hingga Mei 2021 menggunakan data sekunder yang diperoleh daripada buku daftar ujian HPV DNA dan borang permohanan makmal HPV DNA. Wanita yang menghadiri program baru saringan kanser serviks yang memenuhi kriteria telah dimasukkan dalam kajian ini. Persampelan rawak mudah telah digunakan di dalam kajian ini. Semua maklumat dikumpul menggunakan proforma dan dianalisis menggunakan IBM SPSS Versi 26. Para peserta telah dikategorikan kepada jangkitan HPV dan bukan jangkitan HPV. Analisis regresi logistik berganda digunakan untuk menentukan hubungkait antara ciri sosiodemografi dan reproduktif dengan jangkitan HPV.

Keputusan: Sejumlah 789 wanita telah dimasukkan dalam kajian ini. Min umur mereka ialah 38.82 (5.44) tahun, manakala median bilangan anak adalah 3.06 (1.80). Prevalens jangkitan HPV dalam kalangan wanita yang hadir program saringan baru kanser serviks ialah 8.4% (95% CI 6.4%, 10.3%). Umur di antara 30 hingga 39 tahun (AdjOR 2.09; 95% CI 1.16, 3.78, p=0.014), mempunyai anak seramai 5 dan ke atas (AdjOR 2.82; 95% CI 1.58, 5.06, p<0.001) dan pengguna kaedah kontraseptif hormon (AdjOR 7.48; 95% CI 4.07, 13.76, p<0.001) mempunyai hubungkait yang signifikan dengan jangkitan HPV.

Kesimpulan: Prevalens keseluruhan bagi jangkitan HPV dalam kalangan wanita yang menghadiri saringan kanser serviks yang baharu adalah pada tahap yang sama dengan kajian yang lain dan peratusan jangkitan HPV jenis berisiko tinggi adalah tinggi dalam kalangan wanita di Kelantan. Faktor sosiodemografi dan reproduktif menunjukkan hubungkait yang signifikan dengan jangkitan HPV. Oleh itu, dengan mengenalpasti faktor tersebut dalam kalangan wanita membolehkan program saringan menjadi lebih fokus dan dapat menjangkau kumpulan sasaran seterusnya dapat mengurangkan beban kanser serviks.

KATA KUNCI: Faktor berkait, *Human Papillomavirus* (HPV), ujian HPV DNA, kanser serviks, wanita Malaysia

FACTORS ASSOCIATED WITH PRESENCE OF HUMAN PAPILLOMAVIRUS INFECTION AMONG WOMEN ATTENDING NEW CERVICAL CANCER SCREENING PROGRAM IN KELANTAN IN 2019

ABSTRACT

Background: Human Papillomavirus (HPV) infection is known to cause cervical cancer worldwide. Recently, Malaysia has introduced HPV DNA detection testing in the cervical cancer screening program. However, many knowledge gaps regarding associated factors for HPV infection among women have yet to be explored.

Objective: This research aimed to study the prevalence and factors associated with HPV infection among women attending new cervical cancer screening in Kelantan in 2019.

Methodology: A cross-sectional study was conducted between January to May 2021 using secondary data extracted from the HPV DNA test registry book and HPV DNA laboratory request form. Women attending the new cervical cancer screening program who fulfilled the study criteria were included in the study. Simple random sampling was applied. All information was collected using proforma and analysed using IBM SPSS Version 26. The attendees were categorized into HPV infection and non-HPV infection. Multiple logistic regression was used to determine the association of sociodemographic and reproductive characteristic with HPV infection.

Results: A total of 789 women were included in the study. Their mean age was 38.82 (SD 5.44) while, the median was 3.06 (IQR 1.80). The prevalence of HPV infection

among women attending the new cervical cancer screening was 8.4% (95% CI 6.4%, 10.3%). Those with age between 30 to 39 years old (AdjOR 2.09; 95% CI 1.16, 3.78, p=0.014), parity 5 and more (AdjOR 2.82; 95% CI 1.58, 5.06, p<0.001) and hormonal contraception method users (AdjOR 7.48; 95% CI 4.07, 13.76, p<0.001) were significantly associated with HPV infection.

Conclusion: Overall prevalence of HPV infection among women attending new cervical cancer screening was comparable other studies and proportion of high risk type of HPV infection was high among the women in Kelantan. Sociodemographic and reproductive factors were both given the significant association with HPV infection. Thus, identifying those factors among women will allows the screening program to be more focused and able to reach the target group, subsequently reducing the risk of cervical cancer.

KEYWORDS: Factor associated, Human Papillomavirus (HPV), HPV DNA test, cervical cancer, Malaysian women.

CHAPTER 1

INTRODUCTION

1.1 Introduction to cervical cancer

Cervical cancer is still a significant public health concern for women. It has been found in 28 nations as the most frequent cancer among women. In a report published in 2018, the Global Cancer Observatory [GCO (formerly known as GLOBOCAN)] ranked cervical disease as the fourth most frequent cancer in terms of both incidence and mortality, with an estimated 570,000 new cases and 310,000 deaths worldwide (Bray *et al.*, 2018). Recently, the International Agency for Research on Cancer (IARC) presented the most recent update on global cancer burden new estimates indicating cancer cases have increased to 19.3 million and 10 million deaths in 2020. The incidence of cervical cancer has also increased, accounting for approximately 604,127 cases, or 6.5% of cancer incidence in females (IARC, 2020).

Cancer incidences and mortality rates were higher in the low Human Development Index (HDI) countries than in the high HDI countries, as illustrated in Figure 1.1. In Malaysia, cervical cancer is the third most common malignancy among women. According to the data from The Global Cancer Observatory, the incidence of cervical cancer in Malaysia accounted for approximately 7.2% of new cases of total cancer in 2018 (IARC, 2018). The age-standardised incidence rate has increased from 6.2 per 100,000 over five years as reported in Malaysia National Cancer Registry Report (2012-2016) (National Cancer Institute, 2019) to 10.5 per 100,000 population and responsible for an estimated 944 deaths in 2018 (Bruni *et al.*, 2019b).

Furthermore, with an estimate of 4,696 cervical cancer cases per year and 1,372 cases of precancerous lesions, the government spent about RM 39.2 million in direct cost and another RM12.4 million in indirect cost due to loss in productivity (Aljunid *et al.*, 2010).

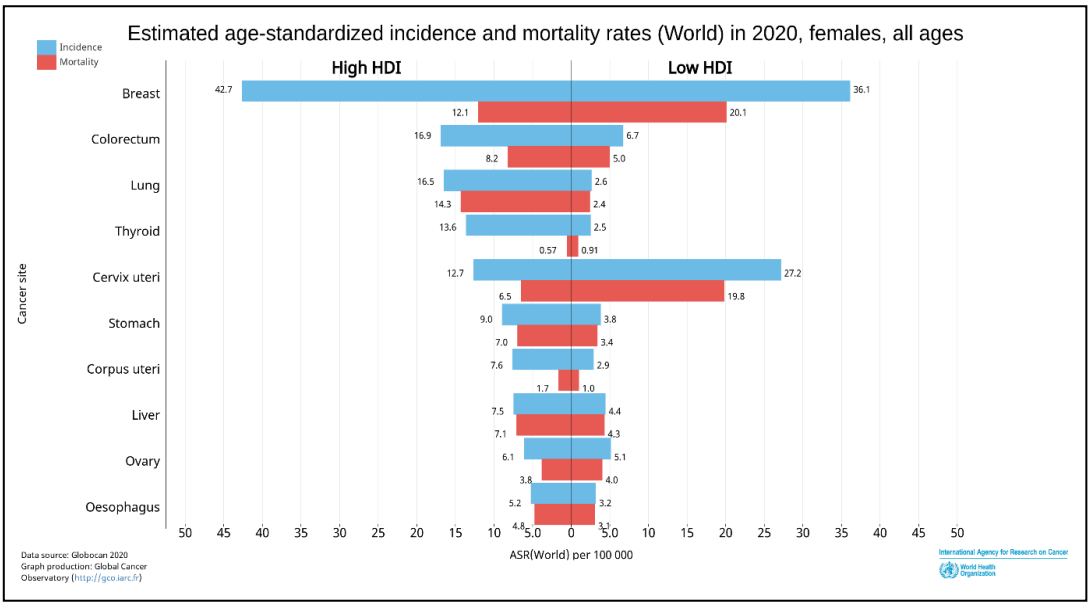

Figure 1.1 Ten most common cancers affecting women worldwide (*Source*: IARC, 2020)

The World Health Organization (WHO) stated that cervical cancer is potentially preventable (WHO, 2014). By understanding the natural history of the disease, multiple strategies can be implemented to prevent the disease and ultimately help to reduce the occurrence of cervical cancer. Cervical cancer prevention can be divided into three stages, i.e., primary, secondary, and tertiary, as shown in Figure 1.2. The goal of primary prevention is to prevent the formation of a precancerous lesion. Healthy living and well-being programmes, boosting public awareness of cancer through safe sex education, and Human Papillomavirus (HPV) vaccination are among the recommended activities. Secondary prevention is concerned with preventing precancerous lesion from progressing to cancerous lesions. It refers to early disease identification and treatment of precancerous lesions at this stage.

The approach emphasised screening cervical cancer among high-risk populations on a regular basis. In addition, surgical procedures such as loop electrosurgical excision procedure (LEEP), cryotherapy, and cold knife conization were carried out. Tertiary prevention strategies, primarily target women who have already been diagnosed with cervical cancer. The goal is to improve one's quality of life by minimising impairment, limiting or postponing complications, and restoring function.

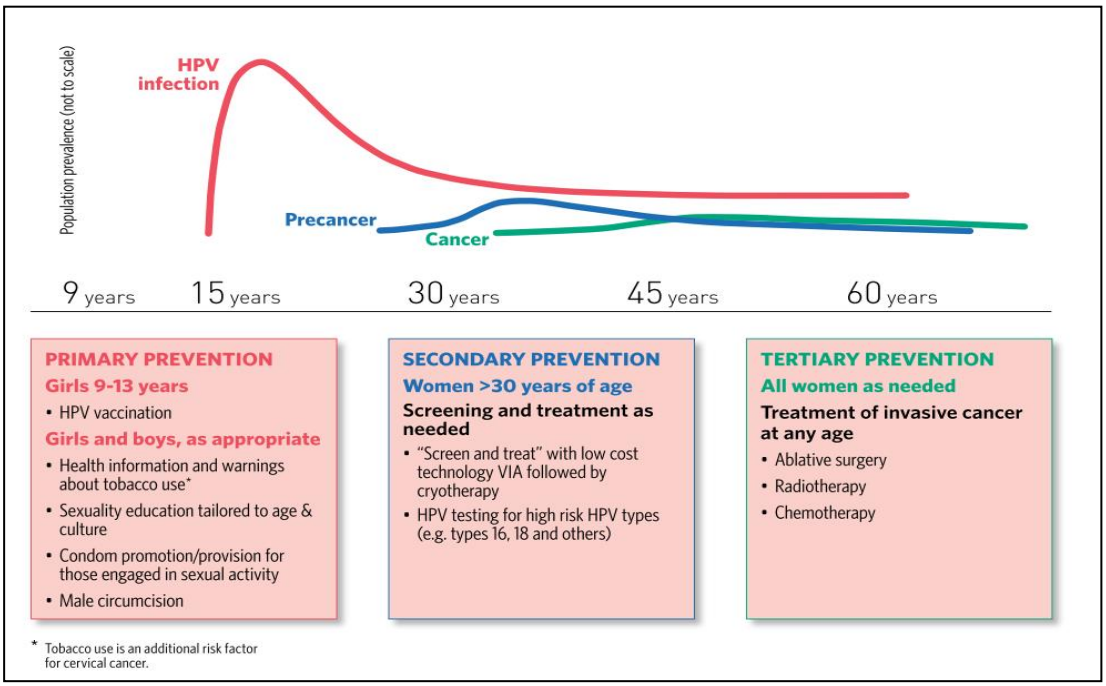

Figure 1.2 Intervention over the life course for cervical cancer prevention (*Source*: WHO, 2013)

For the cost-effectiveness of all preventive interventions, vaccination against HPV plus early diagnosis and treatment of precancerous lesions were considered to be the most cost-effective options (Ralaidovy *et al.*, 2018). However, many middle- and lower-income countries are unable to reap the benefits of vaccination because the financial expenses of both the vaccine and the operational expenses of delivery are prohibitively expensive (WHO, 2013). As a result, screening is the most extensively used strategy for prevention.

1.2 Cervical cancer screening

Research suggests that pairing effective screening with the treatment of precancerous lesions together with a high level of engagement from women at risk can decrease the incidence and mortality of cervical cancer by more than 70% (WHO, 2014). Screening is incorporated as secondary prevention in a public health intervention, which is offered to an asymptomatic person and relies solely on the targeted population. It is not aimed for disease diagnosis but rather for identifying individuals who are more susceptible to develop the disease or having a precursor to the disease (WHO, 2014).

Cervical cancer screening program aims to screen a large proportion of sexually active women to ensure early detection and appropriate management can be done for positive or abnormal result findings. A prior study by Saslow *et al.* (2002) concluded that women with preinvasive lesions have a close to 100% five-year survival rate. This suggests that the precancerous stage of the cervical lesion is completely curable when accompanied by adequate therapy and regular follow-up. Furthermore, the diagnosis and treatment of precancerous lesions and early-stage cervical cancer are more affordable. On the other hand, advanced cervical cancer is hard to treat and frequently requires palliative care to help patients cope at this point (WHO, 2014).

Historically, the Papanicolaou test, which was invented by George Nicholas Papanicolaou, has been the cornerstone of cervical cancer screening. Since 1940s, the test has been used worldwide since it is inexpensive, simple to do, and may detect morphological changes in the cervical epithelium (Tan & Tatsumura, 2015). This procedure, or commonly known as the Pap smear or pap test, is considered the gold standard for cervical cancer screening.

There are two main approaches in providing Pap smear test to the communities: opportunistic or organized population-based, which varies across countries (Nygård, 2011). Under the opportunistic approach, the test is administered to women who demand it or attend a healthcare facility for other reasons. Meanwhile, in the organized programme, eligible women are identified, followed, and invited to the screening test on a regular basis. A well-organized population-based cervical cancer screening appears to be a more effective screening uptake method than opportunistic screening (Paulauskiene *et al.*, 2019).

Cervical cancer screening evolution in Malaysia started in 1969 using Pap smear as a cytology examination. Initially, it served as part of a family services package through the Maternal and Child Health Services in health clinics under the Ministry of Health (MOH). Decades later, "The National Pap Smear Screening Programme" was established in 1998 with the aim for early detection, ensuring prompt treatment, as well as subsequent follow-up following a positive result (MOH 2019a). This test was provided at government health clinics and hospitals at no charge. Furthermore, this program also extended to other facilities, including the National Population and Family Development Board (NPFDB), university hospitals, private hospitals and clinics, health facilities of the Ministry of Defence and non-governmental organizations (NGOs) (MOH, 2004, p. 2).

According to the current national policy, the Pap smear screening programme targets women between the ages of 30 and 65 who are sexually active and is repeated every three years (MOH, 2019a). This is also consistent with the WHO's recommendation to begin screening at age 30 years old. This is because cervical cancer develops slowly, taking 10 to 20 years from early precancerous lesion to invasive cancer (Holowaty *et al.*, 1999). As a consequence, cervical cancer is rarely

developed before 30 years old. MOH incorporate this test as an opportunistic screening tool, with any women who visit health facilities that were offered Pap smear to be conducted.

There are two techniques of cytology examination. Initially, a conventional Pap smear was used as a screening method. In this method, the sample from the cervical scrape is obtained using a cervical brush and smeared directly onto a glass slide. Following that, it is immediately fixed with 95% alcohol and stained for microscopic examination with the Papanicolaou method. Later, in 2014, liquid-based cytology (LBC) was introduced as an alternative approach to cervical cell preparation to address the drawbacks of the traditional Pap test (MOH, 2019a). The Pap smear can be conducted by doctors and nurses who have undergone training to handle the smears. Pap smear results are often interpreted by a pathologist, medical laboratory technologist, or other trained personnel.

The Bethesda Reporting System 2014 is used to report the results. The report includes information on the type of specimen used, whether it was a conventional smear or a liquid-based preparation, in terms of the adequacy of the sample for evaluation, whether it was satisfactory or unsatisfactory, and finally, the findings of the sample. Findings are interpreted as either negative for intraepithelial lesion or malignancy (NILM) or positive for epithelial cell abnormalities, which include squamous cell lesions, glandular cell lesions, and other malignant neoplasms (Nayar & Wilbur, 2015). If epithelial cell abnormalities are found, the procedure is repeated, or a colposcopy will be performed, or a referral to a gynaecological oncologist will be made for further assessment and treatment. The Pap smear screening interval should not be more than three years.

Primary cervical screening by cytology examination through Pap smear is considered the most effective method of cancer detection to date. However, sample collection and laboratory errors restricted the screening and interpretation of the test. Since it was an opportunistic screening, the coverage was less than organized screening. The introduction of HPV DNA testing can overcome the limitation of pap smear screening. Testing for HPV DNA is now recommended for the majority of women due to a high level of evidence demonstrating that screening for carcinogenic HPV DNA is far more sensitive to detect precursor lesions than cytological examination (Bulk *et al.*, 2007; Sankaranarayanan *et al.*, 2009; Ronco *et al.*, 2010). Another recent overview of pooled data has been undertaken by Ronco *et al.* (2014) which conclude that HPV-based screening offers 60% to 70% more protection against invasive carcinomas compared to cytology. Establishing HPV infection status and identifying the genotype in clinical samples are important prognostic indicators in screening women and managing those who have been identified as having a higher risk of cervical cancer.

Malaysia began incorporating HPV DNA test by phases, starting in July 2019. Phase 1 involved four states; Wilayah Persekutuan Kuala Lumpur and Putrajaya, Kedah and Kelantan, and was extended to other states in 2020. The target age group for HPV DNA test is women aged 30 to 49 years old. Those aged between 20 to 29 years old and 50 to 65 are still recommended for Pap smear testing and HPV DNA testing in younger women is not recommended. This may subject them to unnecessary procedures and treatment, as infection in women before the age of 30 years will be transient and spontaneously resolved (Demarco *et al.*, 2020; Ferris *et al.*, 2020).

The HPV DNA test is believed to be beneficial in three clinical settings; 1) triage women with indeterminate or low-grade cytological abnormalities, 2) following treatment of precancerous or cancerous lesions, and 3) primary screening in selected age groups (MOH, 2019b).

1.3 Problem statement

Although pap smear screening test and program were launched in Malaysia four decades ago, cervical cancer continues to be a major public health concern. It is still one of the common cancers and cause of mortality among women. Late presentation and low uptake of pap smear reflect the ineffective of the prevention programs. Recent data showed, only 23.5% to 24.2% women did the Pap smear in 2014 to 2018 (Shazimah, 2019). This also supported by findings from the National Health Morbidity Surveys (NHMS) 2019: Volume 1 found that approximately 63.4% of women aged 20 and above did not undergo pap smear for the last three years (Institute for Public Health (IPH) *et al.*, 2020). Earlier studies have shown factors such as fear and embarrassment were among the known reasons for low uptake of pap smear (Al-Naggar, 2012; Liebermann *et al.*, 2018; Tung *et al.*, 2019).

WHO has released global strategies in eliminating cervical cancer and aimed for achieving screening coverage of 70% by 2030 (WHO, 2020). Additionally, prior studies showed that HPV DNA testing provides an alternative approach in scaled-up cervical cancer screening coverage since it can be self-tested and increased the acceptability among women (Wong *et al.*, 2016; Wong *et al*., 2020). Evidence also showed that 88.7% of invasive cervical cancer in Malaysia is attributed to high-risk genotypes of HPV infection (Bruni *et al.*, 2019b). Hence, MOH has pioneered four states for HPV DNA testing as new cervical screening in 2019 including Kelantan.

To date, research related to cervical cancer prevention in Malaysia mainly focused on HPV vaccination and pap smear screening (Zaridah, 2014). Nevertheless, data and published studies regarding HPV infection among community-based are still scarce. In addition, information on the prevalence of HPV infection and its associated factors among healthy women in Kelantan is still limited.

1.4 Rationale of study

Cervical cancer can be prevented if detected early and treated promptly. As a result, to reduce disease the disease burden and incidence, a comprehensive and efficient screening program is vital. Even though we already have established screening modalities, namely Pap smear test, it has few shortcomings. The most important aspect is that this screening programme is still unable to achieve adequate coverage among targeted populations. Therefore, studies and research have been conducted globally in recent years to develop new tests with greater sensitivity and specificity to detect potential cervical cancer precursors, which include HPV DNA testing.

There was a high level of evidence that showed HPV DNA testing could decrease the cases and death related to invasive cervical cancer (Sankaranarayanan *et al.,* 2009; Ronco *et al.,* 2010). Furthermore, several randomised control studies concluded that HPV DNA test was superior to Pap smear as the sensitivity of HPV DNA testing for cervical intraepithelial neoplasia (CIN) of grade 2 and 3 was 94.6% (95% CI, 84.2% to 100%), compared to Pap smear, which only had a sensitivity of 55.4% (95% CI.33.6% to 77.2%) (Mayrand *et al.*, 2007; Mustafa *et al.,* 2016). Besides, negative HPV DNA testing may warrant the women less likely to develop preinvasive lesion particularly CIN3 within few years (Jentschke *et al.*, 2012).

Despite a bit pricey, incorporating HPV DNA test still considered a cost-effective option as cervical cancer screening for women above 30 years old as

evidenced by previous studies since the interval between screening can be extended approximately 5 to 10 years or in certain condition, perhaps once is enough (Cuzick *et al.*, 2008; MOH, 2011; Jin *et al.*, 2016). Numerous reports also have demonstrated that HPV infection is crucial for cervical cancer development. Thus, this study can ascertain those at higher risk of developing cervical cancer by detecting HPV infection-related characteristics in women. Furthermore, there is still limited research on HPV infection in Malaysia. Since the implementation of HPV DNA testing as a screening programme remains new, this study could provide information on future planning strategies to focus specifically on the target group and give recommendation on screening interval thereby increasing the impact of the screening and, ultimately, reducing the disease's implications. This study also can also identify the burden of HPV infection among women in Kelantan. Moreover, the information and database on HPV infection derived from the study's findings can be used as a starting point by stakeholders to help reduce the number of cases of cervical cancer in Kelantan and throughout Malaysia.

1.5 Research Questions

1. What is the prevalence of HPV infection among women in Kelantan in 2019?
2. Are there any associations between sociodemographic and reproductive characteristics with HPV infection among women in Kelantan in 2019?

1.6 Objectives

1.6.1 General Objective

To study the prevalence and factors associated with HPV infection among women in Kelantan.

1.6.2 Specific Objectives

1. To determine the prevalence of HPV infection among women attending a new cervical cancer screening program in Kelantan in 2019.
2. To determine the association between sociodemographic and reproductive characteristics with HPV infection among women attending a new cervical cancer screening program in Kelantan in 2019.

1.7 Research Hypothesis

There are associations between sociodemographic and reproductive characteristics with HPV infection among women attending a new cervical cancer screening programme in Kelantan in 2019.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology of HPV infection and cervical cancer

HPV is a virus with small, double-stranded DNA that infect the epithelium. It has over 100 genotypes that are distinguished based on the genetic sequence of the outer capsid protein L1. There are 40 genotypes capable of infecting the epithelium, which are further classified into low-risk and high-risk types. Low-risk infection or non-oncogenic types, such as types 6 and 11, can cause benign or low-grade cervical cell abnormalities, genital warts and laryngeal papilloma. In contrast, high-risk kinds are carcinogenic (including types 16 and 18), resulting in cervical cancer and other anogenital cancers (Center for Disease Control and Prevention (CDC), 2015). According to previous studies, HPV is a well-established significant factor that can cause cervical cancer (IARC, 1995). Furthermore, the most virulent kinds, HPV types 16 and 18, are accounted for 70% of all invasive cervical cancers globally (Clifford *et al.*, 2006).

HPV is typically acquired through sexual activity and is one of the most common sexually transmitted infections worldwide. The vast majority of sexually active women and men may contract HPV at some point in their lives, and some may be infected more than once. The peak time for both men and women acquiring infection is shortly after started sexual debut (Bahmanyar *et al.*, 2012). Nevertheless, most of these infections will be transient, with no clinical effects, and 90% of HPV infections will be cleaned up within two years (Rodriguez *et al.*, 2008). However, the possibility of acquiring precancerous conditions is substantial in certain women

whose infections persisted. The precancerous lesion may develop, presumably due to the persistence of infection. If the lesion is not discovered and treated, it may develop into carcinoma in-situ, with a considerable proportion of invasiveness (McCredie *et al.*, 2008). It was estimated that, women with persistent HPV infection can progress to risk CIN3 by almost 50% (Kjaer *et al.*, 2010). However, precursor lesions typically progress into cervical cancer over 15 to 20 years, hence, serves as advantage for screening test.

2.2 HPV genotypes distribution worldwide and Malaysia

Globally, the prevalence of cervical HPV type 16 and/or HPV type 18 infections among women is classified into four types of laboratory outcomes as shown in Table 2.1 (Bruni *et al.*, 2019a). Starting with normal cytology women, the prevalence is approximately 3.9%. Nevertheless, the prevalence of HPV infection increases as the severity of the cervical cell lesion increases; for example, in the low-grade cervical lesion (among the Low Squamous Intraepithelial Lesion (LSIL)/ CIN 1), the prevalence is 25.8%, while in the high-grade cervical lesion (such as High SIL/CIN 2/CIN 3/Carcinoma In-Situ), the prevalence is 51.9% and among women with cervical cancer, the prevalence is 69.4%. The burden of cervical HPV infection was roughly equal between less developed and more developed regions.

Table 2.1 Prevalence of cervical HPV infection 2019

Burden on cervical HPV infection according to cytology type	World	Less developed region	More developed region
Normal Cytology	3.9	3.8	3.8
Low-grade cervical lesions	25.8	25.1	25.9
High-grade cervical lesions	51.9	46.7	54.1
Cervical cancer	69.4	69.5	71.8

Note. From Human Papillomavirus and Related Disease in World Report, by Bruni *et al.* (2019a). Copyright 2019 by HPV Information Centre

There is an absence of national HPV prevalence data in Malaysia, and no study was carried out due to unavailable data in the healthcare system. However, a few individual studies on HPV prevalence were conducted in some Malaysian states, as shown in Table 2.2. In general, HPV infection accounts for about 92% of cervical cancer incidence in Malaysia, and it is caused by oncogenic types of HPV as well as the most common types, which are types 16 and 18. These findings demonstrated the rationale behind HPV vaccination in Malaysia. In various Malaysian states, the prevalence of HPV infection among healthy women ranged from 7.2% to 46.7%. These findings were comparable to those of the systematic reviews and meta-analysis conducted by ICO/IARC Information Centre on HPV, showing the HPV prevalence was estimated as 11.7% (95% CI: 11.6-11.7) worldwide. However, the prevalence was different and varied among regions. Higher rates of prevalence were observed in Nigeria (37%), Australia (38.7%), United States (26.8%) and China (17.7%) (Akarolo-Anthony *et al.*, 2014; Baloch *et al.*, 2015; Dunne *et al.*, 2007; Tabrizi *et al.*, 2014), while South-East Asia had lower rates; Thailand (15.2%), Vietnam (9.7%) and Singapore (9.3%) (Kantathavorn *et al.*, 2015; Tay & Onn, 2014; Tran *et al.*, 2015). The variation in the prevalence most likely due to age of target populations, frequency of screening and rates of follow-up women with abnormal lesions (Ting *et al.*, 2010; Siriaunkgul *et al.*, 2014).

Table 2.2 Prevalence and HPV genotypes distribution among general population and cervical cancer cases in Malaysia

Authors	Study locations	Study population	N	Prevalence (%)	HPV types detected
Tay and Tay (2009)	Johor and Singapore	Healthy women	2364	25.6%	Not genotyped
Chong *et al.* (2010)	Selangor	Healthy women	180	46.7%	16, 18, 31, 33, 58, 87
Noradiyah and Nor Hayati, (2014)	Kelantan and Terengganu	General population	635	4.4%	16, 18, 33, 58, 61, 6
Latiffah *et al.* (2016)	Negeri Sembilan	Healthy women	226	18.1%	16, 18, 31, 33, 45, 11
Nur Ezzah *et al.* (2018)	Sabah	General population	240	10.0%	16, 33, 56, 58, 59, 53, 66, 70, 82, 61, 81, 62, 84
Khoo *et al.* (2018)	Selangor	Healthy women	1190	7.2%	16, 18, 52, 58, 31, 45, 6, 11
Sharifa Ezat WP *et al.* (2010)	Selangor	Preinvasive and invasive cervical cancer cases	80	92.6%	16, 18, 31, 33, 35, 39, 45, 52, 58, 59, 6, 11
Raub *et al.* (2014)	Selangor, Kuala Lumpur, Pahang, Kedah, Kota Bharu	Cervical cancer cases	280	92.5%	16, 18, 58, 52, 33, 45, 39, 56, 59, 51, 35, 31

2.3 Factors associated with HPV infection

Numerous studies have discovered factors associated with HPV infection acquisition correlated with sexual behaviour and lifestyle. Yet, little is known about other factors such as sociodemographic and reproductive characteristics of the women that also have an essential role in the association with HPV infection.

2.3.1 Sociodemographic characteristics

In addition to sexual activity, age is the most consistent predictor of HPV infection. A study conducted in Hong Kong by Chan *et al.* (2010) showed that HPV infection demonstrates a bimodal age distribution with a U-shaped peak. The initial surge occurred in young women between the ages of 26 to 30 years, with a prevalence of 12.4%, and the next peak appeared among older women aged 46 to 50 years with a prevalence of 5.8%. In another study, the aged group of 31 to 40 years old had the highest proportion, approximately 61.3%, compared to other age groups (Chong *et al.*, 2010) . Several other studies have found a declining trend of HPV infection with increasing age (Tabrizi *et al.*, 2014; Tay & Onn, 2014; Kantathavorn *et al.*, 2015).

Since HPV infection is acquired by sexual activity, a study by Clifford (2005) (cited in Chong *et al.*, 2010) found the highest incidence was reported in the younger age range because this is the most sexually active phase. However, these findings were contradicted by a study by Zhang *et al.* (2013) conducted in China involving 10,000 women, which showed that older women have a higher prevalence of HPV infection. The justifications for these two distinct patterns are still controversial. However, a meta-analysis among one million normal women suggests that the differences are due to the interplay of sexual behaviour as well as viral characteristics, including HPV type and variants, host susceptibility, and individual screening practices (Bruni *et al.*, 2010; Brotherton *et al.*, 2015).

Impairment of immune response due to hormonal changes after menopause that may lead to reactivation of existing or latent HPV infections is one theory underlying the higher prevalence in older women. Another explanation can be due to a shift in the pattern of the sexual activity between women and their husband as they reach middle age. Among the survey done in previous study, approximately 95% of older women with HPV infection stated that their husband has an extramarital affair (de Sanjosé *et al.*, 2007).

Aside from age, ethnicity also influences the presence of HPV infection. According to Chong *et al.* (2010), the proportion of Malays with HPV infection contributed about 51.6%. Meanwhile, study by Khoo *et al.* (2018) discovered a significant difference between ethnic groups in Selangor, with Indian women having a higher prevalence of HPV infection. Other studies conducted outside of Malaysia found ethnic differences (Silva *et al.*, 2009; Li *et al.*, 2013; Baloch *et al.*, 2017). HPV infection prevalence varies by race and ethnicity due to differences in health risk behaviour, social norms, and cultural characteristics. Women with a strong sense of family and a more traditional culture were less likely to engage in risky behaviour (Lin *et al.*, 2015).

The type of residential area also influenced the acquisition of HPV infection. Numerous studies demonstrate that the prevalence of HPV varies between rural and urban women. According to the findings of a recent study by Baloch *et al.* (2016), among the rural and urban populations in southern Yunnan, China, women from rural areas had a lower prevalence than women from urban populations, with prevalence rates of 13% and 16.3%, respectively. However, this finding contradicts previous research that found rural populations having a higher HPV prevalence than urban populations (Gupta *et al.*, 2009; Schmidt-Grimminger *et al.*, 2011; Lu-lu *et al.*,

2012; Li *et al.*, 2013; Zahnd *et al.*, 2019). Urban and rural populations have varied socioeconomic circumstances, lifestyles, and life standards (Baloch *et al.*, 2016), as well as varying levels of access to information about the risk of HPV infection (Zahnd *et al.*, 2019), which may explain the disparities in HPV infection prevalence.

Marital or relationship status is also associated with the acquisition of HPV infection. Previous research found that widowed or separated women were more likely to contract HPV infection (Sauvaget *et al.*, 2011; Husaiyin *et al.*, 2018; Khoo *et al.*, 2018). Women who have lost a beloved partner are generally in a state of grieving. Grieving following the loss of a loved one was related to a 62% increased chance of HPV infection and a higher viral load as well as recurring infection, as shown by the Swedish National Cervical Screening Register conducted between 1969 to 2011 (Lu *et al.*, 2016). Traumatic life events, such as the loss of a spouse, may increase the host's susceptibility to the persistence or reactivation of oncogenic HPV infection and the risk of developing cervical cancer (Lu *et al.*, 2016).

In contrast, population-based studies in China found that married women had a lower risk of HPV infection than single women. This is because married women tend to be in a monogamous relationship than unmarried women, who are more likely to have several sexual partners and do not practice safe sex (Lu-lu *et al.*, 2012; El-Zein *et al.*, 2019; Ma *et al.*, 2019). Despite being married as a protective factor, it also can possess a higher risk for HPV infection when relating to polygamous marriage. In a study conducted by Shahramian *et al.* (2011) among Muslim in Iran where polygamy is culturally accepted, 37.8% prevalence of HPV infection types 16 and 18 was shown to be higher among polygamous wives since the risk factor for HPV infection also includes multiple lifetime sexual partners.

Socioeconomic status has been linked with various health conditions. The prevalence of health-related behaviour is influenced by an individual's socioeconomic status, which is also recognised as a significant risk factor for death and morbidity (Braveman *et al.*, 2011). A person with a low socioeconomic position and its correlations, such as lower educational and lower economic circumstance, is more likely to get substandard health treatment and poor health outcome. This condition also worsens when the individual could not afford necessary health care and lives in an area with limited access to medical facilities (Rosengren *et al.*, 2019).

Previous research found that women with lower educational level, lower socioeconomic status, and have poorer financial status were at greater risk of HPV infection (Gupta *et al.*, 2009; Sauvaget *et al.*, 2011; Zhang *et al.*, 2013; Tay & Onn, 2014). Silva *et al.* (2009) conducted a study in Brazil comparing the prevalence of HPV infection among women of diverse socioeconomic status and revealed that women with lower socioeconomic status have a greater prevalence of HPV infection. Moreover, individuals with lower socioeconomic position, lower education and fewer earnings were hypothesised to be involved in high-risk sexual behaviour or experienced a delay in accessing medical screening services, hence, increasing their infection rates (Mitchell *et al.*, 2014).

2.3.2 Reproductive characteristics

Reproductive characteristics of a woman also contribute to the risk of HPV infection. One of the related factors is the age at menarche. Local study done in Selangor showed that most of the girls reach menarche the ages of 9 and 15 (Siti-Arffah *et al.*, 2019). However, there was international variability in menarche age, with the overall mean for menarche age globally being 13.53 (SD 0.98) (Thomas *et al.*, 2001). According to earlier research, menarche at an early age gave rise to a higher risk of

HPV infection (Dannecker *et al.*, 2004; Silva *et al.*, 2009). Those young girls are more likely to initiate early sexual intercourse or involved in risky sexual behaviour, which increases the risk of HPV infection (Kahn *et al.*, 2002). This research is further confirmed by systematic review stated a girl's age of menarche influences her sexual behaviour (Ibitoye *et al.*, 2017).

Another critical characteristic related to HPV infection is parity. The number of parity was found to be substantially linked with HPV infection. Previous research has established that increased parity numbers lead to a higher risk of infection (Gupta *et al.*, 2009; Lu-lu *et al.*, 2012; Vinodhini *et al.*, 2012; Jensen *et al.*, 2013; Tay & Onn, 2014; Baloch *et al.*, 2017). Higher hormone levels and impaired immune response have been proposed as plausible causes for the increased risk of infection in multiparous women (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006). Additionally, it has been proven that the transformation zone remains longer on the ectocervix in multiparous women, allowing for direct HPV exposure (Muñoz *et al.*, 2002). Nevertheless, there have been studies that contradict these previous findings (Kasap *et al.*, 2011).

Contraception used plays an essential role in association with the presence of HPV infection. Existing studies have shown that using contraception has a greater risk to get HPV infection (Sangwa-Lugoma *et al.*, 2010; Vinodhini *et al.*, 2012; Shaw *et al.*, 2016). In addition, when compared to non-hormonal methods, using hormonal methods increases the risk of HPV infection by twofold (Porras *et al.*, 2010; Catarino *et al.*, 2016). One potential reason for the association between hormonal contraception and HPV infection is that oestrogen and progestogens may interact with hormone receptors, specifically progesterone receptors located in cervical tissue, affecting the natural history of HPV infection (Roura *et al.*, 2016).

The menopausal status also determines the risk for the acquisition of HPV infection. Several studies found that menopausal women have a higher risk of HPV infection (Lu-lu *et al.*, 2012; Zhang *et al.*, 2013; Bilibio *et al.*, 2019). Sui *et al.* (2016) did study in China among general populations revealed that, menopausal women had 1.83 times higher risk of persistent oncogenic HPV infection compared to non-menopause and 2.41 times increased risk of infection relative to negative HPV. The cause of this connection is unknown, but it could be due to new sexual exposures, latent infection reactivation due to hormone fluctuations, or a combination of the two (Althoff *et al.*, 2009).

Contrary to this finding, a small number of studies have shown that menopause is protective against HPV infection (Lu-lu *et al.*, 2012; Liu *et al.*, 2013; Lyu *et al.*, 2019). Hormonal changes during pregnancy altered the internal environment and suppressed the reproductive tract's immune system. As a result, latent infections that are mostly concealed remain dormant and may eventually cause serious complications (He *et al.*, 2014). The study also concludes that women who have persistent high-risk HPV infection post-delivery are most likely to have abnormal cervical lesion during pregnancy. The higher grade of CIN lesion during pregnancy is most likely has a more prolonged HPV infection. Despite this, the infection with HPV types 16 and 18 can remain for an extended period, generally for more than 12 months. It has also been proposed that the risk of infection after delivery is linked to post-delivery sexual behaviour.

A recent review concludes that sexual behaviour following pregnancy discovered that the average time for resuming intercourse was 6 to 8 weeks postpartum, with the frequency increasing at 3 to 6 months and returning to pre-pregnancy levels at 12 months postpartum (Chen *et al.*, 2019). The risk of infection

increases between 3 and 6 months after pregnancy since this is close to the expected period required for cervix healing after pregnancy (Jawed-Wessel & Sevick, 2017).

2.3.3 Sexual behaviour characteristics

HPV infection is one of the most prevalent sexually transmitted infection worldwide. As a result, both men and women are involved in the transmission chain and can be asymptomatic carriers, spreader, and HPV infection victims. In this regard, the risk factors of HPV infection are linked to an individual's sexual behaviour. These parameters strongly correlate with the age of first sexual encounter, the number of sexual partners in a lifetime, the number of partners of partners and the history of sexually transmitted infection.

A finding from Tran *et al.* (2015) stated that the older age of first sexual interaction has a higher risk. Other studies by Tay and Onn (2014) and Ginindza *et al.* (2017) showed no association in the age of sexual debut with HPV infection. Also, the number of lifetime partners and husband's partners are related to HPV infection. Higher numbers for those factors lead to a higher risk of HPV infection (Kasap *et al.*, 2011; Lu-lu *et al.*, 2012; Tay & Onn, 2014; Husaiyin *et al.*, 2018). A history of sexually transmitted infection (STI) is also a factor to consider. Prior STI history was significantly associated with HPV infection (Silva *et al.*, 2009). It is critical to highlight that infection by other genitalia pathogens raises the risk for HPV infection by suppressing local immunity (Silva *et al.*, 2009). Furthermore, Ginindza *et al.* (2017) discovered that women with HIV are highly associated with HPV infection.

2.4 Conceptual framework

Based on the literature review, several factors were linked with HPV infection, as presented in the conceptual framework. This framework consists of sociodemographic, reproductive, sexual behaviour, and lifestyle characteristics.

The sociodemographic characteristics were age, ethnicity, type of residential area, marital status, educational level, and economic status. Meanwhile, the reproductive factors included age at menarche, number of parities, contraception used, duration of last childbirth and hormonal status.

Age of first sexual encounter, the number of sexual partners in a lifetime, the number of partners of partners and the history of sexually transmitted infection were all factors in sexual behaviour. In addition, smoking status and alcohol intake were included as lifestyle characteristics.

However, our study only included age, ethnicity, type of residential area, number of parities, contraception used, duration of last childbirth and menopausal status. There were limitations to have other factors due to the unavailability of the existing secondary data.

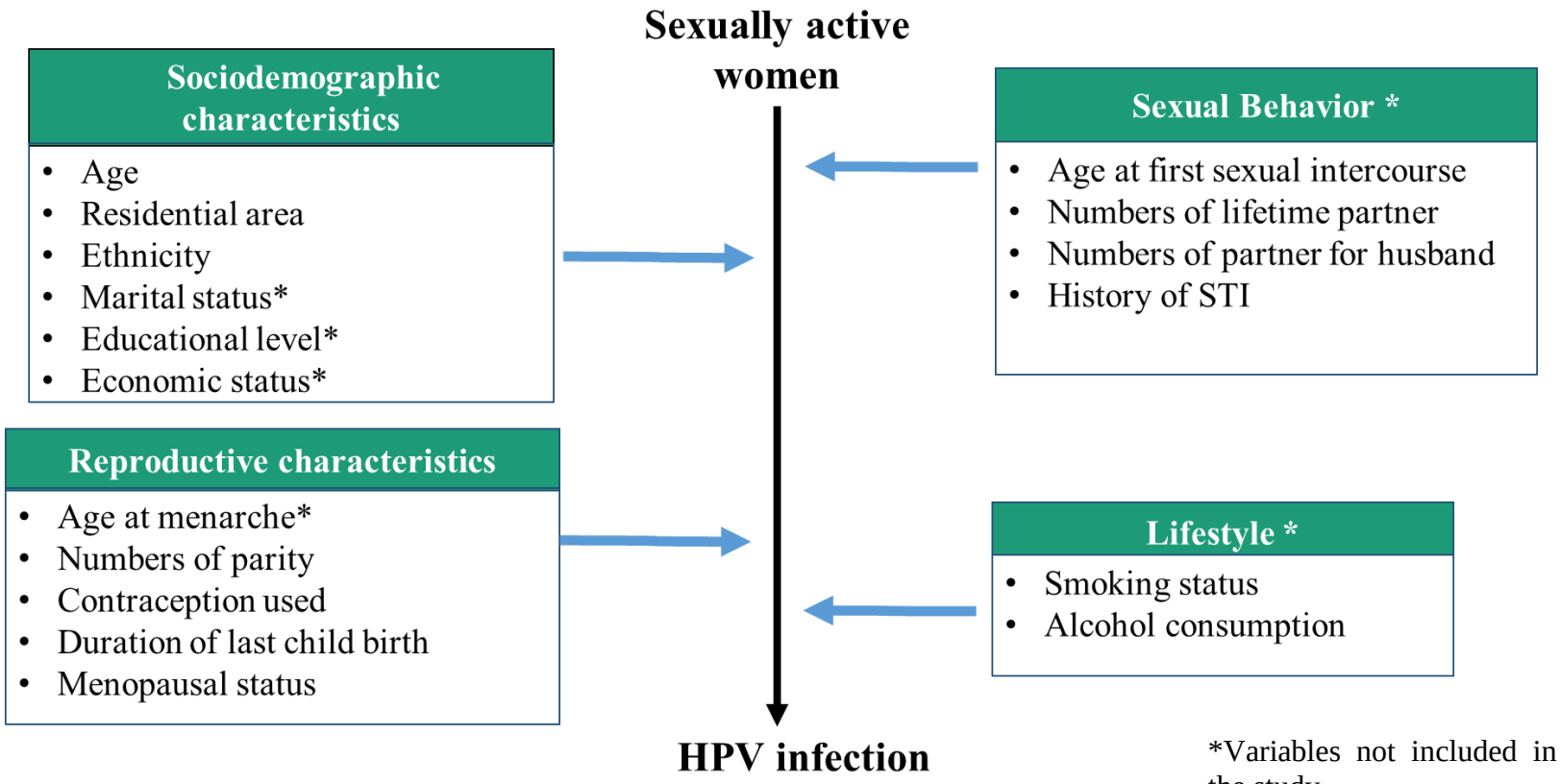

Figure 2.1 Conceptual framework of the study