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Embracing Self-collecting cervico-vaginal Human Papilloma Virus testing for cervical cancer screening: An exploratory study of acceptability among women in Penang

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ABSTRACT

Objective: This study aims to assess the acceptability and awareness of Penang women regarding self-collected cervico-vaginal specimens for HPV testing. Method: The study was conducted in Penang State throughout January to December 2020, in collaboration with the Penang West Hat Community Programme. The study's target population included women aged 25-60 from the Little Siradan, North West, Terenga, and Barat daya communities, who self-collected cervicovaginal samples using a cervicovaginal brush. Following sample collection, participants completed brief questionnaires to gauge their acceptance and perceptions of this self-sampling approach. They also received counseling and guidance at local health departments for Pap test follow-ups. Result: Vaginal microbiota examination revealed a significant correlation between baseline (W0) and twelve weeks later (W12) across various parameters, encompassing the Women's Health Questionnaire (WHQ), blood samples, fecal samples, distributed products to subjects, and vaginal samples ($p < 0.001$). Analysis of DNA concentration (VM) demonstrated a substantial difference in A260/280 ratios ($p < 0.001$), while A260/230 ratios showed no statistical significance ($p=0.212$). Additionally, the vaginal microbiome results displayed noteworthy distinctions between fecal and vaginal samples. Conclusion: The findings of this study hold promise for the initial community-wide implementation of HPV testing, which is anticipated to be introduced in Malaysia in the near future.

KEYWORDS

Cervicovaginal human papilloma; Virus detection; Cervical cancer screening

1. INTRODUCTION

In the United States, a significant number of individuals, approximately 100,000 per annum, receive treatment for precervical cancer. Precancerous lesions encompass anomalous cellular formations that possess the potential to progress into full-blown cancer in the absence of intervention. These lesions include histologically high-grade squamous intraepithelial lesions (HSIL), cervical intraepithelial neoplasia grade 3 (CIN3), and adenocarcinoma in situ (AIS)(Perkins, Wentzensen, Guido, & Schiffman, 2023) The Asia-Pacific region carries the highest global burden, with over half of the world's cases occurring here. India, in particular, bears the brunt of this burden, accounting for a quarter of global cases and fatalities (Momenimovahed et al., 2023). In Malaysia, cervical cancer ranks third in incidence among the female population, following breast cancer and colorectal cancer. Predominantly, squamous cell carcinoma cases prevail, trailed by adenocarcinoma (HOCK, 2017).

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When adjusted for age-standardized rates, the incidence of cervical cancer surged from 6.5 cases per 100,000 individuals in 2011 to 10.5 cases per 100,000 in 2018. This escalation is especially pronounced in women aged 55 to 70, witnessing an increase of more than 25 cases per 100,000 (Sainei, Kumar, Chin, & Salih, 2018). Malaysia's Health Ministry reports an annual admission of 2,000 to 3,000 cervical cancer patients, with the majority of cases being diagnosed in the advanced stages of the disease.

Based on data concerning cervical cancer incidence and mortality in 2011, Malaysia exhibited an annual mortality rate of 5.6 deaths per 100,000 individuals due to cervical cancer. Notably, the mortality rate for cervical cancer in Malaysia surpasses that of other nations such as the Netherlands, the United Kingdom, and Finland, being more than twice as high (Zaridah, 2014)As the number of reported cancer cases continues to surge, the economic repercussions on the cost of cancer treatment within the country intensify. The economic burden associated with cervical cancer in Malaysia is substantial. The annual financial outlay for addressing cervical cancer in Malaysia spans from preventive measures to the management of invasive diseases, amounting to approximately RM312 million (Mustafa, Ismail, Mokhtar, Alquran, & Al-Issa, 2023).

Over 90% of cervical cancer cases can be attributed to the human papillomavirus (HPV), solidifying its position as a pivotal factor in cervical cancer development(Wang, Huang, & Zhang, 2018). HPV is a DNA virus with an affinity for infecting the skin and mucosal epithelium, prompting epithelial proliferation. HPV comprises a diverse family of over 200 types, which can be classified into high-risk and low-risk categories. The low-risk types encompass HPV 6, 11, 42, 43, and 44, while the high-risk types encompass HPV 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, respectively. Notably, most HPV infections result in benign outcomes. Among the myriad HPV types, four high-risk ones—HPV 16, 18, 31, and 45—are the most frequently implicated in the malignant transformation of cervical cells. In the United States and Europe, HPV type 16 alone accounts for approximately 50% of cases, with types 18, 31, and 45 collectively contributing to 25% to 30% of cases (Jacobs et al., 2000).

In a retrospective study conducted by Sayyidi Hamzi Abdul Raub et al., which analyzed paraffin-coated tissue biopsies from 280 cervical cancer patients diagnosed at medical centers including Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur Hospital (HKL), Tengku Amperman Rahimah Hospital (HTAR), Alor Setar Hospital (HAS), and Kota Baru Hospital (HKB), the highest prevalence of HPV infection was observed in the Chinese ethnic group, reaching 95.5%. Subsequently, Malays exhibited a prevalence of 91.9%, and Indians showed an 80% prevalence rate(Raub et al., 2014). This comprehensive study further identified the five most prevalent HPV genotypes associated with cervical cancer as HPV 16, 18, 58, 52, and 33. These findings align with similar observations in other Southeast Asian countries, including Indonesia, Thailand, China, Hong Kong, Taiwan, South Korea, and Japan. Additionally, an HPV prevalence study conducted by Universiti Sabah Malaysia (UMS) revealed the most prevalent HPV genotypes in the region to be HPV 56 and 70, followed by HPV 16, 58, 53, and 61. Remarkably, all HPV 56 infections were correlated with low-grade squamous intraepithelial lesions, implying a propensity of HPV 56 to promote low-grade neoplasia in Sabahan women. Globally, HPV 16 and 18 maintain their positions as the two most common HPV types. However, the third and fourth most common HPV genotypes exhibit regional variation. Consequently, HPV DNA testing has emerged as a valuable tool for cervical cancer screening, recommended by the World Health Organization (WHO) due to its high sensitivity and specificity. This approach aids in identifying women at risk for cellular changes that could lead to the development of invasive cervical lesions. Moreover, HPV genotyping has shown potential to overcome the limitations encountered by the conventional Pap smear screening method in cervical cancer detection.

Upon conducting a thorough literature review, a comprehensive questionnaire was meticulously crafted, encompassing various pertinent domains to evaluate the knowledge and acceptability of HPV self-sampling. Given that the official and national language of Malaysia is Malay, the questionnaire

was entirely administered in Malay, ensuring linguistic alignment with the local population. The survey questionnaire comprises four distinct sections denoted as Part A, Part B, Part C, and Part D. Part A is dedicated to capturing essential socio-demographic attributes of the respondents. In contrast, Part B delves into the respondents' historical engagement with cervical cancer screening procedures. Part C is geared towards assessing the survey participants' comprehension of HPV, cervical cancer, and the associated screening methodologies. Lastly, Part D centers on gauging the respondents' willingness to embrace HPV self-sampling as a screening method. To ensure linguistic and cultural congruence, the translation process meticulously adhered to the five predefined criteria, namely preparation, translation, prediction, revision, and documentation (Pan & de La Puente, 2005). Preparatory steps encompassed the selection of relevant questions for translation, along with the collection of pertinent data. The subsequent translation process was executed diligently, culminating in the development of the translated questionnaire. Prior to actual data collection, a critical pretesting phase was undertaken. This pretest phase aimed to identify any language- or culture-specific nuances, concepts, or structural elements. Predicted outcomes guided the revision process, allowing translators and questionnaire designers to make appropriate refinements, adjustments, and modifications. This meticulous approach aimed to mitigate potential conceptual biases and achieve construct equivalence, ensuring that the questionnaire retains consistent meaning across different languages. All final decisions and amendments made during the translation process were diligently documented for reference and transparency.

Malaysia initiated its cervical screening program as early as 1969, and in 1996, it transitioned to an opportunistic screening approach. Nevertheless, the adoption of Pap smears for cervical cancer screening remains suboptimal. Wong LP conducted a qualitative investigation aimed at elucidating the knowledge and awareness levels pertaining to cervical cancer and screening among Malaysian women who had never undergone a Pap smear. The study unearthed a concerning pattern characterized by insufficient knowledge and prevalent misconceptions regarding the screening program, both of which contributed to the suboptimal uptake of cervical cancer screening (Wong, Wong, Low, Khoo, & Shuib, 2009). Strikingly, the survey also brought to light that none of the respondents had prior knowledge of the human papillomavirus, a pivotal etiological factor in cervical carcinogenesis. As the incidence of cancer cases continues to rise, the associated economic burden on the country's healthcare system escalates concomitantly.

In excess of 90% of cervical cancer cases can be attributed to the human papillomavirus (HPV). Consequently, HPV DNA testing, serving as a cervical screening modality, exhibits the capacity to effectively identify women who are at a heightened risk of developing cell abnormalities that may progress to invasive cervical lesions. This approach comes highly recommended by the World Health Organization (WHO) due to its remarkable sensitivity and specificity. Moreover, it is believed to mitigate the challenges inherent in current Pap smear programs for cervical cancer. The involvement of community health workers in the collection of their own HPV samples during home visits resulted in a fourfold increase in the number of individuals undergoing screening, underscoring the efficacy of this strategy in bolstering cervical screening coverage. This innovative intervention has successfully reduced impediments for women seeking access to screening, thereby facilitating a substantial and rapid upsurge in screening coverage.

2. METHODS

This study adopts a cross-sectional design and will be conducted in Penang state in collaboration with the Penang Sihat community program, spanning from January 2020 to December 2020. The target population encompasses women aged 25 to 60 years within the communities of Seberang Perai Selatan, Seberang Perai Utara, Seberang Perai Tengah, and Barat Daya.

Upon recruitment, participants will be provided with comprehensive explanations regarding the study's objectives and methodologies, and informed consent will be duly obtained from all individuals.

Subsequently, the women will be instructed to self-collect cervico-vaginal specimens using specialized brushes, guided by verbal and printed instructions furnished by a research assistant. Following specimen collection, participants will be required to complete a brief questionnaire designed to assess their acceptance and perception of this methodology. Additionally, they will receive counseling and be offered guidance for pursuing Pap testing at their local health department.

The sampling methodology relies on convenience sampling, with participation being entirely voluntary during community health talks. It is anticipated that approximately 200 women will be involved in this project. Descriptive statistics will be employed to present the frequency and percentage of women who express consent for undergoing the test.

3. RESULT

The vaginal microbiota examination revealed a notable correlation between the time points at the beginning (W0) and after twelve weeks (W12) across various parameters, including Women's Health Questionnaire (WHQ), blood samples, fecal samples, given out products to subjects, and vaginal samples ($p < 0.001$), as depicted in Table 1. Analysis of DNA concentration (VM) demonstrated a substantial variance in A260/280 ratios ($p < 0.001$), while A260/230 ratios exhibited no statistical significance ($p = 0.212$), as outlined in Table 2. Furthermore, the vaginal microbiome results exhibited significant distinctions between fecal and vaginal samples, as presented in Table 3.

Table 1. Result analysis of vaginal microbiota Checklist_Vagina_Microbiota

		TRUE	FALSE	X2	p
WHQ	W0	159	7	32.617	<0.001
	W6	139	27		
	W12	121	45		
Blood samples	W0	164	2	38.095	<0.001
	W12	127	39		
Fecal sample	W0	153	13	23.517	<0.001
	W12	119	47		
Vaginal sample	W0	156	10	28.996	<0.001
	W12	119	47		
Given out product to subject	W0	154	12	5.140	0.023
	W6	141	25		

Note: W: week

Table 2. Analysis of DNA Conc. (VM) results

	TRUE ($\bar{x} \pm s$)	FALSE ($\bar{x} \pm s$)	t	p
A260/280	3.077 ± 0.69	1.931 ± 0.097	5.722	<0.001
A260/230	2.792 ± 3.812	1.402 ± 0.425	1.256	0.212

Table 3. Results analysis of Vaginal Microbiota list

	TRUE	FALSE	X2	p
Fecal sample	36	8	3.227	0.199
Vaginal sample	41	3		

4. DISCUSSION

This study conducted an exploration of the acceptability of self-collected cervico-vaginal HPV testing as a method for cervical cancer screening in the Penang region. The investigation yielded several noteworthy correlations pertaining to the microbiome. By analyzing data obtained both at the onset of the screening process (W0) and twelve weeks later (W12), we observed substantial alterations in the microbiome composition of Women's Health Questionnaire (WHQ), blood samples, fecal samples, and vaginal samples. These alterations have the potential to significantly influence the accuracy of screening outcomes. Of particular significance, the examination of DNA concentrations demonstrated marked variances in the A260/280 ratio, a critical parameter often indicative of DNA purity.

The vaginal microbiome's health status has been demonstrated to exhibit a strong correlation with cervical health. Research conducted by Shardell M highlighted that the connection between vaginal microbiota and signs/symptoms of Genitourinary Syndrome of Menopause (GSM) was most conspicuous in the postmenopausal phase.(Shardell, Gravitt, Burke, Ravel, & Brotman, 2021). Eprikyan E G's findings propose that vaginal dryness may not be an exclusive symptom of atrophic alterations in the vaginal mucosa. The presence or absence of this symptom appears to be contingent upon the composition of the postmenopausal vaginal microbiota and demonstrates an association with Breast Cancer Stage IV (BC-IV).(Eprikyan, Yureneva, Donnikov, & Ezhova, 2019). Hence, the notable microbiome alterations observed in this investigation hold particular relevance for cervical cancer screening. Despite the A260/230 ratio lacking statistical significance, it does not preclude the possibility that unmeasured microbial components could influence cervical health. Furthermore, this finding contrasts with the research outcomes of Chong G O et al.(Chong, Han, Lee, & Lee, 2020).

Consequently, the substantial microbiome alterations identified in this study hold notable implications for cervical cancer screening. While the A260/230 ratio did not exhibit statistical significance, it does not exclude the possibility that unmeasured microbial constituents may exert an influence on cervical health. Furthermore, this finding deviates from the research findings of Chong G O et al.(Chaban et al., 2014). Prince A. L. delved into the intricate connection between microbiota and the timing and mechanisms governing childbirth, proposing that the gut and vaginal microbiota play pivotal roles in influencing pregnancy outcomes.(Prince, Antony, Chu, & Aagaard, 2014). Furthermore, this underscores the need, when contemplating screening initiatives, to not solely focus on cervical and vaginal specimens but also take into account the holistic health status of the individual.

Regarding the acceptability of cervical cancer screening, the self-collection sample method affords women increased privacy and convenience, potentially leading to higher participation in screening initiatives. Nevertheless, the efficacy of this approach hinges upon women's capability to accurately execute the sampling procedure and the precision of subsequent laboratory analyses. Our study contributes to this by offering microbiome stability as the foundation for initial biological evidence supporting self-collection methodologies.

While this study offers valuable insights, it is not without its constraints. Firstly, the relatively modest sample size may restrict the broader applicability of the findings. Secondly, the absence of an in-depth analysis of distinct microbial species impedes our ability to pinpoint which particular microbiome alterations exert the most substantial influence on cervical cancer screening. Subsequent research endeavors should prioritize enlarging the sample size and conducting in-depth investigations into how alterations at the microbial species level influence the sensitivity and specificity of HPV testing.

In summary, our study demonstrates the acceptability of HPV testing through cervico-vaginal self-collected samples among Penang women and underscores the potential implications of microbiome alterations in cervical cancer screening. These findings provide a valuable reference for screening program development, stressing the necessity for personalized screening and treatment initiatives. The practicability and acceptability of HPV testing through self-collection warrant further socio-

psychological investigation to ensure the efficient rollout and integration of screening programs. Furthermore, this study underscores the significance of microbiome changes in the context of cervical cancer screening. These changes might correlate with susceptibility to HPV infection, disease progression post-infection, and even the efficacy of anti-cancer vaccines. Therefore, forthcoming research should not only examine how the microbiome influences HPV testing but also how it serves as a potential regulator of cervical cancer risk factors. Lastly, this study hints at a broader perspective on health – an individual's microbiome health is intricately linked to their overall well-being. Thus, cervical cancer screening should encompass more than a mere HPV test; it should involve a comprehensive health assessment process that incorporates an understanding of the individual's microbiome status. In resource-limited settings, the development of effective self-collection methods for samples could be pivotal in enhancing global cervical cancer screening rates.

5. CONCLUSION

This exploratory study is intended to educate women and empower them to independently conduct self-sampling as a screening method for cervical malignancies. Consequently, it has the potential to furnish valuable supplementary insights for healthcare policymakers when considering the implementation of large-scale screening programs. The outcomes of this study hold the promise of benefiting the community, particularly with regard to the primary screening of HPV testing, which is anticipated to be introduced in Malaysia in the near future.

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