

## RESEARCH ARTICLE

## Assessment of the Reliability of a Novel Self-sampling Device for Performing Cervical Sampling in Malaysia

Latiffah A Latiff<sup>1,3\*</sup>, Sabariah Abdul Rahman<sup>2</sup>, Wong Yong Wee<sup>1</sup>, Sareh Dashti<sup>3</sup>, Andi Anggeriana Andi Asri<sup>1</sup>, Nor Hafeeza Unit<sup>1</sup>, Shirley Foo Siah Li<sup>1</sup>, Ali Jafarzadeh Esfehiani<sup>1</sup>, Salwana Ahmad<sup>1</sup>

### Abstract

**Background:** The participation of women in cervical cancer screening in Malaysia is low. Self-sampling might be able to overcome this problem. The aim of this study was to assess the reliability of self-sampling for cervical smear in our country. **Materials and Methods:** This cross-sectional study was conducted on 258 community dwelling women from urban and rural settings who participated in health campaigns. In order to reduce the sampling bias, half of the study population performed the self-sampling prior to the physician sampling while the other half performed the self-sampling after the physician sampling, randomly. Acquired samples were assessed for cytological changes as well as HPV DNA detection. **Results:** The mean age of the subjects was  $40.4 \pm 11.3$  years. The prevalence of abnormal cervical changes was 2.7%. High risk and low risk HPV genotypes were found in 4.0% and 2.7% of the subjects, respectively. A substantial agreement was observed between self-sampling and the physician obtained sampling in cytological diagnosis ( $k=0.62$ , 95% CI=0.50, 0.74), micro-organism detection ( $k=0.77$ , 95% CI=0.66, 0.88) and detection of hormonal status ( $k=0.75$ , 95% CI=0.65, 0.85) as well as detection of high risk ( $k=0.77$ , 95% CI=0.4, 0.98) and low risk ( $K=0.77$ , 95% CI=0.50, 0.92) HPV. Menopausal state was found to be related with 8.39 times more adequate cell specimens for cytology but 0.13 times less adequate cell specimens for virological assessment. **Conclusions:** This study revealed that self-sampling has a good agreement with physician sampling in detecting HPV genotypes. Self-sampling can serve as a tool in HPV screening while it may be useful in detecting cytological abnormalities in Malaysia.

**Keywords:** Cervical cancer - screening - physician obtained smear - self-sampling - Malaysia

*Asian Pac J Cancer Prev*, 16 (2), 559-564

### Introduction

Invasive cervical cancer (ICC) is the third most common cancer worldwide (Ferlay et al., 2010). Likewise ICC is amongst the common cancers in South East Asia (Ferlay et al., 2010). The age-standardized rate (ASR) of ICC varies from country to country based on their income, health policy and screening coverage (Ferlay et al., 2010). While the ASR was reported to be 20.2 and 19.8 per 100,000 in Vietnam and Thailand respectively, the ASR of 15.7 per 100,000 was reported for Malaysia (Ferlay et al., 2010).

Even in one country the incidence of ICC varies based on the different ethnicities (Ferlay et al., 2010). For instance, the incidence of ICC was reported to be the highest (ASR: 28.8 per 100,000) amongst the Chinese ethnicity while it was less common amongst Indians (ASR: 24.4 per 100,000) and Malay ethnicities (ASR: 10.5 per 100,000). Although a reduction was observed in

the trend of ICC in developed countries, the incidence of ICC remains stable or increased in other low or middle income countries (Domingo et al., 2008a; Ferlay et al., 2010). The reduction in incidence of ICC in developed countries was mainly due to the high coverage of screening tests (Ferlay et al., 2010).

Cervical sampling has long been approved as an accepted screening test for ICC (Fahey et al., 1995; Pan et al., 2011). Cervical sampling coverage varies in countries based on their health policy and economic status (Ferlay et al., 2010; Nahvijou et al., 2014). Malaysia is a fast-developing country with different ethnicities. Cervical cancer screening has become free in Malaysia since 1995 but its coverage has remained as low as 47% while most smears were collected from young women during their antenatal and postnatal check-ups (Hayati, 2003). The low participation rate of Malaysians is mainly due to the inequality in health service distribution in rural and urban areas, lack of knowledge, difficulty in accessing

Department of Community Health, Universiti Putra Malaysia, <sup>1</sup>Cancer Resource and Education Centre, Faculty of Medicine and Health Sciences, <sup>3</sup>Faculty of Medicine and Health Sciences, Serdang, Selangor, <sup>2</sup>Department of Pathology, Faculty of Medicine, Universiti Teknologi Mara, Malaysia \*For correspondence: [latiffah.latiff@gmail.com](mailto:latiffah.latiff@gmail.com)

the centres for taking the smear, fear of cancer and low family support (Othman and Rebolj, 2009). Therefore, it is hypothesised that a self-sampling device may increase the cervical cancer screening coverage by facilitating the sample collection procedure.

It is hypothesised that the participation of women will increase if effective self-sampling techniques are introduced (Gravitt et al., 2011; Belinson et al., 2012; Aziz et al., 2013). It was proven that self-sampling for HPV is not inferior to the physician obtained samples (Gravitt et al., 2011; Belinson et al., 2012; Hamzah et al., 2013). Currently available self-sampling techniques are designed for collecting samples for HPV DNA assessment (Gravitt et al., 2011; Belinson et al., 2012; Hamzah et al., 2013). Self-sampling can be based on swap, brush, tampon or lavage (Lorenzato et al., 2002; Belinson et al., 2010). A few studies have assessed the reliability of these techniques against physician obtained sampling only in terms of HPV detection (Dijkstra et al., 2012; Aziz et al., 2013). To the best of our knowledge no self-sampling technique has yet been assessed against physician obtained sampling in detecting cytological abnormalities in Malaysia. Therefore, a device was designed and produced in Malaysia. This device has a handle through which an anatomically designed petal is inserted into the vagina (Figure 1). The smear is obtained by rotating the knob which allows the device to collect smear from cervical area. The accuracy and usability of this new instrument has not yet been assessed. The aim of this study was to evaluate the reliability of sampling collection of self-sampling against samples taken by physician.

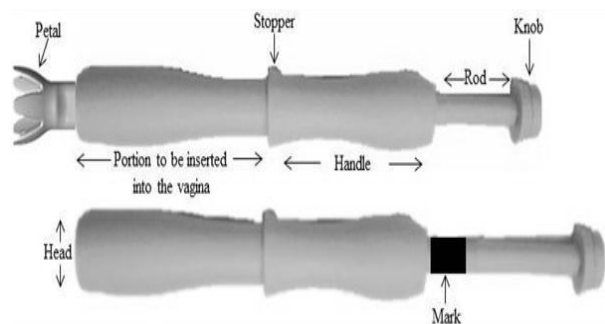
## Materials and Methods

### Ethical approval

This experiment was approved by the Faculty of Medicine and Health Sciences Medical Research Ethics Committee, Universiti Putra Malaysia.

### Study design

This cross sectional study was performed from December 2012 till February 2013. Subjects were recruited from the participants in health campaigns in Selangor state, Malaysia. Subjects were recruited if they were in reproductive age (15-49 years old). Subjects were excluded if they were virgin, pregnant, in menstruation phase or performed vaginal intercourse or vaginal rinsing prior to the test.



**Figure 1. The Cervisafe® Self-sampling Device**

### Sampling instruments

The cervical smear was performed based on liquid-based cytology technique using the BD SurePath® (BD Diagnostics, TriPath, Burlington, NC, USA). This technique detects two molecular markers of cervical squamous cell carcinoma including minichromosome maintenance protein 2 and topoisomerase II (Kelly et al., 2006). Samples taken by the physician were obtained using endocervical brush with detachable tip. The tips were then separated and were placed in BD SurePath® collection vial and were processed using BD PrepStain Slide Processor (BD Diagnostics, TriPath, Burlington, NC, USA). The specimens were held in alcohol for staining.

The self-administered cervical smear known as Cervisafe® device was used to obtain samples performed by the individuals. Subjects were instructed on the procedure of sampling and were encouraged to perform the test by themselves. In order to obtain samples, subjects were asked to wash their hands, unseal the sterile device and while sitting in either squatting or lithotomy position subjects were instructed to insert the device in the vagina till it reaches the ridge on the instrument (stopper). The device was fixed in position with one hand grabbing the handle while the knob was pressed by the other hand until it reached the mark on the rod. In that condition the petal would be in contact with the cervix. Subjects had to turn the knob 3 times in order to obtain the sample. The petal was separated from the device after withdrawal and transferred to BD SurePath collection vial and were processed using the same method as with the Surepath® method.

Cervical specimen analysis for both sampling techniques was performed by a pathologist and the results were reported in Bethesda system. The adequacy of the samples were identified as unsatisfactory, satisfactory but limited and satisfactory based on the Bethesda system terminology (Solomon and Nayar, 2004).

### Procedure

A total of 258 subjects participated in this study after giving a written informed consent. Specimens from both techniques were obtained for each subject by a trained physician. Subjects were randomly allocated into two equal groups, a group that underwent physician obtained cervical smear prior to self-sampling and a group that performed self-sampling followed by physician obtained cervical smear. This method resulted in 534 specimens. Specimens were then stained by hand and analysed by an experienced pathologist for the presence of abnormal cell, inflammation and infection. Subsequently, the specimens were tested for the subtypes of the human papilloma virus (HPV).

The epithelial cervical cells were collected from the cellular residues of BD SurePath specimens. The cells were washed by deionized water twice and were resuspended in 6 ml of normal saline. Staining was performed using Sakura DRS 601 automatic slide stainer (Sakura Finetek USA, Inc., Torrance, Calif). The slides were assessed for adequacy of the cellularity and based on the Bethesda System for Reporting Cervical Cytology (Erozan, 2011). The pathologist was blinded regarding the

source of sampling.

HPV DNA genotyping was performed for all BD SurePath specimens using the HPV XpressMatrix™ kit which comprised polymerase chain reaction (PCR) amplification and hybridization technology to detect the presence of certain HPV types either in single or multiple HPV subtype infection. This kit is able to detect common HPV subtypes including fifteen high risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 & 68) and six low risk subtypes (6, 11, 42, 43, 44 & 81). Each membrane array contained a total of 21 different HPV type-specific and human GAPDH as internal hybridization control oligonucleotide sequence probes. Other HPV positive specimens were analysed by DNA sequencing. Firstly DNA Extraction was carried out on the samples. These DNA samples were amplified using HPV consensus primers targeted at HPV L1 gene. A pair of primers that amplified the human GAPDH gene was also included as internal PCR Control. Each PCR reaction was set as follows: PCR mix: 22.25ul, 1.25U/ $\mu$ l of Taq DNA Polymerase and 10  $\mu$ l of each DNA sample. PCR Amplification was carried out in PCR thermal cycler (Biometra) with activation of Taq DNA Polymerase at 95°C for 15 minutes, 40 cycles of denaturation at 94 °C for 15 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute. Finally extension was performed at 72°C for 5 minutes. Each PCR product was used for subsequent hybridization to membrane array, colormetric method (BCIP/NBT) was used to stain for positive hybridization.

#### *Statistical analysis*

Descriptive analysis was performed for the study variables. Mean and standard deviation (SD) were used to describe the continuous variables while frequency and percentage was used for categorical variables. Reliability of the diagnoses based on self-sampling device and physician obtained sampling cytology was assessed using the Cohen's Kappa. Kappa values below 0.0 were considered as poor agreement, kappa below 0.2 as slight agreement, while kappa values between 0.21 and 0.40 were considered as fair agreement, values between 0.41 and 0.60 as moderate and values between 0.61 and 0.80 as substantial agreement and kappa values greater than 0.81 were considered as almost perfect agreement (Landis and Koch, 1977). The Fisher's exact test and chi-square test were used to assess the relationship between each technique and the outcomes of the sample analysis. In order to assess the effect of menopausal state on the specimen collection properties of the methods, logistic regression was performed with menopausal state (being menopause or non-menopause) as dependent variable and specimen adequacy and endocervical cell presence in both cytology and virology assessments as independent variables using backward elimination method. The resulted significant variables were then used in separate models in order to assess the effect of menopausal state on each variable. The statistical package for social sciences (SPSS) software version 19.00 (IBM Inc, Chicago, IL, USA) was used for the analysis. The p value less than 0.05 was considered as statistically significant and the

confidence limit was considered as 95%.

## **Results**

A total of 258 women participated in the study. Mean (SD) for the age of the subjects was 40.41 $\pm$ 11.28 years. Among the study subjects 56 (21.7%) were in menopausal period while 202 (78.3%) were in reproductive age. Normal cytology was found in 207 (80.2%) of subjects using self-sampling and 202 (78.3%) using physician-obtained sampling. Self-sampling technique resulted in finding 46 (17.8%) reactive cellular changes while 45 (17.4%) of the subjects were found to have reactive cellular changes in physician-obtained sampling. Atypical squamous cells of unknown significance (ASCUS) was found in 2 (0.8%) and 5 (2.0%) of samples obtained using self-sampling and physician-obtained sampling respectively. Both techniques resulted in detection of 2 (0.8%) low grade squamous intraepithelial lesion (LGSIL). Only one (0.4%) sample was unsatisfactory in physician-obtained samples while none of the self-obtained samples were unsatisfactory. The agreement between both techniques in terms of endocervical findings is shown in Table 1. Although there was a significant agreement between the two techniques, but the agreement was low in terms of specimen adequacy, endocervical cell and inflammatory cell findings (Table 1). The Fisher's exact test revealed that self-sampling was significantly related to lower collection of endocervical cells ( $p < 0.001$ ), while chi-square test revealed a significant relationship between the use of self-sampling and higher detection of marked and moderate inflammation ( $\chi^2 = 199.41$ ,  $p < 0.001$ ).

The agreement between the two techniques in terms of virological assessment is shown in Table 1. Although the agreement between the two techniques was significant in all categories the Kappa value was low for specimen adequacy (Kappa=0.27,  $p < 0.001$ ) (Table 2). On the other hand self-sampling was found to be related to significantly higher detection of high risk ( $p = 0.001$ ) and low risk ( $p < 0.001$ ) genotypes.

Performing the separate analysis for menopausal and non-menopausal subjects revealed that the kappa was higher in menopausal subjects in specimen adequacy and presence of endocervical cells for cytological assessment while the kappa for hormonal changes, microscopic appearance and diagnosis was found to be higher in non-menopausal subjects (Table 2). The kappa for specimen adequacy and detection of high risk genotypes was higher in menopausal subjects (Table 2). No case of infection with low risk genotype of HPV was detected in the menopausal subjects in this study.

Performing logistic regression, with menopausal status as dependent variable and specimen adequacy, presence of endocervical cells in cytological assessment as well as specimen cell adequacy in virological analysis in both self-sampling and physician obtained specimen as independent variables, using backward elimination method revealed that only endocervical presence in cytology assessment and specimen cell adequacy in virology assessment were significantly related to menopausal status in this study therefore the other non-significant variables were

**Table 1. Agreement between Self-sampling and Physician Obtained Sampling in Terms of Cytological and Virological Findings**

		Self-sampling n=258	Physician obtained sampling n=258	Kappa	95%CI for Kappa		p
					Lower	Upper	
Cytological findings							
Specimen adequacy	Unsatisfactory	0	1	0.13	-0.02	0.28	0.03*
	Acceptable	24	30				
Endocervical cell	Satisfactory	234	227	0.27	0.17	0.37	<0.001**
	Absent	139	65				
Hormonal status	Present	119	193	0.77	0.64	0.9	<0.001**
	Non-atrophic	235	228				
Microscopic appearance	Atrophic	23	30	0.19	-0.15	0.52	<0.01**
	Normal	255	251				
Diagnosis	Abnormal	3	7	0.62	0.5	0.74	<0.001**
	Normal	206	201				
Virology findings	Abnormal	52	57				
	Normal						
Virology findings							
Specimen adequacy	Low	27	38	0.27	0.17	0.37	<0.001**
	Moderate	33	46				
	satisfactory	197	173				
	Insufficient	1	1				
Detection of high risk genotypes	15	10	0.71	0.44	0.98	<0.001**	
Detection of low risk genotypes	7	7	0.71	0.5	0.92	<0.001**	

\*Statistically significant at  $\alpha=0.05$ ; \*\*Statistically significant at  $\alpha=0.01$

**Table 2. Agreement between Self-sampling and Physician-obtained Sampling in Terms of Cellular and Virological Findings in Menopausal and Non-Menopausal Subjects**

		Kappa	95%CI for Kappa		p
			Lower	Upper	
Cytological findings					
Specimen adequacy	Menopause (n=52)	0.29	0.02	0.57	0.03*
	Non-menopause (n=206)	-0.05	-0.08	-0.02	0.365
Endocervical cell presence	Menopause (n=52)	0.37	0.04	0.7	0.01**
	Non-menopause (n=206)	0.22	0.13	0.32	<0.001**
Hormonal status	Menopause (n=52)	0.64	0.47	0.81	<0.001**
	Non-menopause (n=206)	0.74	0.4	1.09	<0.001**
Microscopic appearance	Menopause (n=52)	0.65	0.46	0.85	<0.001**
	Non-menopause (n=206)	0.21	-0.16	0.57	0.002**
Diagnosis	Menopause (n=52)	0.37	0.04	0.7	0.01**
	Non-menopause (n=206)	0.66	0.54	0.79	<0.001**
Virology findings					
Specimen adequacy	Menopause (n=52)	0.36	0.16	0.55	<0.001**
	Non-menopause (n=206)	0.14	0.02	0.25	0.01**
Detection of high risk genotypes	Menopause (n=52)	0.79	0.39	1.19	<0.001**
	Non-menopause (n=206)	0.69	0.45	0.92	<0.001**
Detection of low risk genotypes	Menopause (n=52) <sup>†</sup>	-	-	-	-
	Non-menopause (n=206)	0.7	0.43	0.98	<0.001**

\*\* Statistically significant at  $\alpha=0.01$ ; <sup>†</sup>No result was displayed due to the absence of low risk genotypes in menopausal subjects in this study

excluded from the model. Logistic regression revealed that menopausal state was related to 8.39 times increase in the odds of collecting endocervical cells (OR=8.39, 95% CI for OR: 3.87, 18.18) and in contrary to 0.13 times reduced odds of collecting adequate cells for virological assessment (OR=0.13, 95% CI for OR: 0.06, 0.25).

## Discussion

This study revealed that the prevalence of abnormal cellular changes was (7/258, 2.7%). The prevalence of cellular abnormalities was reported to be 14/702 (2%) by

physician-obtained smear in Malaysian subjects (Othman and Othman, 2012). Although this study was not intended to identify the prevalence of abnormal results in the population, the findings of this study was in line with the previously reported data.

This study revealed the overall prevalence of HPV infection to be 8.5%. It was previously shown that the prevalence of HPV infection was 11.3% in a sample of 345 Malaysian patients (Hamzah et al., 2013). The difference between the findings of the current study and the study by Hamzah et al. (2013) was due to the study subjects. While Hamzah et al. (2013) recruited their

subjects from patients attending gynaecologic clinics, the current study was conducted on community dwelling women, therefore the prevalence of HPV infection in this study was found to be lower than the previous study. The prevalence of high and low risk genotypes was 5.8% and 2.7% respectively. It was previously reported that low risk genotypes were found more frequent compared with high risk genotypes when compared with cervical biopsy (Petignat et al., 2007). This finding was attributed to the hypothesis that vaginal sampling techniques obtain HPV viruses from the vagina other than the cervix (Petignat et al., 2007). While the prevalence of high risk HPV was reported to be between 15.9 and 17.9 cases per 100,000 in different states of Malaysia, the overall prevalence of HPV infection was reported to be 11.3% which is lower (14% and 21%) than the prevalence of HPV infection reported in Europe (Domingo et al., 2008b; Bruni et al., 2010; Hamzah et al., 2013).

The findings of this study revealed a substantial agreement in detecting both high risk and low risk HPV between self-sampling and physician obtained sampling ( $k=0.77$  for each). It was previously shown that self-sampling techniques provided a good agreement with either biopsy or physician-obtained smear and the agreement ranged from  $k=0.65$  to  $k=0.70$  (Gage et al., 2011; Dijkstra et al., 2012; Hamzah et al., 2013). In a previous study by Hamzah et al. (2013) the agreement between Fournier-sampler specimens and physician obtained specimen was reported to be 0.65 which was lower than the self-sampling technique used in this study ( $k=0.77$ ). Higher agreement for self-sampling provides evidence for the superiority of this self-sampling device over the other self-sampling techniques.

The results of this study revealed that self-sampling could result in a better sample collection for both cytological and virological assessments compared with physician obtained specimen. In contrast, the agreement between self-sampling endocervical cell collection and physician obtained specimen was fair. This controversy might be due to the blind nature of self-sampling technique. Moreover, substantial agreement was identified between self-sampling and physician-obtained sampling results in terms of diagnosis of cervical abnormalities ( $k=0.62$ ), detecting hormonal changes ( $k=0.75$ ) and microorganisms ( $k=0.77$ ). It was previously shown that self-sampling using the Fournier-sampler on 292 subjects was not clinically acceptable due to lower sensitivity (41%) in sampling collection compared with conventional physician-obtained sampling (Aziz et al., 2013). It was previously shown that different methods of self-sampling obtain various amounts of cell mixture comprising more vaginal cells and less endocervical cells (Othman and Zaki, 2014). Another reason that might contribute to the difference in sample collection between self-sampling technique and physician-obtained sampling methods might be due to the existence of postmenopausal subjects.

It was previously shown that the squamo-columnar junction is less exposed in postmenopausal age which makes it difficult to obtain sufficient sample from the endocervix (Jordan et al., 2008). Thus self-sampling might be less appropriate for this age group due to its blind

sampling nature. Further analysis was performed to assess the effect of menopausal state in the properties of sampling methods in this study revealed that the only significant relationship between menopausal status and sampling properties were pertaining to self-sampling while the physician obtained sampling properties seemed to remain unchanged in menopausal subjects. This finding can be best described by the existence of guidelines for obtaining samples in menopausal subjects taken by physician, in which procedures are defined to facilitate sampling from the endocervical region (Arbyn et al., 2007). On the other hand, this study revealed that the self-sampling properties for cytological assessment increases with menopause while its properties for virological assessment decreases with menopause. These findings indicate that self-sampling might be able to collect more endocervical cells for cytology assessment in menopausal women but since the total number of subjects in menopausal state was small. These findings require verification by further studies with larger sample of menopausal subjects.

Although there was a fair agreement between self-sampling and physician-obtained sampling in this study, a substantial agreement was found for the overall cytopathological diagnosis based on the provided samples. This study revealed that self-sampling might be considered as a sampling device for cervical smear but more studies are needed to assess the agreement between self-sampling and cervical biopsy.

One of the strengths of this study was the design of the study where samples were collected from women in different rural and urban settings. Although this study was not intended to identify the prevalence of HPV in Malaysia, it provided good information on the pattern of high risk and low risk HPV infection in community dwelling Malaysian women. An important limitation of this study was lack of a gold standard assessment such as cervical biopsy due to financial and ethical issues. It was previously shown that the agreement between self-sampling and cervical biopsy was high (Dijkstra et al., 2012). Therefore, it is recommended for further researchers to conduct studies on subjects with a biopsy confirmed diagnosis. Another limitation of this study was low prevalence of abnormal endometrial cells as well as HPV infection among the samples which was due to the study design that obtained samples from community dwelling women. It is recommended that future studies should further assess the reliability and validity of this technique in populations with higher prevalence of HPV and abnormalities (gynaecological patients).

The results of this study revealed a good agreement between self-sampling and physician obtained sampling in terms of high risk and low risk HPV detection. Moreover this study provided evidence that self-sampling might be used to collect cervical smear especially in menopausal women but more studies should be performed prior to suggesting recommendations on the use of self-sampling for cancer screening.

## Acknowledgements

The financial source of this study was supported by

## References

- Arbyn M, Herbert A, Schenck U, et al (2007). European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. *Cytopathology*, **18**, 133-9.
- Aziz A, Hamzah H, Lim B, et al (2013). The effectiveness and acceptability of self-sampling against conventional Pap smear in university Malaya medical centre (UMMC). *J Health Translatl Med*, **16**, 97.
- Belinson JL, Du H, Yang B, et al (2012). Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing. *Int J Cancer*, **130**, 1855-60.
- Belinson JL, Hu S, Niyazi M, et al (2010). Prevalence of type-specific human papillomavirus in endocervical, upper and lower vaginal, perineal and vaginal self-collected specimens: Implications for vaginal self-collection. *Int J Cancer*, **127**, 1151-7.
- Bruni L, Diaz M, Castellsague M, et al (2010). Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infectious Diseases*, **202**, 1789-99.
- Dijkstra MG, Heideman DA, van Kemenade FJ, et al (2012). Brush-based self-sampling in combination with GP5+/6+-PCR-based hrHPV testing: High concordance with physician-taken cervical scrapes for HPV genotyping and detection of high-grade CIN. *J Clin Virology*, **54**, 147-51.
- Domingo EJ, Noviani R, Noor MRM, et al (2008a). Epidemiology and prevention of cervical cancer in Indonesia, Malaysia, the Philippines, Thailand and Vietnam. *Vaccine*, **26**, 71-9.
- Domingo EJ, Noviani R, Noor MRM, et al (2008b). Epidemiology and prevention of cervical cancer in Indonesia, Malaysia, the Philippines, Thailand and Vietnam. *Vaccine*, **26**, 71-9.
- Fahey MT, Irwig L, Macaskill P (1995). Meta-analysis of Pap test accuracy. *Am J Epidemiology*, **141**, 680-9.
- Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.
- Gage JC, Partridge EE, Rausa A, et al (2011). Comparative performance of human papillomavirus DNA testing using novel sample collection methods. *J Clin Microbiol*, **49**, 4185-9.
- Gravitt PE, Belinson JL, Salmeron J, et al (2011). Looking ahead: A case for human papillomavirus testing of self-sampled vaginal specimens as a cervical cancer screening strategy. *Int J Cancer*, **129**, 517-27.
- Hamzah H, Aziz A, Lim B, et al (2013). Evaluation of human papillomavirus (HPV) infection among women in UMMC-comparison between thin prep and fournier's self sampling. *J Health Translatl Med*, **16**, 92.
- Hayati ON (2003). Cancer of the cervix-from bleak past to bright future; a review, with an emphasis on cancer of the cervix in Malaysia. *Malaysian J Med Sci*, **10**, 13.
- Jordan J, Arbyn M, Martin-Hirsch P, et al (2008). European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1. *Cytopathology*, **19**, 342-54.
- Kelly D, Kincaid E, Fansler Z, et al (2006). Detection of cervical high-grade squamous intraepithelial lesions from cytologic samples using a novel immunocytochemical assay (ProEx™ C). *Cancer Cytopathology*, **108**, 494-500.
- Landis JR, Koch GG (1977). The measurement of observer agreement for categorical data. *Biometrics*, **33**, 159-74.
- Lorenzato FR, Singer A, Ho L, et al (2002). Human papillomavirus detection for cervical cancer prevention with polymerase chain reaction in self-collected samples. *Am J Obstet Gynecol*, **186**, 962-8.
- Nahvijou A, Hadji M, BaratiMarnani A, et al (2014). A systematic review of economic aspects of cervical cancer screening strategies worldwide: discrepancy between economic analysis and policymaking. *Asian Pac J Cancer Prev*, **15**, 8229-37.
- Othman N, Othman NH (2012). Adequacy of cellular material in split-sampling of cervical scrapings for routine cancer screening: an analysis of 702 smears. *Malaysian J Pathol*, **34**, 115-21.
- Othman NH, Rebolj M (2009). Challenges to cervical cancer screening in a developing country: the case of Malaysia. *Asian Pac J Cancer Prev*, **10**, 747-52.
- Othman NH, Zaki FHM (2014). Self-collection tools for routine cervical cancer screening: a review. *Asian Pac J Cancer Prev*, **15**, 8563-9.
- Pan Q, Belinson JL, Li L, et al (2011). A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma. *Acta Cytol*, **47**, 45-50.
- Petignat P, Faltin DL, Bruchim I, et al (2007). Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? a systematic review and meta-analysis. *Gynecol Oncol*, **105**, 530-5.
- Solomon D, Nayar R (2004). *The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria and Explanatory Notes*. Springer.