



UNIVERSITI PUTRA MALAYSIA

***COMPARISON BETWEEN SELF-SAMPLING AND GYNECOLOGIST
SAMPLING OF CERVICAL SPECIMEN FOR PAP CYTOLOGY AND HPV
DNA DETECTION AMONG WOMEN IN JEMPOL, NEGERI SEMBILAN,
MALAYSIA***

ZAIDAH IBRAHIM

IB 2015 2



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MALAYSIA**

By

ZAIDAH IBRAHIM

**Thesis Submitted to the School of Graduate Studies, Universiti Putra
Malaysia, in Fulfilment of the Requirements for the Degree of Master of
Science**

APRIL 2015

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I would like to dedicate this work to my beloved son, Muhammad Imran Kausar, my mother and my family. You are my love, my strength and my support. And to all women out there who can benefit from this writing.



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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

COMPARISON BETWEEN SELF-SAMPLING AND GYNECOLOGIST SAMPLING OF CERVICAL SPECIMEN FOR PAP CYTOLOGY AND HPV DNA DETECTION AMONG WOMEN IN JEMPOL, NEGERI SEMBILAN, MALAYSIA

By

ZAIDAH IBRAHIM

April 2015

Chair: Prof. Latiffah A. Latiff , PhD

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Self-sampling for cervical screening have shown good acceptance among hard to reach women and in low healthcare resource setting area. This study was to measure the agreement and available differences between Kato self-sampling device (KSSD) and gynecologist sampling for PAP cytology and Human Papillomavirus DNA (HPV DNA) detection. Cytology specimens (486 specimen pairs) and HPVDNA specimens (226 specimen pairs) from women attended screening at 2 Primary Health Clinics, in Jempol Negeri Sembilan, Malaysia were assessed. All women underwent self-sampling first followed by gynecologist sampling. The prepared PAP cytology slides were evaluated for specimen adequacy, presence of endocervical cells or transformation zone cells and cytological interpretation for cells abnormalities. For HPV testing, samples were measured for DNA concentration and quality and underwent HPV DNA detection using nested PCR (primer MY 9/11 and GP5+/6+). Specific HPV genotype was determined by gene sequencing which referred to the online NCBI gene bank. The result between self-sampling and gynecologist sampling were compared using statistical Wilcoxon signed rank test, Kappa agreement and McNemar Chi Square test. In PAP specimen adequacy, KSSD showed 100% agreement with gynecologist sampling with all samples showed satisfactory for evaluation however had only 32.3% agreement for presence of endocervical cells. For cytological interpretation both sampling showed 100% agreement with only 1 case detected HSIL favor CIN2. Median DNA concentration for KSSD and gynecologist sampling were 30.0 ng/ul and 36.0 ng/ul respectively ($p=0.045$). For detection of HPV DNA, 86.2% agreement ($k = 0.64$, 95% CI 0.524-0.756, $p= 0.001$) was found between technique of sampling with KSSD and gynecologist sampling HPV positive were 22.6% and 27% respectively ($p>0.05$). Both techniques detected HPV 11, 16, 18, 31, 33 and 45. KSSD and gynecologist identified high risk HPV 17.3% and 23.9 % respectively ($p= 0.014$). HPV 18 showed a significant different ($p=0.02$) but HPV type 16 showed no significant different ($p=1.00$) between the sampling techniques. As conclusion, the self-sampling using Kato device is comparable to the gynecologist sampling for PAP cytology and HPV DNA detection and a good potential as an alternative to increase cervical screening participation among women especially in rural area or low healthcare setting.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana

PERBEZAAN ANTARA PENSAMPELAN SENDIRI DAN PENSAMPELAN GINEKOLOGIS UNTUK SPESIMEN SERVIK MELALUI UJIAN SITOLOGI PAP DAN UJIAN PENGESANAN DNA HUMAN PAPILOMAVIRUS DI KALANGAN WANITA DI JEMPOL NEGERI SEMBILAN, MALAYSIA

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April 2015

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Pensampelan sendiri untuk ujian saringan servik menunjukkan penerimaan yang baik di kalangan wanita yang sukar hadir menjalani ujian saringan dan juga di kawasan yang kurang mempunyai kemudahan perkhidmatan kesihatan. Kajian ini bertujuan untuk mengukur persamaan dan perbezaan yang ada di antara kaedah pensampelan sendiri menggunakan alatan Kato dengan pensampelan pakar ginekologi melalui ujian sitologi PAP dan ujian pengesanan DNA Human papillomavirus (HPV DNA). Sebanyak 486 pasangan spesimen slaid sitologi dan 226 pasangan spesimen HPV dari kalangan wanita yang hadir untuk ujian saringan servik di dua Klinik Kesihatan di Jempol, Negeri Sembilan, Malaysia di analisa. Kesemua wanita melakukan pensampelan sendiri dahulu dan kemudian menjalani pensampelan oleh pakar ginekologi. Slaid Pap sitologi yang disediakan dinilai pada adekuasi spesimen, kepadatan sel endoserviks atau sel zon transformasi dan juga interpretasi sitologi keatas abnormaliti sel. Untuk ujian HPV, kepekatan spesimen DNA dan kualiti DNA diukur dan kehadiran DNA HPV di kesan melalui 2 pusingan (nested) PCR (menggunakan primer MY9/11 dan GP5+/6+). Genotaip spesifik HPV ditentukan melalui sekuen gen yang dirujuk kepada pangkalan data atas talian bank gen NCBI. Hasil keputusan diantara pensampelan sendiri dan pensampelan oleh ginekologis dibandingkan menggunakan ujian statistic Wilcoxon Signed Rank , ujian kesamaan Kappa dan ujian Chi Square McNemar. Untuk adekuasi specimen, KSSD mempunyai 100% persamaan dengan ginekologis dengan keputusan semua sampel memuaskan untuk dievaluasi. Bagaimanapun hanya menunjukkan persamaan 32.3% pada kepadatan sel endoservik. Untuk interpretasi sitologi kedua teknik pensampelan menunjukkan persamaan 100% dengan hanya 1 kes HSIL dengan jangkaan CIN2 dikesan. Didapati median kepekatan spesimen DNA bagi KSSD dan ginekologis adalah 30.00ng/ul dan 36.00 ng/ul ($p=0.045$). Pada pengesanan HPV DNA, 86.2% persamaan ($Kappa =0.64$, 95% CI 0.524-0.756, $p= 0.001$) didapati di antara kedua teknik dimana positif HPV DNA pada KSSD dan ginekologis ialah 22.6% dan 27.% ($p>0.05$).

Kedua-dua teknik mengesan HPV 11, 16, 18, 31, 33 dan 45. KSSD dan ginekologis mengenalpasti sebanyak 17.3% dan 23.9% ($p=0.014$) HPV risiko tinggi. HPV 18 menunjukkan perbezaan ($p=0.02$) manakala HPV 16 tidak menunjukkan perbezaan ($p=1.00$) diantara kedua pensampelan tersebut. Kesimpulannya pensampelan sendiri alatan Kato mempunyai perbandingan yang baik dengan pensampelan ginekologis untuk sitologi PAP dan ujian DNA HPV serta berpotensi baik sebagai alternatif untuk meningkatkan penyertaan saringan servik di kalangan wanita di kawasan luar bandar atau kawasan yang terhad sumber perkhidmatan kesihatan.



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I certify that a Thesis Examination Committee has met on 23rd April 2015 to conduct the final examination of Zaidah binti Ibrahim on her thesis entitled "Comparison Between Self-Sampling And Gynecologist Sampling Of Cervical Specimen For Pap Cytology And Hpv Dna Detection Among Women In Jempol, Negeri Sembilan, Malaysia "in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the (insert the name of relevant degree).

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TABLE OF CONTENTS

ABSTRACT	Page
ABSTRAK	i
ACKNOWLEDGEMENT	ii
APPROVAL	iv
DECLARATION	v
LIST OF TABLES	vii
LIST OF FIGURES	xii
LIST OF ABBREVIATION	xiv

CHAPTER

1	INTRODUCTION	1
	1.1 Research Background	1
	1.2 Research problem	2
	1.3 Hypothesis	3
	1.4 Study Objectives	3
	1.5 Rationale of study	3
2	LITERITURE REVIEW	5
	2.1 Cervical cancer	5
	2.1.1 Incidence and mortality of cervical cancer worldwide	8
	2.1.2 Incidence and mortality rate of cervical cancer in Malaysia.	8
	2.2 Cervical Cancer Screening : Current status	9
	2.2.1 Cervical cancer screening in developing countries and Malaysia	10
	2.2.2 Non screening in Malaysia: Women views	11
	2.3 Infection of HPV and cervical cancer.	12
	2.3.1 HPV type distribution in Malaysia	13
	2.3.2 Pathogenesis of cervical cancer and relationship to HPV infection	14
	2.3.3 Integration of viral DNA into host cells DNA	17
	2.4 Cervical cancer screening test	19
	2.4.1 The PAP test	19
	2.4.2 The role of of HPV DNA testing	29
	2.5 Self sampling as an alternative	32
	2.5.1 Self-sampling devices	32
	2.5.2 Quality of specimen device	33
	2.5.3 Validity of self-sampling compared to clinician-sampling	33
	2.5.4 Malaysia screening scenario and potential of self sampling application	36

	2.5.5	Kato self-sampling for cervical specimen	36
3		MATERIALS AND METHODS/ METHODOLOGY	39
	3.1	Sampling	39
	3.1.1	Sample size calculation	39
	3.1.2	Sampling Population	42
	3.1.3	Cervical/vaginal specimen sampling	44
	3.3	Cytology	48
	3.3.1	Laboratory investigation	48
	3.3.2	Cytology statistical analysis	49
	3.4	HPV DNA detection assay	50
	3.4.1	Specimen DNA extraction	50
	3.4.2	DNA Quantification	51
	3.4.3	Detection of DNA quality by β -globin PCR	51
	3.4.4	Detection of HPV DNA by PCR Amplification using Nested PCR primer MY 9/11 AND GP5+/6+	52
	3.4.5	Gene Sequencing- HPV genotyping	54
	3.4.6	Quality Assurance	54
	3.4.7	Statistical analysis	54
4		RESULTS	57
	4.1	Population demographic (age, race, occupation) and menopausal status	57
	4.2	Diagnostic agreement between KSSD and gynecologist sampling for PAP cytology specimen adequacy and presence of endocervical cells/TZ cells	59
	4.2.1	Specimen adequacy	59
	4.2.2	Presence of endocervical cells	59
	4.3	Diagnostic agreement between specimens collected by KSSD and gynecologist sampling for PAP cytological interpretation :cells abnormality or malignancy	62
	4.4	Comparing specimen DNA concentration (quantity) and DNA quality	64
	4.4.1	Comparing DNA concentration	64
	4.4.2	Comparing DNA quality	66
	4.5	HPV DNA detection and diagnostic agreement of HPV positives between KSSD and gynecologist sampling	66
	4.6	Detection, comparison and diagnostic agreement for specific HPV genotype, high risk HPV (HRHPV) and low risk HPV (LRHPV) between KSSD and gynecologist sampling	69

4.6.1	Distribution of detected HPV genotype	70
4.6.2	High risk HPV (HRHPV) analyses	70
4.6.3	Comparison of specific HPV genotype	71
4.6.4	Analysis among concordant pairs of HPV positives of both sampling techniques.	73
4.6.5	Additional Dat	73
5	DISCUSSION	75
5.1	Sampling population	75
5.2	Comparison on specimen adequacy	75
5.3	Comparison on cytological interpretation	78
5.4	Comparison on cytological interpretation	78
5.5	Detection and comparison on HPV DNA	78
5.6	Comparison of specific HPV genotype, HRHPV and LRHPV	80
5.7	Study Limitation	82
6	CONCLUSION, SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH	84
	REFERENCES	87
	APPENDICES	
	BIODATA OF STUDENT	114
	LIST OF PUBLICATIONS	115

LIST OF TABLES

Table		Page
2.1	FIGO staging for cervical cancer.	8
2.2	HPV types found in cervical cancer cases in Malaysia.	14
2.3	Bethesda 2001 terminology for cervical cytology.	22
2.4	Conceptual categorization of PAP cytological finding of Bethesda system finding correspond with CIN staging System.	25
2.5	Other cytological classification system in relation to The Bethesda system.	29
3.1	Kappa agreement.	50
3.2	PCR reagent volume for β -globin gene amplification.	51
3.3	PCR reagents volume for first round nested PCR using MY 9/11 primers.	53
3.4	PCR reagent volumes for second round nested PCR using GP5+/ 6+ primers.	53
4.1	The demographic data of women included in the study screened for Pap smear cytology and HPV DNA test.	58
4.2.	Concordance of Kato self-sampling versus gynecologist sampling for PAP cytology specimen adequacy.	59
4.3	Concordance of Kato self-sampling versus gynaecologist sampling for presence the of endocervical cells or transformation zone (TZ) cells.	60
4.4	Concordance of Kato self-sampling versus gynaecologist-sampling for cytological interpretation: cell abnormality and malignancy.	62
4.5	Concordance of HPV DNA detection among 226 pairs specimen between Self-sampling and gynecologist sampling.	68
4.6	Distribution of HPV genotypes by KSSD and gynecologist-sampling.	69
4.7	Concordance of KSSD versus gynecologist-sampling in detecting HRHPV.	71
4.8	Concordance of specific HPV type between Self-sampling and gynecologist sampling.	72
4.9	Descriptive data between PAP cytology and HPV DNA detection result.	74

LIST OF FIGURES

Figure	Page
1.1 Conceptual framework.	4
2.1 Anatomy of the cervix.	6
2.2 Histology of the normal cervix (H &E stain).	6
2.3 Histology structure of the ectocervix.	7
2.4 Histology of normal endocervix.	7
2.5 HPV genome using HPV 16 model.	15
2.6 Lifecycle of High-Risk HPVs in cervix.	17
2.7 The organization of circular HPV DNA and its integration into host-cell DNA.	19
2.8 The conceptual of summarized Bethesda reporting focusing on squamous cells abnormalities.	28
3.1 Study flow chart of cervical sampling and testing.	44
3.2 Illustration of Kato Self-collection device	47
3.3 Illustration of Kato Self-collection device specimen Preparation.	47
3.4 Rovers® Cervex-Brush®, (Netherlands) used in gynecologist sampling to scrap cervical samples for Pap smear cytology and HPV DNA test.	48
3.5 Pap cytology variables with dichotomous result	49
3.6 Variables assessed in HPV DNA detection assay.	55
3.7 Flowchart for Sampling Methodology and Analysis	56
4.1 PAP smear cytology slide from gynecologist sampling (A) and self-sampling (B).	61
4.2 Comparison of KSSD and gynecologist- sampling in specimen adequacy, presence of endocervical cells and cell abnormalities of Pap smear cytology.	63
4.3 Distribution of each DNA concentration value of gynecologist-samples and self-samples in 226 women.	65
4.4 Gel electrophoresis photo from beta-globin PCR.	66
4.5 Detection of HPV DNA at first round PCR (primer MY9/11).	67
4.6 Detection of HPV DNA at round 2 nested PCR using primer GP5+/6+	67
4.7 The overall proportion of HPV, HRHPV and LRHPV in Self-sampling and gynecologist sampling.	70
4.8 Proportion of specific HPV type detected by self-sampling and gynecologist sampling among all (226 pairs) specimens.	70

LIST OF ABBREVIATIONS

ASCUS	Atypical squamous cells of undetermined significance
ASCH	Atypical squamous cells cannot exclude high grade lesion
BLASTn	Basic Local Alignment Search Tool, nucleotide
CC	Cervical cancer
CCS	Cervical cancer screening
CIN1	Cervical intraepithelial neoplasia 1
CIN2	Cervical intraepithelial neoplasia 2
CIN3	Cervical intraepithelial neoplasia 3
DNA	Deoxyribonucleic acid
EC	Endocervical cells
HPV	Human papillomavirus
HPV DNA	Human papillomavirus DNA
HR HPV	High risk Human papillomavirus
HSIL	High grade squamous intraepithelial lesion
Clinic I	Primary Health Clinic SertingHilir
Clinic II	Primary Health Clinic Bahau
IQR	Interquartile range
KSSD	Kato Self-Sampling Device
k	Kappa value
NCBI	National Centre for Biotechnology Information
NCR	National Cancer Registry, Malaysia
MOH	Ministry of Health, Malaysia
ng/ul	nanogram/ mikroliter
PCR	polymerase chain reaction
PBS	Phosphate buffer saline
PST	Pap smear test
SS	Self-sampling
TBS	The Bethesda System
TZ	Transformation zone

CHAPTER ONE

INTRODUCTION

1.1 Research Background

Cervical cancer is a serious burden around the globe. It is ranked the fourth most common cancer among women worldwide, after breast, colorectal and lung cancer (Ferlay *et al.*, 2013). In Malaysia, cervical cancer is the third most common cancer among its women (National Cancer Registry 2007 -NCR 2007). Among the case reported in Malaysia, almost half (45%) of this cervix uteri cancer diagnosed at the late stages (Zainal Ariffin & Nor Saleha, 2011).

In contrast to other types of cancers, cervical cancer can be prevented if early detection is made. The early screening through PAP smear identifies cervical abnormality and therefore early lesion are treated accordingly and prevent it from progressing into cancer (Biewenga *et al.*, 2011; Lowy *et al.*, 2008). However, even though the screening tests are available, the participation of women towards screening in Malaysia is still low, which contributes to the high burden of the disease. In records, among patients with cervical cancer in 8 major hospitals in Malaysia between year 2000 and 2006, there were 48% have never had any Pap smear test, while 95% have not had smear in the past 3 years (Othman *et al.*, 2009). The PAP smear screening in Malaysia was adopted mainly by opportunistic screening among women who visit the medical facilities during antenatal and postnatal check-ups (Chye *et al.*, 2008). While rural women of developing countries reported to have higher cervical cancer prevalence compared to their urban counterpart (Smailyte & Kurtinaitis, 2008; Palacio-Mejía *et al.*, 2003). In Malaysia, a survey among young females in rural population demonstrated that they have extremely poor knowledge of HPV, HPV vaccination or cervical screening, and cervical cancer risk factors (Wong, 2010). The most vital factor for the lack of screening is attributable to the women personal barriers to the current screening. Among the reasons reported for not having had a Pap smear in Malaysia include “never heard about it”, “feel shy”, “afraid to do it”, thinking that the test is not important and no encouragement from family (Othman *et al.*, 2009). Many other reports on women screening barriers in developing countries also state feelings of embarrassment associated with its procedure (Markovic *et al.*, 2005), having fear of pain, lack of time (Dunn & Tan, 2010) and inconvenience to get to the health facilities (Wee *et al.*, 2012). In Malaysia, currently, there is no national individual call-recall system available, and mainly women are encouraged to go for screening primarily through mass media advertising. Free of charge smears are available in public hospitals and clinics, however the waiting times reported are often long. The healthcare structure is unequally dense distributed, with rural areas being underserved compared to the urban areas (Othman & Rebolj, 2009). This discrepancy should be addressed, to enable accessible screening provided by health authorities in order to increase screening coverage in the target population. Due to the lack of cervical cancer screening coverage, self-sampling (SS) has been initiated in many other countries as an alternative method for clinician cervical sampling to increase women participation (Virtanen., 2011).

Self-sampling had been reported to have a good acceptance among women (Dijkstra et al., 2012; Barbee et al., 2010; De Alba et al., 2008) and able to reachout women with low or no opportunity for screening (Gök et al., 2012). In fact, HPV test through self-sampling is the most feasible method to get to women who never participated in screening programs (Ogilvie et al., 2007). Studies suggest that this method is especially suitable in low resource setting and particularly attractive for primary screening (Gravitt et al., 2008). Furthermore, adult women discover self-sampling for HPV DNA test is more acceptable than clinician sampling (Cuzick et al., 2012; Dzuba et al., 2002).

A meta-analysis in 2007, which include studies using many types of self-sampling devices, showed that overall, there were good agreement between self-sampling and clinician sampling for the detection of any HPV types and high risk HPV (Petignat et al., 2007). However there were considerable variations on validities of self-sampling compared to clinician sampling in across different settings of population under study (Schmeink et al., 2011). The variations were also derived from one self-sampling device to another with a wide range of agreement when compared to clinician sampling (Schmeink et al., 2011).

1.2 Research problem

Self-sampling can be most useful in the expected lower screening coverage of rural and low resource setting in Malaysia. However, currently there is limited information of self-sampling and no study ever reported on self-sampling usage in this area. As a possible intervention to enhance screening in rural area, a self-sampling device using the Kato Self-Sampling (Noguchi et al., 1982) was evaluated in this current study.

The self -scrapping Kato device was first invented in Japan for the purpose of providing mass cervical screening in Japan population (Noguchiet al, 1982). However there is still limited information of the device validity. The Kato self-sampling device was tested among women in Thailand and had showed similar PAP cytology results in comparison with gynecologist sampling (Pengsaa et al., 1997) and also showed good acceptance among women with less skeptically accepted among women in rural area (Sanchaisuriya et al., 2004). In PAP cytology result, previous study found that the Kato self-sampling showed moderate agreement for specimen adequacy and substantial agreement in detection of cellular changes when compared to gynecologist sampling (Pengsaa et al., 2003). Later, Okayama et al. (2012) had retested the Kato device in Japan by setting up the Kato's specimen in liquid based preparation and compared it with the Kato's original recommended preparation method to see its ability to produce positive rates in PAP cytology. The study found the positive rates in liquid base preparation of Kato device was relatively higher than the original recommended preparation (Okayama et al., 2012). However the difference in the result can be disputed and might render a sampling bias because the specimen sampling and preparation of the two methods was done in separate clinics and taken from different set of patients. Moreover, most studies on self-sampling including self-sampling of Kato device had only been used to detect abnormal cytology but leaving the information on specimen's quality indicator such as the presence or absence of

endocervical or transformation zone cells. The presence of endocervical cells in cytology report is significant to help clinician to make decision whether to repeat the PAP test, as a part of patient management. Furthermore as HPV test is feasible through self-sampling, the Kato self-sampling device (KSSD) device is assumed to be functional for the application of HPV tests too. However, the KSSD has never been tested for HPV test.

Since KSSD shown good potential for sampling tools but still has limited data of its usage, a further study is important to verify the true validity of the sampling device in hope to be useful in Malaysia rural setting. In this study the Kato self sampling and gynecologist sampling among women screened at clinics in rural area of Jempol District, Negeri Sembilan, Malaysia were assessed for the PAP cytology test and HPV DNA detection. The study hypotheses were:

1.3 Hypothesis

1. The Kato self -sampling device (KSSD) is comparable/good agreement with gynaecologist sampling for PAP cytology results; in specimen adequacy, in collecting endocervical cells or transformation zone cells and in cytological interpretation.
2. The KSSD is comparable/agreement with gynaecologist sampling in the DNA quantity (DNA concentration) and the DNA quality of specimen collected, in detection of HPV DNA, and in detection of specific HPV genotypes, high risk HPV type and low risk HPV types.

1.4 Study Objectives

The general objective of study is to compare between self-sampling and gynecologist sampling of cervical specimen for PAP cytology and HPV DNA detection. The specific objectives were:

1. To determine socio-demographic (age, race, occupation) and menopausal status among the respondents.
2. To assess and compare the diagnostic agreement of specimen adequacy and presence of endocervical cells/ or transformation zone cells between specimen collected by KSSD and gynecologist.
3. To assess and compare the diagnostic agreement of cytological interpretation between specimens collected by KSSD and by gynecologist.
4. To compare DNA concentration and DNA quality between specimens collected by KSSD and gynecologist.
5. To detect HPV DNA and determine the diagnostic agreement of HPV detection between specimens collected by KSSD and gynecologist.
6. To detect and compare the diagnostic agreement of specific HPV genotype, high risk HPV and low risk HPV between specimen collected by KSSD and gynecologist.

1.5 Rationale of study

As there were very limited studies conducted in Malaysia on cervical cancer screening and women from the rural areas had been reported to have low awareness and participation in cervical cancer screening (Li, 2010), this study

intended to look at the device's potential as a screening tool in providing a solution to the problem. Hence, the purpose of the study was to evaluate the Kato's Self-sampling device (KSSD) in comparison with gynecologist- sampling technique, for both cytological Pap test and HPV DNA detection. The data from this study may provide a new approach for cervical specimen collection in Malaysia especially in rural area and also in countries where the population and environment are relatively similar in aspects of socio-economics, levels of education and accessibility to health facilities. Figure 1.1 showed conceptual framework of the study.

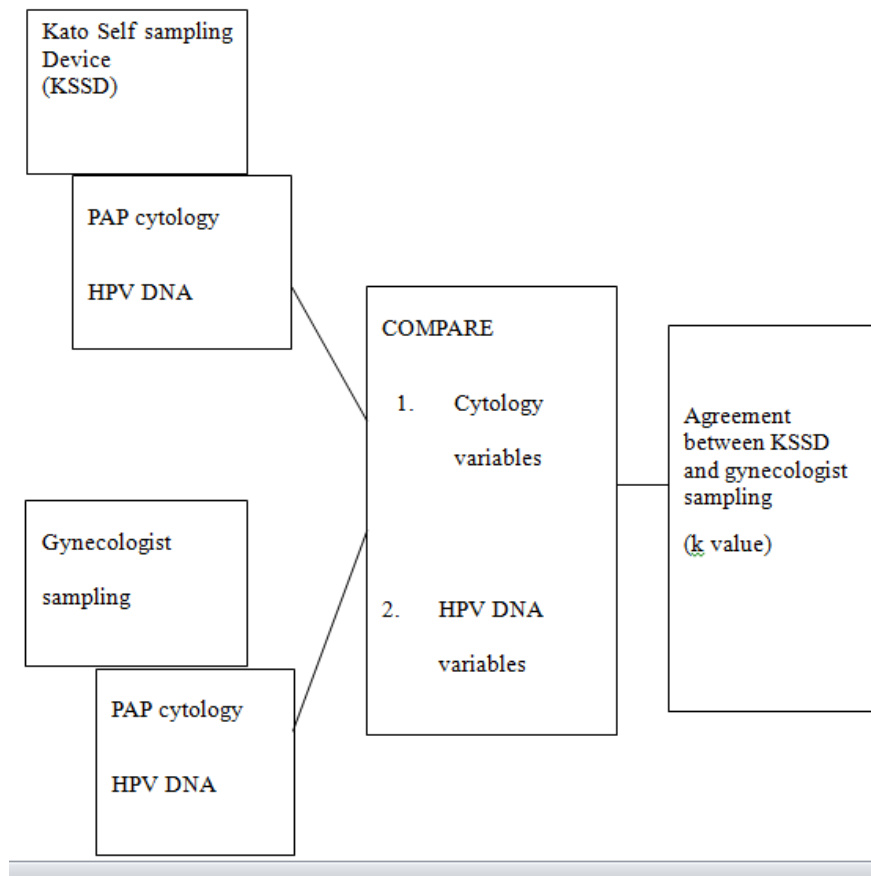


Figure 1.1: Conceptual framework of comparison between Kato self-sampling and gynecologist sampling of cervical specimen for pap cytology and HPV DNA detection.

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