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Acceptability and adequacy of vaginal self sampling for HPV DNA testing in cervical cancer screening among women attending a tertiary hospital clinics in Nairobi Kenya

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ACCEPTABILITY AND ADEQUACY OF VAGINAL SELF SAMPLING FOR HPV DNA TESTING IN CERVICAL CANCER SCREENING AMONG WOMEN ATTENDING A TERTIARY HOSPIATL CLINICS IN NAIROBI KENYA

By

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DEDICATION

This study is dedicated to all women especially women with cervical cancer who everyday contribute to the wealth of knowledge and provide us an opportunity to better the prevention and early management of cervical cancer

ABSTRACT

Background

Cervical cancer is a main concern of women's health globally. In Kenya, Cervical cancer is the second most common cancer in women and the leading causes of cancer related deaths.

Several screening methods exist including cytology, human papilloma virus DNA test and visual inspection with Acetic Acid or Lugol's Iodine (VIA/VILI). The current screening rate uptake in Kenya is poor, HPV DNA self-sampling may have a role in increasing the screening uptake as many studies have shown that self-sampling for HPV DNA testing is acceptable, though some others favoured over self-sampling. This study aims to assess whether vaginal HPV self-sampling is acceptable to women, and if the results are adequate compared to cervical samples taken by health care provider (HCP).

Study objective

Primary objective: to determine the acceptability of vaginal self-sampling for HPV DNA testing in cervical cancer screening among women attending tertiary hospital clinics in Kenya.

Secondary objective: to determine the adequacy of self-sampling for HPV DNA compared to HCP sampling.

Materials and Methods

A Cross sectional study was conducted at the gynaecology clinic from December 2018 to February 2019. One hundred twenty-four (124) women between 30 to 65 years of age were recruited. Women underwent self-sampling for HPV DNA, HCP sampling and Pap smear. Afterwards, the participants filled a post self-sampling acceptability questionnaire. A Likert scale was used to assess patient's acceptance to self-collected sampling.

Results

The mean age of the participants was 40.3years. The overall acceptability score for self-sampling was 23.2 out of 25 indicating a high acceptability rate for HPV DNA self-sampling. For the adequacy, a Cohen kappa of 0.935 was found which indicates a high level of agreement among

the self –sampling and HCP collected samples. The HPV DNA prevalence was 15.3% in HCP samples and 13.7 in self-samples.

Conclusion

The study demonstrated that HPV DNA self – sampling was highly acceptable and concordance rate was high between the self –sampling and the HCP sample results. Therefore, it is hoped that self- collection may have potential for increasing cervical cancer screening in Kenya.

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Virus
ASCUS	Atypical Squamous Cells with Undetermined Significance
AKUH	Aga Khan University Hospital
DNA	Deoxyribonucleic Acid
ECSA	East, Central and Southern Africa
ECSA-HC	East, Central and Southern Africa Health Community
HCP	Health Care Provider
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR-HPV	High-risk Human Papilloma Virus
HSIL	High-grade Squamous Intraepithelial Lesion
KAVI	Kenya AIDS Vaccine Initiative
LSIL	Low-grade Squamous Intraepithelial Lesion
STI	Sexually Transmitted Diseases
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organization

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Thank you all

DECLARATION

I declare this dissertation does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another person except where due reference have been made in the text.

(Signature of Candidate)

30th May 2019

Date

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CHAPTER ONE

INTRODUCTION (LITERATURE REVIEW)

Cervical cancer is a main global health concern and also a public health issue both in low and medium income nations. Cervical cancer ranks the fourth most commonly diagnosed malignancy in women globally surpassed only by breast, lung and colorectal cancers with about 570,000 reported cases per annum. It is also the fourth leading cause of cancer death with (311.000 deaths in 2018) in women worldwide (1, 2).

The leading cause of cancer related deaths and the second most common cancer among females in Kenya is cervical cancer, with 3,286 deaths and 5,250 new cancer cases per annum (3). About 70% of the global burden happens in developing nations (4). And in these zones; it is the number one cause of cancer death and premature death among women. One in every nine new cancer cases in those regions is cervical cancer (1, 4).

In addition to the high cervical cancer incidence and mortality rate on the African continent, about ten million people live with human immunodeficiency virus (HIV) and are consequently at significant risk for developing cervical cancer with premature deaths; thus making the screening and prevention crucial to this already susceptible women (5, 6).

In many central, east and southern African countries, cancer of the cervix accounts for most gynaecology cancer admissions in young females peaking in incidence at age 45 years; and over half the women come with late stage disease (7). The peak age for cancer of the cervix is 35-45 years, but for women with HIV/AIDS, cervical cancer usually occurs a decade earlier (8).

Cervical cancer is a uniform disease around the world in terms of etiology and pathogenesis, and found to be exclusively due to the effects of an infectious agent (HPV) (9). About 80% of women who is sexually active will become infected with HPV at some point in their life, with peak incidence time being shortly after becoming sexually active (10). Luckily in young women more than 80% of HPV infections are transient and resolve naturally without causing any symptoms due to natural cell-mediated immunity. Thus HPV DNA testing is not suggested as the principal screening method for women below 30 years of age (3).

The major risk factor for cancer of the cervix is persistent infection of the 15 high risk HPV DNA strains, with type 16 and 18 causes around 70% of the total number of cases (11).

Other risk factors include multiple sexual partners, first sex at young age, immunosuppression like (HIV) and tobacco smoking are all cofactors to persistent HPV infection and progression to cervical cancer (12).

Human Papilloma Virus (HPV)

The human papilloma virus is a DNA virus which causes proliferation of the epithelium at mucosal and cutaneous layers. Over hundred different strains exist, 30 to 40 of these types infects the genital tract of humans. "(Types 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58)" are the high-risk strains which are related to vaginal, vulvar, cervical and anal cancers. Low risk-types which are associated with genital warts are (type 6, 11, 40, 42, 43, 44, and 54) (13). The most oncogenic among them all is HPV 16 causing almost half of all cervical cancers, HPV 16 together with HPV 18 accounts for about seventy percent of cervical cancers (14).

HPV infection of the cervix is transmitted during sexual intercourse, and it has a tendency for the metaplastic squamous epithelium. It may remain latent for long periods or become productive, with release of infectious virus in the terminally differentiated squamous epithelium.

The morphologic hallmark of HPV infection of the cervical squamous epithelium is koilocytosis also called (koilocytic atypia), the change in these cells is thought to be affiliated to manifestation of the viral E4 protein and the interruption that this causes in the cytoplasmic matrix of the keratin.

Koilocytes are the intermediate or superficial squamous cells with irregular and large defined perinuclear halos and a cookie cutter border with thickening of the cytoplasm; nuclear enlargement (2 to 3 times' normal size) which is charcoal black.

Screening for cervical cancer

Cervical cancer is a preventable disease; when recommended screening guidelines are strictly followed. There are several screening approaches for cervical cancer. These include cytology (conventional, liquid based, automated pap), HPV DNA test and visual inspections (VIA/VILI).

The primary advantage of screening is to identify and treat women with premalignant lesion before they develop cancer. Furthermore, screening can detect women with early stages of cervical cancer when it can still be effectively treated. Timely detection, through screening all females in the target age group, with subsequent treatment of diagnosed premalignant lesions prevents majority of cervical cancers and decrease mortality (15).

The benefits of cervical cancer screening have been clearly demonstrated in several studies. In 1960s, Sweden, Finland and Iceland adapted screening programs for their women but Norway did not implement. The four countries incidence for cervical cancer was similar before screening but fell by half within two decades, in the countries that adapted screening. Norway saw no such reduction (9). Thanks to the national screening programme implementation the Canadian Cancer Institute has also demonstrated a threefold decrease in the age-standardized mortality rate from invasive cervical cancer between 1969 and 1990 (11).

In Africa, data reported from different countries show variations. In Uganda, data from the cancer registry from 1991-2010 showed an increase of the incidence rate (1.8% per year) although the rates appeared to be declining from 2006 to 2010 owing to the screening programs offering VIA and preventive treatment measures like cryotherapy that has been implemented (16).

Findings from WHO report shows that in developing countries only less than five percent of women are screened for cervical cancer annually, in contrast to developed countries where rates are 45-50% (13). In Kenya, only 14% of women have undergone cervical cancer screening (17).

The standard practice for screening and managing cervical cancer in high income countries is to screen women with cytology (Pap test) and refer the women with abnormal cytology for colposcopy and biopsy of the suspicious lesions. The challenges in applying and sustaining the standard cytology screening in low income countries led to the development of other screening programs such as visual inspection with acetic acid (18). Such programs have been implemented in some of the low and middle income countries like Bangladesh and Zambia and have been quite successful, but because of the barriers in accessing screening centers and issues related to women's participation still makes this option a challenge to implement effectively (19, 20).

In Kenya, all screening methods for cervical cancer are recommended including VIA/ VILI, Pap and HPV DNA (8), as the World Health Organization (21) recommendation for resource constrained setting where HPV test is not feasible is to screen with VIA and treat (22).

The Summary of the Kenya national guideline for cervical cancer screening is as follows (8):

"Any woman who has ever had sexual intercourse is eligible for cervical cancer screening. The target group is women between 25-49 years of age.
Screening is not recommended for women above 65 years.
HPV testing is recommended as the primary screening method for women above 30 years of age.
Where HPV testing is not yet available, or loss-to-follow-up is a risk, then Visual Inspection with Acetic acid (VIA) or Visual Inspection with Acetic acid and Visual Inspection with Lugol's iodine (VIA/VILI) is recommended as the primary screening method

Pap smear is recommended as a primary screening method in the following situations:

For women not eligible for VIA or VIA/VILI because their squamo-columnar junction (SCJ) is not visible, and HPV screening not accessible
As a primary test in women under 30 years of age
As a co-test with HPV in HIV positive women where the resources are available
Women who are HIV positive or immune-suppressed for any other reasons.
Begin cervical cancer screening at the point of diagnosis or at 25 years, whichever comes earlier
Screening should continue throughout their lifetime
Screening frequency should be yearly if using VIA or VIA/VILI, every 2 years if using HPV testing and yearly if using cytology
Screening can be done during the 1st trimester of pregnancy".

HPV DNA test

Testing for HPV DNA promises to be a more sensitive screening test for cervical cancer. In a cluster randomized controlled trial in rural India, women who had no or very little screening for cervical cancer were randomized to either Pap smear test, human papilloma virus testing, or VIA. Incidence of advanced cancer was lower in women who had one HPV screen compared to no intervention. No significance reduction in the figures of advanced cancers were observed in the cytology-testing group or in the VIA group as compared with the control group (23).

The conclusion of the authors was that in a low income setting, a solitary round of HPV testing has a considerable reduction in numbers of invasive cervical cancers and mortality from cervical cancer. A recent follow up of four European randomized trials has shown that screening with HPV DNA delivers 60-70% greater protection against invasive cervical cancer compared with cytology (24).

Cost effectiveness of cervical cancer screening in five unindustrialized nations was studied by Goldie et al; he mentioned that those required fewest appointments were the most effective strategies resulting in better follow-up testing and management. Screening women once in their life time with a single visit using VIA or HPV DNA testing at 35 years age reduces the lifetime risk of cancer by 25-36% and cost less than $500 per year of life saved. With a negative HPV DNA result, one can reduce screening to once every 5 years thus reducing the number of clinical visits needed (25).

HPV DNA testing can either be done by a health care provider during a speculum exam or by self-sampling by the women. Self-collection uptake showed HPV DNA from these samples is very sensitive for detection of precancerous lesions. A systematic review of 25 studies (26) showed that women were greatly successful in collecting samples for HPV DNA testing. In three of the studies it was found that the quality of samples from patient was as good as HCP samples with more than 95% of samples yielding HPV results (27-29).

The level of acceptability in previous studies showed different outcomes. Study done in rural china showed a high acceptability to self-sampling (30).Yao Yao et al found that the mean overall acceptability to self-sampling was 4.3 out of 5 which indicates a high acceptability rate.

A multi-center international study conducted in three different countries (India, Nicaragua and Uganda)showed that 75% of the participants reported the self-sampling test was easy to do and 52% were worried about hurting themselves, while 24% were concerned of not getting a good sample (31).

Other study done in Mombasa, Kenya with 200 women showed a poor acceptance rate for HPV DNA self-sampling with acceptability of only 32% to self-sampling compared to 68% of physician sampling (32). Qualitative study done in London, United Kingdom on Muslim

women's attitude to self-sampling for HPV DNA showed most women prefer sampling by a health provider; feared they may not do it correctly (33).

This study seeks to find out if women attending an outpatient clinic in a tertiary hospital in Nairobi Kenya would be receptive to screening of cervical cancer by self-sampling. It is hoped that this will increase the uptake of cervical cancer screening. It will be important to ensure that self-collected samples for HPV DNA are as adequate as those performed by a health care provider during a pelvic examination to allay fears that self-samples are not as adequate by the general population as well as health care providers and the public health stakeholders.

STUDY JUSTIFICATION

Given the findings that HPV DNA testing has been shown to decrease the numbers of advanced cervical cancers and deaths from cervical cancer, as well as the greater protection against invasive cervical cancer; This study was being conducted to determine the acceptability of self-vaginal HPV DNA sampling in the local population in order to determine if implementation of the same would eliminate the need for physician guided speculum sampling. It is postulated that if acceptable, self-sampling may improve screening rates.

RESEARCH QUESTION

What is the acceptability of vaginal self-sampling of HPV DNA testing in cervical cancer screening among women attending clinics at a tertiary hospital in Nairobi Kenya?

STUDY OBJECTIVES

Primary objective

To determine the acceptability of vaginal self-sampling for HPV DNA tests, for cervical cancer screening among women attending Clinics at a tertiary hospital in Nairobi Kenya.

Secondary Objective

To determine the adequacy of self-sampling for HPV DNA compared to HCP sampling.

CHAPTER TWO

MATERIALS AND METHODS

Research design

Cross-sectional analytical study

Study variables

Dependent variables: the acceptability of vaginal self-sampling for HPV DNA.

Independent variables: include socio-demographic features including (Parity, marital status, age, educational level, race, religion and residence).

Research Location

This study was conducted in the Gynecology clinic and Aga Khan Outreach clinics in Nairobi.

Study Population

Women between 30 to 65 years attending the Gynecology clinic and Aga Khan Outreach clinics in Nairobi.

Inclusion Criteria

All sexually active women between 30 to 65 years, who are having a Pap smear test.

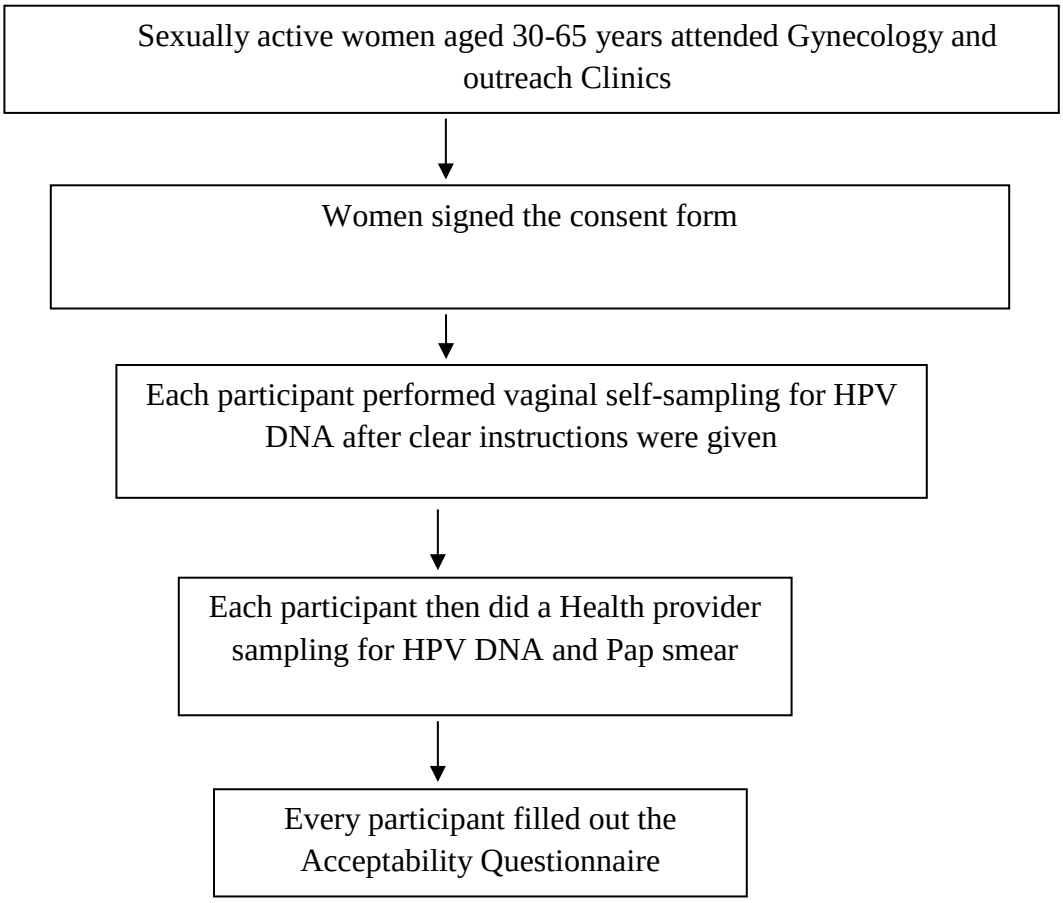
Exclusion Criteria

Currently on menses

Pregnant

History of hysterectomy

Study Flow Chart



Research Tools

A Likert scale questionnaire designed and adopted from previous studies was used to measure the acceptability rate of vaginal HPV DNA self-sampling of the participants. For the adequacy; two different brushes were used for collecting vaginal self-sampling and health worker sample.

Sampling Procedure

The participants were recruited from gynecology and outreach clinics. All eligible participants were approached and enrolled in a consecutive manner until the required number of participants was achieved. Women started by signing the consent form after receiving a brief education session on cervical cancer, HPV and benefits of screening. A model/cartoon picture was used to describe the method of performing the self-sampling procedure; an explanation was also given for the pelvic examination procedure on the use of speculum for the HCP sample and the Pap smear test.

Women started by taking the self-sample in a private room using Qvintip brush, and then underwent through pelvic examination with obtaining a health worker sample for HPV DNA and a Pap smear sample.

Finally, all participants completed the acceptability questionnaire which is composed of two sections, a socio-demographic detail and a Likert scale questions about acceptability. Acceptability questionnaire is detailed in appendix 2

Self-Sampling procedure

The participants used the Qvintip brush for collecting their samples, they started by gently pushing the Qvintip self-sampler brush in to the vagina until they felt a resistance afterward, they made a circular brushing with repeating it as they turn the brush 3 times, then pulling the brush out slowly. Next the brush was inserted in to the transport tube after bending the shaft.

Samples are then taken to the lab and were kept in -80ºC freezer before transferring it to Kenya AIDS Vaccine Initiatives KAVI laboratory at Kenyatta National Hospital for analysis. Sampling device description: Qvintip is a single used self-sampler kit which analysis for high risk HPV DNA, it can be used for vaginal and ectocervical sampling.

Health provider sampling procedure

A pelvic examination was done by using a speculum to visualize the cervix, HPV DNA and Pap smear samples was obtained by using a brush to collect the HPV DNA sample and a broom for Pap smear collection, after obtaining the sample the brush was put in a tube with a transport media after breaking the shaft at the marked line.

Data Collection Procedure

All collected HPV DNA samples for both self-sampling and health provider sample were labeled with three identifiers (two Aga Khan identifiers and one given by the primary investigator) and kept in -80ºc freezer before sending the samples to Kenya AIDS Vaccine Initiatives (KAVI) laboratory at Kenyatta National Hospital for DNA analysis. The filled acceptability questionnaire was collected and kept in a locked cabinet, before loading the data in to excel sheet.

Procedure for HPV DNA analysis through HYBRID CAPTURE II

1. Labeling the hybridization micro tubes and preparing denaturation reagents
2. Pipetting denaturation reagents with a volume equal to half of the sample volume into (calibrators, quality controls and samples).
3. Afterword all samples will go individually through vortex including the calibrator and quality controls at high speed for five seconds, all samples should turn in to purple color.
4. Incubate samples at 65±2ºC for 45±5 minute using a water bath.
5. HPV probe mix preparation.
6. Mixing the denatured samples well then pipetting 75µl in to the tubes and incubating for 10 minutes at 20-25 ºC.
7. Pipetting 25µl high risk HPV probe mix into the tubes and covering the micro tubes with a plate lid and vibrate on Rotary shaker l at 1100±100 rpm for 3 ± 2 minutes, all tubes must show yellow color.
8. Incubation for 60±5 minutes at 65±2ºC, followed by microplate preparation.
9. Transfer the subjects from all hybridization plate well to matching well in microplate capture by 8-channeled pipette and seal with a plate lid. Then quiver at 1100±100 rpm at 20-25 ºC for 60 ± 5 minutes. Mix the washing buffer.
10. Pour and blot microplate capture.

11. Pipette in-to every well of microplate capture a 75µl of detection substance 1, and seal with plate cover. Incubate for 30–45 minutes at 20–25ºC.
12. Decant and blot capture microplate and wash 6 times with buffered water, afterward blot on lint-free paper towel.
13. Pipette in to every well of microplate capture a 75µl of detection substance 2 and Incubate for 15–30 minutes at 20–25ºC.
14. Reading the microplate capture on luminometer and validating assay with interpretation of the results.

All high-risk HPV types including "16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68"; were tested and the result was either negative or positive. However, the test did not identify the specific HPV type which was present.

Data management analysis

A complete data of the questionnaire, results from both HPV DNA samples were entered into excel sheet then transferred to SPSS Version 20 for analysis.

A five item Likert scale tool was used to measure the acceptability of self-sampling for HPV DNA. Five different categories of questions which are Ease, Convenience, Embarrassment, Discomfort and Confidence about HPV DNA self-sampling were rated by the participants by choosing options from 1 to 5 in the Likert score, 1 being strongly disagree and 5 is strongly agree. The sum of the scores was obtained with a minimum sum of 5 and maximum of 25. We used mean and (SD) to determine the acceptability by using descriptive statistics.

Socio-demographic details of the participants were analyzed using mean (SD) and median (IQR) for continuous data; and for categorical data, a frequency and percentages was used. Linear logistic regression was used to determine socio-demographic factors associated with the acceptability of self-testing.

A calculation of sensitivity and specificity was done for self-sampled HPV DNA results using the HCP obtained samples as a reference standard and then a Cohen-Kappa test is used to assess the level of agreement between the two tests.

Sample size calculation

To calculate the sample size a Likert scale formula was used as shown below (34).

$$n = \frac{z_{\frac{\alpha}{2}}^2 \cdot C^2}{kD^2}\{1 + (k-1)\rho\},$$

"Where

$Z\alpha/2 = 100(1-\alpha/2)$ the percentile of the standard normal = 1.64 (90% level of significance)

C = Coefficient of variation of each=1

D = Relative tolerable error (desired precision of the estimate) = 0.1

k = No of items/questions in the category or domain of interest = 5

ϱ (rho) = Pair wise correlation coefficient. For different items within each respondent = 0.3"

This gave 118 sample size, and after adding 5% attrition, the final sample size for this study was 124.

Ethical consideration

Ethical approval was obtained to conduct this study from the research ethics committee of the University before commencement. Participants were assured that their participation is voluntary and they can decline to continue at any time during the study. Informed consent was taken from each participant who accepted to join the study (appendix 1). Discomfort was not more than expected in standard practice for HPV sample collection by HCP. Clients were given full instructions on self-collection samples to minimize discomfort & injury. All information obtained was maintained with highest confidentiality. The cost of both self-sampling and HCP collected HPV DNA samples were covered by the project.

CHAPTER THREE
RESULTS

Socio-demographic characteristics

A total of 129 women were initially approached to participate in the study. Five of them declined to be enrolled due to lack of interest in self-sampling. The other 124 women agreed and consented to join the study.

Women aged 30 to 65 years were recruited; the mean and median age of the 124 women in the study was 40.3 and 39.0 respectively with standard deviation of 8.6. Age distribution histogram of the 124 women is shown in figure 3.1. Most women (42) fell in the 30-34 years age group and the lowest age group was those aged 60-65 years old accounting only 3 cases.

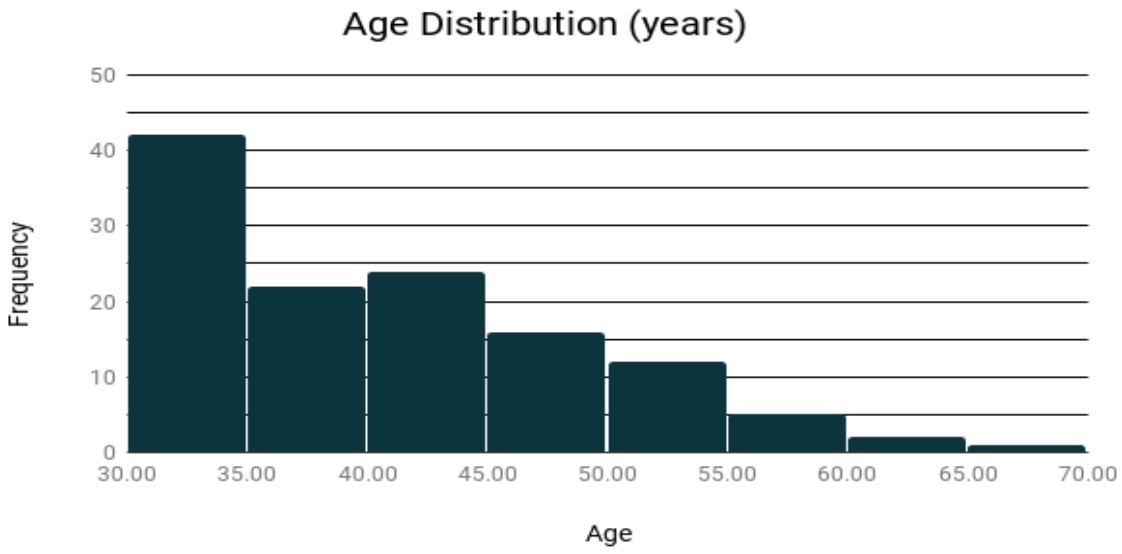


Figure 3.1 Age distribution of the participants

Most of the women, 95 (76.6%) were married; majority of them had two children (mean of two). The most self-reported race was African 121 (97.6%) followed by Asian two (1.6%). Seventy four percent of the participants were Nairobi residents and the remaining proportions were from other Kenyan counties and foreign countries. Most of the study participants were well educated, 83.1% had university level education and only 2.4% had less than secondary school education.

Only two women (1.6%) reported smoking, while approximately 30% of the women had a family history of cancer. Majority of the women (70.2%) had a previous Pap smear test done. The full detailed socio-demographic characteristics of all the participants including each variable result are shown in Table 3.1

Table 3.1 Socio-demographic characteristics of the participants

Variable	Frequency	Percentage %
Age: Mean (SD); Median (IQR)	40.3 (8.6); 39.0 (33-45)	
Marital Status:		
Single	29	23.4
Married	95	76.6
Parity: Mean (SD)	2.4 (2.1); 2.0	
Ethnicity %		
African	121	97.6
Asian	2	1.6
Caucasian	1	0.8
Residence %		
Nairobi	92	74.2
Other Counties (in Kenya)	24	19.4
Other Nationalities	8	6.5
Religion %		
Christian	113	91.1
Islam	8	6.5
Atheist	2	1.6
Hindu	1	0.8
Educational level %		
Basic	3	2.4
Secondary	18	14.5
University	103	83.1

Smoking Status %		
Yes	2	1.6
No	122	98.4
Family History of Cancer %		
Yes	37	29.8
No	87	70.2
Previous Pap Smear %		
Yes	87	70.2
No	37	29.8

The education background of most of the participants was University level 103 (83.1%); those women with basic education were only 3 (2.4%). Full details are shown in the below figure 3.2

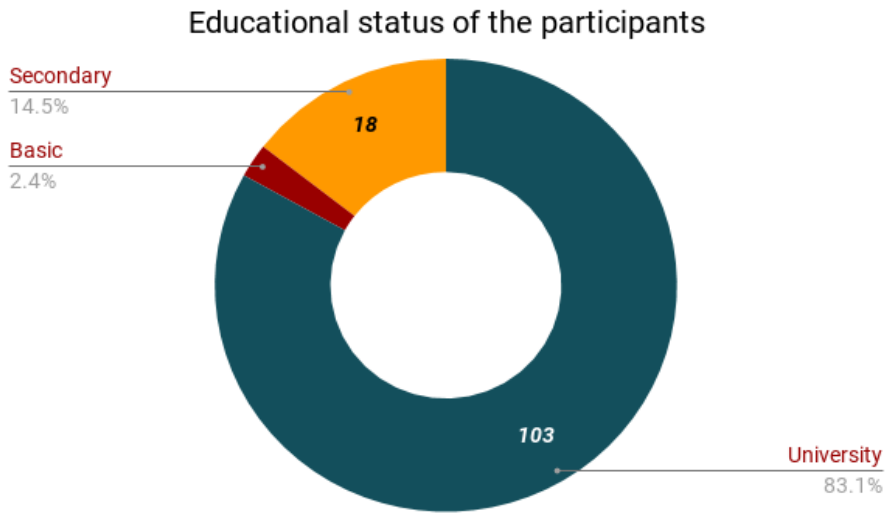


Figure 3.2: Educational status of the participants

Majority of the women 87 (70.2%) had a previous Pap smear test done and about 37 (29.8) had never had Pap as shown in the below figure 3.3.

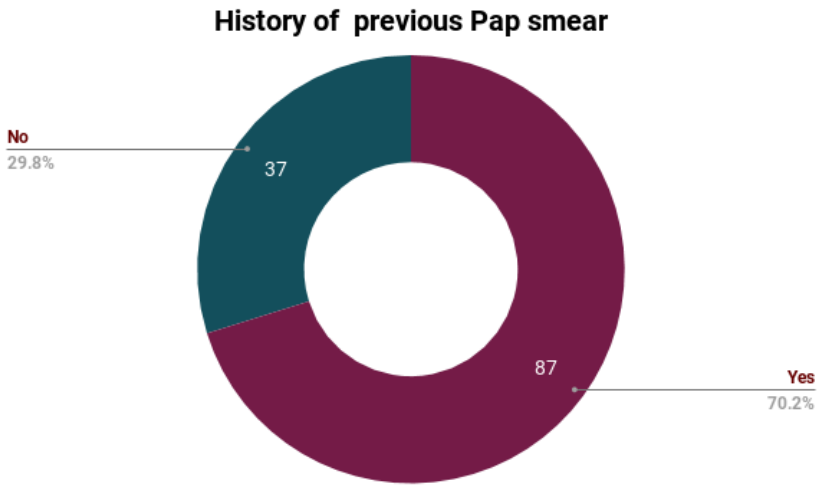


Figure 3.3: History of previous Pap smear

Acceptability of HPV DNA self-sampling

Regarding the acceptability of HPV DNA self-sampling, we summed the numbers in the rows of each women's five indices of the Likert score. The sum of each participant's score that could be obtained was a minimum sum of five indicating poor acceptability and a maximum of 25 indicating high acceptability. In this study, the overall acceptability score of all women for HPV DNA self-sampling was 23.2 which indicates that majority of the participants found the self-sampling technique is highly acceptable.

Analysis of each of the five acceptability indices (ease of collecting the self-sampling specimen correctly, convenience, embarrassment felt during the self-collection procedure, discomfort felt during the procedure and the confidence which is the ability to collect the self- sampling

specimen correctly) was also carried out as shown in Table 3.2. A minimum of one and a maximum of five are obtainable from each of the above indices when analyzed. The mean score of all the study participants in each of the five acceptability indices was above 4 which indicate the self-sampling HPV DNA technique was acceptable. Confidence, the ability to collect the self-specimen correctly had the lowest mean score of 4.36 and the embarrassment from the self-sampling procedure had the highest mean score of 4.74. The scores and the standard deviations of the five indices are shown in Table 3.2

Table 3.2: Acceptability score for HPV DNA self-sampling

	Mean(90% CI)	Standard deviation
Overall Acceptability	23.2	2.5
Easiness	4.69(4.60-4.77)	0.63
Convenience	4.72(4.59-4.83)	0.79
Embarrassment	4.74(4.59-4.84)	0.76
Discomfort	4.72(4.61-4.80)	0.63
Confidence	4.36(4.21-4.51)	0.95

A score of 1 = less; a score of 5 = more

Adequacy of self-sampling compared to the HCP

The HPV DNA prevalence in this study was 15.3% in HCP samples and 13.7 in self-samples. The HPV DNA concordance rate between HCP sampling and the self-sampling specimens were compared using an exploratory analysis to calculate the sensitivity and specificity of self-sampling HPV DNA by taking the HCP collected samples as a reference (or gold standard). Then a Cohen kappa test was used to measure the level of agreement between the two tests.

The sensitivity and specificity of the HCP sampling was 89.5% and 100% respectively while the sensitivity and specificity of the self-sampling was 100% and 98.1% respectively. The level of agreement between HPV DNA HCP sampling and HPV DNA self-sampling was 0.935 indicating a high level of agreement. Details of the sensitivity and specificity are given in table 3.3

Table 3.3: Concordance rate between HPV DNA Health care provider and HPV DNA self-sampling

	HPV DNA Health care provider Sample		
HPV DNA self-Sample	Positive n (%)	Negative n (%)	Total
Positive	17 (13.7%)	0	17
Negative	2	105 (86.3)	107
Total	19 (15.3%)	105 (84.7)	124

Pap smear test results

The target population of study was women who came to have a Pap smear test; their results showed that close to 90% of them had a normal pap smear (negative for cervical intraepithelial lesion). Few women were diagnosed with cervical intraepithelial lesions, ASCUS being the most frequent with 5.6% followed by HSIL at 2.4% and LSIL at 1.6%. All women with ASCUS had a negative HPV DNA, while women with LSIL and HSIL had a positive HPV DNA in both samples (self-sampling and HCP samples).The detailed results of the Pap smear results are presented in Table 3.4.

Table 3.4 Pap smear results and their respective HCP HPV DNA results.

Pap smear results	***Total*** **Frequency/percent**	**HPV DNA (negative)**	**HPV DNA (Positive)**
Negative	*112 (90.3%)*	*98*	*14*
ASCUS	*7 (5.6%)*	*7*	*0*
LSIL	*2(1.6%)*	*0*	*2*
HSIL	*3 (2.4%)*	*0*	*3*
Total	*124*	*105*	*19*

Linear logistic regression was used to determine socio-demographic factors associated with the acceptability of self-testing. As indicated in the Table 3.5 below, no statistical significance was found.

Table 3.5 Socio-demographic factors in correlation with acceptability

Over all Acceptability	Coefficient	P-value	90%CI
Marital Status			
Single	0.399	0.506	-0.594-1.393
Married	Reference		
Age	-0.004	0.904	-0.055-0.048
Parity	-0.199	0.139	-0.419-0.022
Ethnic Groups			
African	3.860	0.091	0.898-6.822
Caucasian	Reference		
Residence Groups			
Nairobi	-0.674	0.224	-1.829-0.240
Other countries	Reference		
Religion Groups			
Christian	-1.035	0.271	-2.587-0.517
Islam	Reference		
Education Groups			
University	-0.519	0.444	-1.639-0.601
Basic	Reference		
Previous PAP			
Yes	0.109	0.835	-0.757-0.976
No	Reference		
Family history Cancer			
No	Reference		
Yes	0.258	0.619	-0.598-1.113

CHAPTER FOUR

DISCUSSION

Cervical cancer is the leading cause of cancer related deaths among women in Kenya; However cervical cancer is preventable if the screening guidelines are followed (3). Screening and early detection with management of pre-cancerous is the best way to reduce both the incidence and mortality burden from cervical cancer.

The study has focused on one of the most feasible screening methods for cervical cancer screening, the HPV DNA; because of high sensitivity rate and it is the only test amenable to self-sampling (24). In Kenya, the national guidelines for cancer screening recommends Human papilloma virus DNA test as one of the primary cervical screening ways for women above 30 years of age since HPV infection in younger women is most often transient (3).

There are two ways of collecting a sample for HPV DNA testing; the traditional method which is collected by a HCP (physician or a nurse) using a speculum. The other method is the self-collection method, where women collect their own samples.

This study was mainly conducted to determine the acceptability of self-sampling for HPV DNA in women who attend tertiary hospital clinics in Nairobi. All the participants were in the recommended screening age population (30-65 years old) as the guidelines of national cancer screening in Kenya, WHO and many international organizations including the American Society of colposcopy and cervical biopsy recommend (2, 3, 35).

None of the socio-demographic characteristics of the participants had any association with the acceptability level of self-sampling in this study. However, our study was not sufficiently powered to conduct this exploratory analysis hence the possibility of a type II error. Previous studies have shown mixed results about correlations between certain socio-demographic factors and acceptability level. Age of the woman, educational background, religion and previous Pap were reported as the most significant factors (30, 36-38); in this study, none of these factors had correlation with the acceptability of self-sampled HPV DNA test. Interestingly, a high percentage (70.2%) of women in this study reported to have had previous Pap test. This is unlike the overall reported cervical cancer screening rate in Kenya of 14% (17); the difference noted in this study may be due to the fact that our target population ware women coming to the clinics for

Pap smear test with higher educational level; therefore likely to be more aware of the benefits of cervical cancer screening. Majority of the women in this study (74.2%) live in Nairobi, with 83.1% having a tertiary education level. the study findings may not be generalizable for both urban and rural women.

Participants of this study showed a high acceptability level to HPV DNA self-sampling. The findings of this study are consistent with previous studies conducted in the region and globally. Seven out of 37 studies in a systematic review with a total 1470 women found a 97% acceptability rate to self-collection (39). The participants in these studies preferred the self-sampling because of its ease, convenience and privacy, lack of embarrassment and greater self-involvement of their own medical care. In comparison, lower embarrassment compared to HCP sampling, privacy and convenience of the self-sample collection had the highest scores of acceptability in our study.

A recent study from Senegal, a sub-Saharan African country with similar epidemiological features as Kenya assessed the feasibility and acceptability of HPV DNA cervical self-sampling and recruited 136 women in their reproductive years, found 98.5% acceptability of self-sampling. Moreover, the women in that study provided adequate samples indicating the self-sampling technique was not only highly acceptable but also acceptable in adequacy (40).

In another study of a rural community in Gambia, by Lack N et al found an acceptability rate of 97.1% in 377 women; a major drawback of this study was the lower number enrolled of the overall eligible women, 946 (41).Our results are also similar to a recent study in rural Malawi, where 200 women enrolled showed an acceptability to self-sampling of 99% (42).

A study about knowledge and acceptability of Pap smear and self-sampling conducted in Kenya by Rositch et al between 2007 to 2009 showed that 80% of the participants felt comfortable with self-sampling especially when the sample was taken at home (37). Although a high acceptability score is reported in the above study, the woman did not have the real experience to perform the self-sampling procedure and the study was limited to the use of a questionnaire. In contrary, our study participants experienced the self-sampling method and filled the questionnaire afterwards, therefore the acceptability level obtained in our study is probably more reliable. Another study performed in Mombasa by Manguro et al from 2013 to 2015 with 200 women show

contradicting results, a preference and acceptability of only 32% to self-sampling compared to 68% of HCP sampling. Reliability of the self-collected sample results was the strongest factor contributing to the low preference and acceptability in the Manguro et al study; as 59.1% of women who collected their own samples had concern about the results' reliability compared to only 1% of those collected by a HCP (32).

We believe these two studies had different primary objectives other than acceptability and the women's socio-demographic characteristics were different from those of the women in our study; Most importantly their educational background was lower than our study population as there is a clear association between educational level and confidence and acceptability for the self-sampling (36). The Manguro et al study in Mombasa enrolled young women (<30years old), this may be explain the lower acceptability rate reported in their study. Studies have shown that young women have less confidence in collecting and performing the self-sampling correctly compared to the elder women.

Globally, a Mexican study with a larger sample size recruiting women in reproductive years found that women had higher acceptability of HPV DNA self-sampling compared to HCP testing because they believed the self-sampling was less painful, more comfortable, less embarrassing and they were more confident in their ability to do it correctly (43).

Similarly, a study performed in rural China showed a high acceptability to self-sampling (30). Yao Yao et al found that the mean overall acceptability to self-sampling was 4.3 out of 5 which indicates a high acceptability. The Chinese women in the study had lower scores for the confidence to collect the self-specimen correctly. Although the confidence score in our study was the lowest compared to the other items with in the questionnaire, it still has a higher score compared to the Yao Yao study.

This difference may be related to the educational level of their study population as the authors even mentioned or cultural differences; Most (83.1%) of our study participants had a university level education compared to majority (88.5%) of the Chinese women who had only middle school or lower educational background (30). It has been shown that African women have less confidence that they can perform self-testing correctly, in a diverse population study in United

Kingdom with Africans and Indians having an attitude of doing the self-test less correctly than other ethnic groups (44).

Regarding the adequacy of HPV DNA self-sampling test in this study, a high concordance rate was noted between HCP collected samples and self-sampled HPV DNA test. Prior studies comparing the concordance rates between the two tests showed an excellent level of agreement (42, 45, 46). Esber et al, in a study in Malawi reported a high level of concordance between physician and self-collected samples (42). Other Studies from Uganda, South Africa and Brazil support this finding of high agreement with a kappa value ranging from 0.70 to 0.87(45-47). Although the three studies found a similar level of agreement, variations exist between the current study and theirs. Firstly, the study from Uganda used both hybrid capture II to detect HPV and PCR for genotyping but this study used Hybrid capture II only. Secondly, the South African study targeted adolescents and their sample size was only 15 cases. Lastly, the Brazilian study recruited a larger sample size, but younger women were included (15-69 years). The level of agreement between the two tests in our study was 0.94 indicating an excellent concordance between HCP and self-collected samples.

Prevalence of HPV in this present study was 15.3% in HCP collected samples and 13.7% in self-collected samples. The prevalence rate in this study is lower than the reported prevalence in other studies in Kenya and the region. Bruni et al shown a prevalence of 20% in Kenya, Uganda and Tanzania and a rate ranging 40-70% in other sub-Saharan African countries (48). A study in Mombasa reported a high risk HPV prevalence rate of 28.8% among 496 women; we believe their rate is high due to their enrolment of younger women, 15 years and above and it is known that HPV is common in younger women, but that it is transient and most women clear up the virus and it is not recommended to screen women less than 30 years of age (49). The worldwide HPV prevalence in adult women is 11.4% (48); this indicates a higher prevalence of HPV in Kenya and also in the region.

The target population of this study was women who came to have Pap smear test, 90.3% had normal cytology (Negative for intraepithelial lesion). Of these, several women tested positive for HPV DNA, which show the high sensitivity of the HPV DNA test (50). In terms of sensitivity, those with a lesion tested positive for HPV DNA, but not all who tested HPV positive had a lesion in the Pap smear test (specificity).

HPV DNA testing is available and offered in both public and private laboratories in Kenya mainly in the big cities; it is worth noting that public facilities perform these tests with less cost than private laboratories.

This study has several unique strengths. Most of the studies in Kenya, to our knowledge have focused on preference and majority of these studies have enrolled populations at high risk of cervical cancer. But our study evaluated normal population without targeting any specific group and they were able to report on real experience of self-sampling and compare it with the health care provider sample collection, unlike the other studies. In addition to that, both young and elder women (30-65) were included in our study thus making our results generalizable to both young and elder women. The technique used to analyze the HPV DNA samples was Hybrid capture II which is one of the globally standardized methods.

Study Limitations

The study is conducted in an urban population and majority of women undergone a previous Pap smear screening and had high level of education so the generalizability of our study to rural women may be affected by those factors.

None of the socio-demographic characteristics of the participants had any association with the acceptability level of self-sampling in this study. Because our study was not sufficiently powered to conduct this exploratory analysis hence the possibility of a type II error

Study is done in a private health facility where most participants can afford the health care, this may be a selection bias and result may differ if it is conducted in a public facility.

Conclusion

Vaginal self-sampling for HPV DNA as a screening tool for cervical cancer is highly acceptable in non-high-risk Kenyan women presenting to tertiary hospital clinics in Nairobi. The world Health Organization recommends HPV DNA test as the preferred method for cervical cancer screening in developing countries.

HPV DNA self-sampling is an acceptable and efficient method that may increase the cervical cancer screening coverage in Kenya both in women who have access to or those who have no access to preventive screening programs

Recommendations

1. Health facilities in Nairobi should consider using HPV DNA test as one of the primary cervical cancer screening method in line with WHO recommendations. Currently the method is used worldwide but with variations in its uptake. This is the only screening method that women can perform themselves.

2. AKUH should start to offer the self-sampling for HPV DNA. And a subsequent study could be done, in order to determine if this indeed increases cervical cancer screening rate.

3. Further, similar studies should be performed on population with more representation of the population with respect to socio-cultural, economic, and religious diversity.

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APPENDICES

APPENDIX ONE

Consent Form

AGAKHAN UNIVERSITY HOSPITAL, NAIROBI-KENYA

Name of Principle Researcher: Dr. Patricia Muthaura

Supervisors: Dr. Patricia Muthaura, Prof. Lucy Muchiri, Dr. Samuel Gakinya

Principle Researcher's Note:

Thank you for accepting to read this form. This informed consent form has two parts:

A. Information Sheet (gives you information about the study)
B. Consent form (this is where you sign if you agree to participate)

Part I: Information Sheet

Introduction of Study: Cancer of the Cervix (opening of the uterus) is a major problem in the Kenyan population and it is the fourth commonly diagnosed cancer in women worldwide. Currently, there are several screening methods available in the country each with its limitations. Understanding the best screening method for the Kenyan women would decrease both the number of advanced cervical cancers and deaths. Traditionally the sample for screening has been taken by a doctor or a nurse for a variety of tests which are carried out in the laboratory. Other methods now include having the women take the sample herself.

Purpose of the Study: to determine the acceptability and adequacy of self-sampling for cervical cancer screening.

Choice of participation

Your participation in this study is voluntary and you can decline to continue at any time during the study. If you decide not to be in this study, it is ok and you will still receive the health services to which you are entitled in this institution.

Procedure of Study:

If you accept and give consent to participate in this study:

A. Your details will be recorded in the data collection form
B. Do cervical vaginal self-sample (you will be taught how to perform)
C. A HCP will take cervico-vaginal sample from you (both for HPV DNA and Pap smear)
D. Fill out Acceptability Questionnaire

Risks and benefits of study participation:

There is no harm or risk anticipated to take part of this study. However, if anything unusual happens to you, please feel free to inform us. The major benefit for this study is that the results will improve screening for cervical cancer and help create a better screening protocol. There will be no additional cost in participating the study

Confidentiality:

Any information that you provide will be strictly confidential and will only be used for the purpose of the study. However, should there be any positive finding in your results; this will be communicated to your doctor for your continued care.

Contacts & Questions:

The researcher conducting this study is Dr. Sagal Omar Salad. You may ask any questions you have now or If you have any question later, you can contact her through: Mobile Number: 0720407915 or Email: sagal.salad@aku.edu. Should you have any concerns on how the study is being conducted, please feel free to contact my Supervisor: Dr. Patricia Muthaura: Mobile Number 0736369777 or Email:patricia.muthaura@aku.edu. Or contact the Research Office in the hospital.

Part Two: Consent Form

I have read and understood the above information, my questions have been answered and I am free to ask any further questions that may arise in future.

I consent to participate in this research.

Participant's name_____

Participant's signature_____

Date_____

Day/month/year

Statement by the Researcher

I confirm that I have accurately read out the information to the participant and answered correctly to any question asked by her. I confirm that consent has been given freely and voluntarily.

Researcher's Name: Dr. Sagal Omar Salad

Signature of Researcher_____

Date_____

Day/month/year

Witness: _____, Clinic Nurse

Date_____

Day/month/year

Appendix TWO

Questionnaire

The questionnaire was adapted and modified from previous studies (30, 43, 51), then the scales were organized into appropriate categories and finally some of the wording of the questions was changed so that the participants can easily comprehend; So this questionnaire fits and matches our study since it was already validated and the indices measured in those studies are similar to ours. We will use English language in the questionnaire because most of the Kenyans prefer reading and writing in English rather than Kiswahili, we also conducted a pilot study for 10 participants to look for clarity and language preference; All of the participant indicated it was clear and understandable and they all preferred English language over the Kiswahili. A research assistant will help the research participant if further language assistance needed. The estimated time for filling the questionnaire is 5 to 8 minutes.

“AGA KHAN UNIVERSITY HOSPITAL, NAIROBI-KENYA

QUESTIONNAIRE FOR A STUDY ON ACCEPTABILITY OF SELF SAMPLING FOR HPV DNA

Participant Characteristics:

A. Study serial No: B. IP/OP No:

1. DOB

2. Marital Status: Single ☐ Married ☐

3. Number of Pregnancies (Parity)

4. Ethnicity:

5. Religion:

6. Education Level: Basic ☐ Secondary ☐ University ☐

7. Smoking: YES ☐ NO ☐

8. Previous Pap smear: YES ☐ NO ☐

9. Family History of Cancer: YES ☐ NO ☐

10. Where are you from?

Acceptability Questionnaire for self-sampling

Please tick your preferred answer

How easy was it to collect this self-sample?

	1	2	3	4	5	
Very HARD						Very EASY

How convenient was it to collect this self-sample?

	1	2	3	4	5	
NOT at all Convenient						Very Convenient

How embarrassed were you to collect this self-sample?

	1	2	3	4	5	
Very Embarrassed						NOT at all Embarrassed

How much discomfort/pain did you experience while collecting this self-sample?

	1	2	3	4	5	
Severe discomfort/pain						No discomfort/pain

How confident are you that you collected this self-sample correctly?

	1	2	3	4	5	
NOT at all Confident						Very Confident

Thank you for filling this Questionnaire

APPENDIX THREE

Procedure for Vaginal Self Sampling

The participants used the Qvintip brush for collecting their samples, they started by gently pushing the Qvintip self-sampler brush in to the vagina until they feel a resistance or they reach the marked area for the brush afterward, they made a circular brushing with repeating it as they turn the brush 3 times, then pulling the brush slowly. Next the brush was inserted in to the transport tube after bending the shaft.

Samples are then taken to the lab and were kept in -80ºC freezer before transferring it to Kenya AIDS Vaccine Initiatives KAVI lab at Kenyatta National Hospital for analysis.
Sampling device description: Qvintip is a single used self-sampler kit which analysis for high risk HPV DNA, it can be used for vaginal and ectocervical sampling.

APPENDIX FOUR

Data Tools

Data Collection Sheet (Sample)

No	Date	Name	Age	HPV DNA health worker sample)	HPV DNA (self-sample)
1	09.03.2018	Patient	32	negative	negative
2	09.03.2018	Patient	40	positive	positive
3	20.03.2018	Patient	35	negative	negative

APPENDIX FIVE

Principle of the HPV DNA test

"The hybrid capture method mainly is hybridization assay of nucleic acid which amplifies efficient signals by using chemiluminescence microplate for qualitative detection.

A specific probe for HPV RNA hybridizes with the specimens that have the target DNA.

The microplate well surface which is coated with antibodies specific for DNA: RNA hybrid will capture the resultant DNA: RNA hybrids.

An alkaline phosphatase conjugated antibodies specific for the DNA: RNA hybrids will then react with the immobilized hybrids, and identifies chemiluminescence substrate.

Each antibody are conjugated to numerous alkaline phosphatase particles.

Each captured hybrid binds multiple conjugated antibodies with significant signal amplification.

While the bound alkaline phosphatase cleaves the substrate, a light is emitted and measured as a relative light unit (RLU) using the luminometer. The absence or presence of target DNA in the sample will be signified by the intensity of the light produced."