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Research Article

Self-Administered Pap Smear, Selfpap®: An Acceptable and Effective Cervical Cytology Sampling Method

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Abstract

Objective: Cervical cancer remains pervasive even in much of the developed world despite advances in prevention and early detection. Screening with the traditional Papanicolau (Pap) smear presently requires that trained professionals perform it, usually in the setting of an office visit, which, for a variety of reasons, can present as a barrier to universal screening. The SelfPap® kit, which allows women to self-collect cervical cytology specimens, was designed as an alternative to the traditional Pap test for those who would not otherwise undergo routine screening. Our objective was to evaluate the patient acceptability of the SelfPap® kit and to compare diagnostic accuracy of the SelfPap® cervical-collection method for detecting abnormal cervical cytology assessed by a cervical physician-obtained sample.

Methods: Women 21 to 65 years presenting for cervical cancer screening to three separate designated study sites were recruited between January and December of 2011. Each cytology specimen (a SelfPap®-collected specimen and a physician-collected specimen), obtained two weeks apart, underwent review by a board-certified pathologist in a blinded manner. Results were reported according to the 2001 Bethesda System and appropriate follow-up was obtained for abnormal results, including high-risk HPV testing when indicated. Study participants were asked to fill out a five-question survey following use of the SelfPap® kit.

Results: Of the 308 eligible women who presented to the three study sites, 282 agreed to participate, indicating a 91% acceptance rate of the cervical self-sampling kit. Over 90% of the 272 evaluable self-collected specimens were adequate for cytopathologic evaluation and 100% of the 38 sent for HPV testing were adequate. Estimated sensitivity and specificity to detect abnormal cytology in self-collected samples were 80% and 97%, respectively. Cytology findings were abnormal for 68 subjects (25%), all of whom underwent colposcopy with biopsies. Twenty of the twenty-five who were found to have colpos-

copy-guided biopsy-confirmed CIN1 or greater were identified by the SelfPap®. There was an 83% concordance between the two collection methods. Overall, the SelfPap® was well-tolerated and greater than 95% of subjects said they would recommend it to friends or family.

Conclusion: Cervical self-sampling using the SelfPap® kit produced reproducible results when compared to physician-obtained traditional sampling for detection of abnormal cervical cytology. The SelfPap® method was acceptable and was recommended by most participants in this study.

Keywords: Cervical Cancer Screening; Self-Collection; Pap Smear

Introduction

Cervical cancer is the fourth most common cause of cancer death in women worldwide [1]. In the US alone, the CDC estimates that 12,109 cases of cervical cancer were diagnosed in 2011, accounting for 4,092 deaths [2-6]. Worldwide, there are an estimated 528,000 new cases of cervical cancer annually, with an estimated 266,000 deaths per year. In most developing countries, cervical cancer is responsible for the largest cause of mortality in women due to cancer [7].

Not only does cervical cancer represent one of the few cancers which, if caught early, is amenable to curative-intent surgical approaches, but it also is one of the few with an established means of early detection by screening: the Papanicolau (Pap) smear and HPV testing. Since the introduction of the Pap test in the 1950s in the United States and with its widespread use in other industrialized nations, the incidence and mortality of cervical cancer have decreased dramatically [8,9]. A 70% decrease in mortality was observed in the US from the years 1955 to 1992 [7]. Worldwide, cervical cancer incidence and mortality remain disproportionately high in developing nations due to lack of organized screening programs and scarce resources [2-6]. Despite efforts to improve screening, however, morbidity and mortality from cervical cancer remain high in developing nations, with such women estimated to be at a 35% greater lifetime risk of cervical cancer when compared to women in high-income countries [10].

In much of the developed world, cervical cytologic examination still remains the primary screening test despite advances in HPV testing and vaccination [2-7]. Advantages of the Pap test include relatively low cost and a high specificity (94-97%) in identifying high-grade cervical intraepithelial neoplasia (CIN). However, at present, this test requires that trained professionals perform it, usually during the setting of a routine pelvic examination. In developing nations, a variety of economic, logistical and sociocultural factors have been implicated in the low rate of cervical cancer screening, including such limitations as fragmented health care systems, inadequate health infrastructure for cervical cancer care, and a lack of training of clinicians [10]. In the US, certain subgroups of patients were found to be least likely to participate in Pap smear screening and include women who are less educated, older, uninsured, lesbians, homeless, and migrant workers who face language barriers [7]. Approximately one-half of the women diagnosed with cervical cancer in the US were never screened [7]. Due to such barriers preventing women from obtaining routine Pap testing, the need for an alternative cervical cancer screening strategy is apparent.

In the past few years, home diagnosis and monitoring of various disease states has become more prevalent [11-21]. Tests of a wide variety, including pregnancy tests, hemoglobin A1C, HIV and urinalysis can now be performed in the comfort and privacy of a patient's home. These new avenues of self-testing can be attributed to patients' more conscientious role in disease management, busier lifestyles, concern over privacy issues and/or apprehension about undergoing full screening. At-home cervical cancer screening has also been proposed and tested recently, including various cervico-vaginal self-sampling methods to detect abnormal cervical cytology and high-risk HPV DNA [22-29].

Recently, several large studies have demonstrated the acceptability and efficacy of cervical self-sampling screening programs [22-29]. Vaginal self-sampling has been found to increase participation in cervical cancer screening among unscreened women in various settings [23]. These studies have consistently demonstrated high acceptability rates in women both in the US and abroad. Despite concerns that at-home self-sampling eliminates the pelvic examination historically included in screening visits, there is no evidence to suggest that the use of routine pelvic examination (excluding cervical cytologic examination) reduces the morbidity or mortality of any condition [30]. The SelfPap® Kit (SHL Pharma, Deerfield Beach, FL) (Figure 1)

Figure I: SelfPap® kit contents with box.

was initially designed as a means for women who would not otherwise undergo cervical cancer screening to be able to complete a test comparable to the standard Pap test in a convenient and private way. Once the sample is collected, users can ship the tissue sample to a designated laboratory for processing. In the course of development of the SelfPap® Kit, there have been several clinical evaluations. Three studies were conducted to determine whether SelfPap® is as effective as clinician-collected Pap smears for the detection of cervical dysplasia. Each study explored various aspects of ease of use of this self-administered Pap smear kit. Results from study questionnaires and study data guided changes to the preliminary products before finalizing the product as the SelfPap®.

The purpose of this study was to evaluate the patient acceptability of the SelfPap® kit for cervical cell self-collection in a group of women presenting for screening and to compare results from these samples to those obtained during a physician-obtained Pap smear for detecting abnormal cervical cytology.

Materials and Methods

Between January 2011 and December 2011, subjects who presented for cervical screening at the three designated study sites were considered for the study. The sites included the Lantana Health Department (Site 1), a private gynecology office, both in Palm Beach County, FL (Site 2), and a family practice clinic at Nellis Air Force Base in Nevada (Site 3).

Patients were screened and consented by a designated registered nurse at each site, where they each gave written, informed consent. Exclusion criteria included positive pregnancy (confirmed by urine beta-hCG test), prior hysterectomy, history of cervical cancer or dysplasia, abnormal vaginal bleeding at the time of visit, and history of severe neuropathy, arthritis of the hands, or history of other major illness causing limited dexterity of the hands. Once patients were enrolled, each patient was given a SelfPap® kit (Figure 1),

SelfPap Kit Use and Application Guide

IMPORTANT: Read all instructions first. Fill out the patient information form and the Customer ID Card and return them with the sample in the delivery bag.

Dispose of all remaining kit components after use.

Use of Vaginal Products
The most common cause of false negative Pap smears is sample failure, which means that no abnormal cells are present in the slide or sample given.

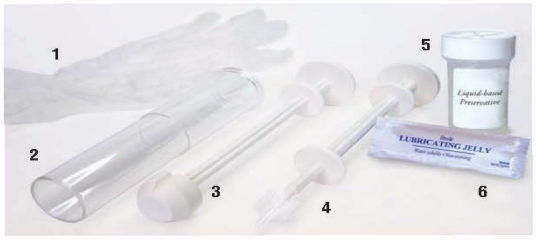
To minimize the chance of sample failure, avoid intercourse or the use of douches, vaginal medicines, spermicidal foams, creams or jellies for two days prior to performing the Pap test.

These products may wash or obscure abnormal cells.

Timing of Pap Test
The best time to have a Pap test is the week after your period. You can take the test at any time if you are postmenopausal.

The SelfPap Test Kit consists of the following components:

1. Disposable Gloves
2. Tube Speculum
3. Introducer
4. Brush Sampling Unit
5. Sample Container
6. Surgical Lubricant
7. Biohazard Bag (Not shown)
8. Instructions (Not shown)
9. Delivery Bag (Not Shown)
10. Customer ID Card (not Shown)
11. Patient Information/Consent Form (not shown)
12. Consent Policy Form (not shown)



IMPORTANT – Before proceeding, find a private place where you can remove your underwear, sit comfortably in position, and put the kit adjacent to allow you easily access to the kit materials.

You will also need about 10 minutes to complete the sample collection steps. Wash your hands with warm water and soap and dry them before proceeding. Gloves are provided for your protection. It is optional but not required.

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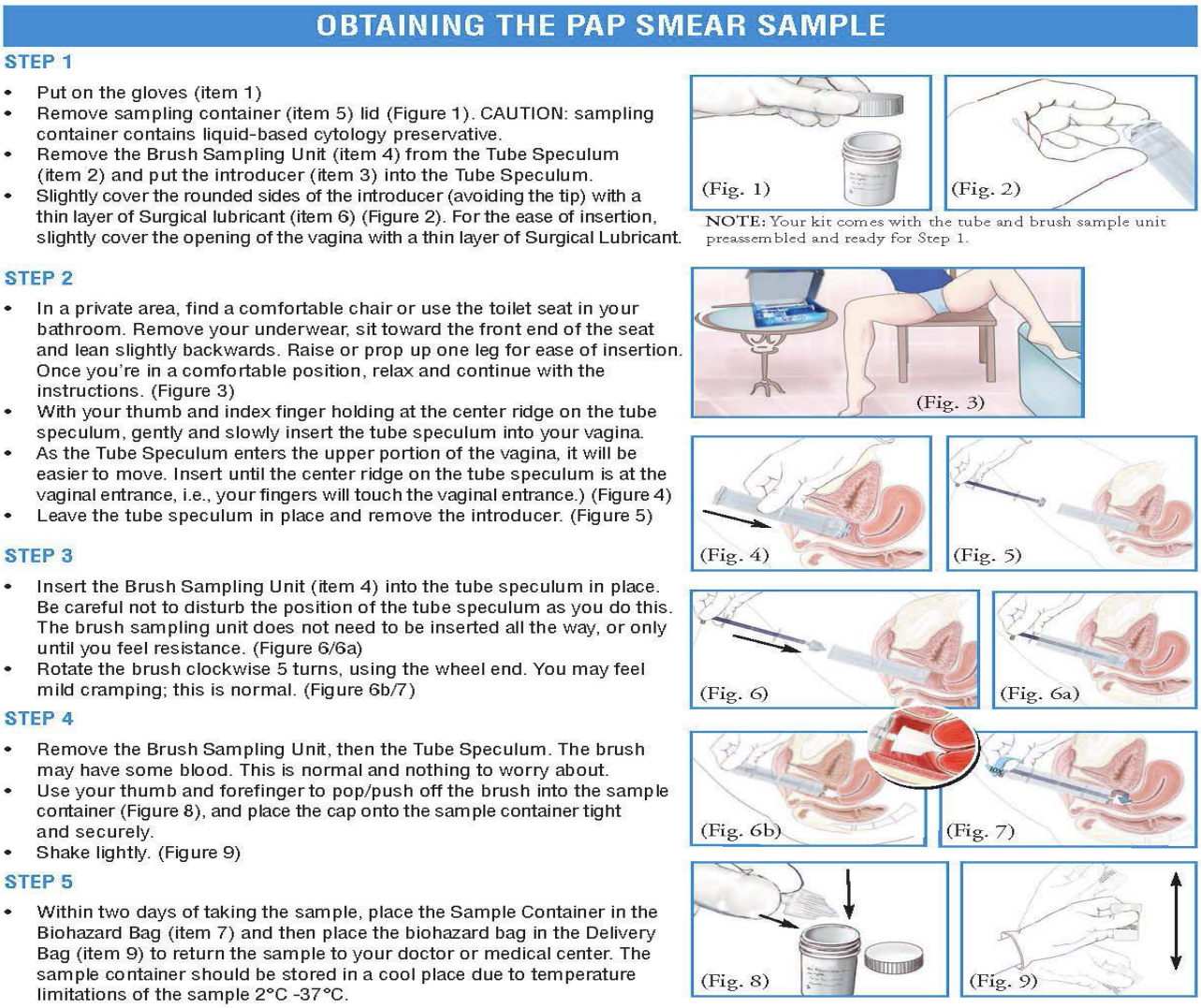

Figure II: SelfPap® kit instructions for use and application guide

which included disposable gloves, tube speculum, introducer, brush, lubricant, sample container with cell fixative, plastic bag, mailing container, customer ID card, patient consent form, and instructions for use (Figure 2). In order to mimic home use of the kit, the subjects were instructed to perform the self-collection alone in a designated room without assistance or further instructions from the medical team or office staff. The samples were labeled only with randomized numbers assigned to each subject (with a different number for both the SelfPap® sample and the physician-obtained sample to facilitate blinding of the pathologist) and mailed in by the office staff to the designated testing facility. For Sites 1 and 2, the facility was CytoPath lab of West Palm Beach, FL, where the same board-certified cytopathologist evaluated all study samples. For Site 3, samples were mailed to and evaluated by a board certified cytopathologist at San Antonio Military Medical Center in San Antonio, TX.

Immediately following self-collection using the SelfPap®, participants were given a brief five-question survey to complete and turn in before leaving (Table 1). The questions were as follows: 1. Did you experience any discomfort while using the SelfPap® (Y/N)? 2. If you answered yes to question 1, how would you describe your discomfort (mild/moderate/severe)? 3. Would you use the SelfPap® for future Pap tests (Y/N)? 4. Would you recommend the SelfPap® to a friend or family member (Y/N)? 5. Please report any complications or problems

which resulted from using the SelfPap® kit.

Question	Responses (n=272)		
	Yes:	No:	
1. Did you experience any discomfort while using the SelfPap® Kit?	97	175	
	Mild:	Moderate:	Severe:
2. If you answered yes to the above question, how would you describe your discomfort?	81	16	0
	Yes:	No:	
3. Would you use the SelfPap® Kit for future Pap tests?	243	29	
	Yes:	No:	
4. Would you recommend the SelfPap® Kit to a friend or family member?	261	11	
	Problems:	No problems:	
5. Please report any problems or complications which resulted from use of the SelfPap® Kit.	4	268	

Table I: SelfPap® Kit Subject Questionnaire Responses

The subjects were then scheduled for another visit in two weeks, at which time a traditional Pap smear would be performed by the designated physician at each study site using liquid-based thin prep (thinPrep®, Cytotec). For this method, a speculum exam is performed and a cytobrush and spatula are used to collect the specimen from the cervix. The brush and spatula are immediately placed in the PreservCyt and vigorously swished around. The vial is then capped, placed into a biohazard bag, and sent to the laboratory. The minimum two-week time frame in between Pap tests was thought to be adequate to allow the cervix to recover from the previous sampling in order to improve study accuracy.

All samples were sent to the lab the same day they were obtained. The samples were reported as either satisfactory or unsatisfactory and cytological analysis findings were reported according to the 2001 Bethesda System. Results classified as "abnormal" for this study included ASC-US, ASC-H, LSIL, HSIL, or AGC.

Management and follow-up for the results was based on the published American College of Obstetrics and Gynecology (ACOG) guidelines from 2006 [31]. If indicated, samples were tested for high-risk HPV DNA strains. This testing was performed at the same laboratory that the samples were initially sent to. HPV testing was carried out with a nucleic acid hybridization method utilizing a DNA probe cocktail specific for intermediate/high risk serotypes (types 16,18,31,33,35,39,45, 51,52,56,58,59,68). Results were reported as "not detected" or as "detected" for one or more high-risk HPV serotypes, but the specific serotypes were not reported.

Subjects whose results indicated that further colposcopic examination was recommended were notified of their results within five days of their second Pap test and instructed to come in for this testing within two weeks of notification. For these subjects, a standard colposcopic examination was performed at their initial clinic site. The physicians performing the exam were provided with the Pap testing results and HPV testing results (if obtained), but were blinded as to which Pap test (SelfPap® and/or physician-obtained Pap) coincided with which result. Lesions were graded using the Reid index [32] and colposcopy-directed biopsies were collected from areas of suspected cervical abnormalities. Biopsies were reviewed and diagnosed independently by the same pathologist mentioned previously who was blinded to the subject's information, colposcopy data, Pap smear testing results and hrHPV testing results. If further testing or management was indicated, the subjects were notified and managed as per the standard of care, but this information was not recorded.

Subjects were not compensated for their participation in this study. However, SelfPap® samples were given to the subjects without an additional charge for their visit. All other examinations and tests were provided free of charge by the participating laboratories.

Results of the study data from each study site, product information for SelfPap® and study protocols were reviewed and approved by the investigational research review boards overseeing each site prior to the conduction of the study.

Statistical Analysis

Prior to conducting any data analysis of the survey questionnaire results, the data was to be examined for the assumptive of normality. If the data was found not to follow a normal distribution then the appropriate transformative or nonparametric tests would be used to analyze the data. A paired t-test with a 0.050 two-sided significance level was to be used to analyze data. The survey results were to be analyzed by a paired t-test with a 0.050 two sided significance level utilizing a Statistical Package for the Social Sciences (SPSS).

Analysis of concordance of Pap smear results between the two methods of collection was performed. A McNemar's chi-squared test was used to determine the difference between the sensitivities and specificities of the two collection samples. A Kappa test was employed to detect whether the two methods were concordant within individual patients.

Results

Between Jan 2011 and Sep 2011, a total of three-hundred eight women presented for cervical screening at the designated study sites. Of those, nine refused to participate and twenty-seven failed the initial screening. Two-hundred eighty-two women total from the three sites participated (Site

1: 64, Site 2: 68, Site 3: 150). Nine women were excluded from the final analysis due to various reasons as shown in Table 3.

Therefore, the analysis was restricted to two-hundred seventy-two evaluable women with valid cytology results (Table 2). The age range for the study population was twenty-one to sixty-four years, and the median age was twenty-nine. Patient demographics are shown in Table 4.

Study Site	Method of Collection	Normal	ASCUS/AGUS	LSIL	ASC-H	HSIL	Total subjects from each site	Subjects referred for colposcopy +/- biopsy (Total from each site)
		n=458	n=58	n=26	n=1	n=1	n=272	
1	SelfPap ®	57	5	2	0	0	64	9
	Physician-collected	59	3	2	0	0		
2	SelfPap ®	57	8	2	1	0	68	13
	Physician-collected	66	2	0	0	0		
3	SelfPap ®	113	19	8	0	0	140	46
	Physician-collected	106	21	12	0	1		
								Total: 68

Table II: Cytology Results from SelfPap ® and Physician-Collected Samples, by Site

	Number of Subjects Excluded
Lost to follow-up	1
Physician-obtained Pap was lost	1
Unable to perform SelfPap ®	3
Left before appointment	1
SelfPap ® results unsatisfactory	1
Unable to schedule appointment	1
Physician-obtained Pap was unsatisfactory	1
	Total: 9

Table III: Exclusion Criteria

Of the five-hundred forty-four total samples tested (two-hundred seventy-two SelfPap® samples and two-hundred seventy-two physician-obtained samples), forty-two of the physician-obtained and forty-six of the SelfPap® samples were reported to have abnormal cytology. SelfPap® results were concordant with physician-obtained Pap results in two-hundred twenty-seven of the two-hundred seventy-two subjects (83.4%) (Table 5).

A total of sixty-eight subjects were referred for subsequent colposcopic examination based on abnormal cytology results (Table 2). Of those, twenty-five were found to have cervical lesions consistent with CIN1 or greater. Twenty of those subjects had abnormal cytology identified from the SelfPap®.

	Range	Median
Age (years)	18-64	29
Weight (lbs)	89-284	156
Height (inches)	58-72	64

Table IV: Patient Demographics

Cellular material collected for cytologic evaluation was consistent. Over ninety percent of specimens collected were satisfactory for cytopathologic interpretation, consistently providing adequate numbers of cells for evaluation. For HPV testing, one-hundred percent of samples collected were satisfactory for evaluation and results between the two groups were concordant. Moreover, all samples which were sent for high-risk DNA testing were adequate (n=38). Of those, high-risk HPV DNA was detected in 14 samples.

	Number of Subjects	Percent of Subjects
Same Results Obtained	227	83.40%
Different Results Obtained	45	16.60%
	Total: 272	

Table V: Concordance of Results

For each of the study sites, McNemar's test was used to evaluate the differences between self-collected and physician-collected sampling techniques. The p value for all three study sites is 0.3173, which indicates that there was no significant difference observed between the two test methods of sampling modalities. Hence, SelfPap® is at least as reliable as the traditional physician-collected Pap smear.

We conducted Kappa statistic for agreement of the two sampling methods. The Kappa statistic was 0.7922 with a p-value almost equal to 0, which demonstrates that this is significant agreement between the sampling techniques. Kappa statistic is equal to 1 if and only if there is complete agreement between the two sampling methods [33]. One can state that 79.22% of the difference between perfect agreement and the agreement expected by chance is accounted for by the agreement between the two sampling methods.

		Biopsy-confirmed (+)*	Negative biopsy	
SelfPap ®	Abnormal	16	30	Total: 46
	Normal	4	18	Total: 22
		Total: 20	Total: 48	Total: 68
Physician-collected Pap	Abnormal	13	29	Total: 42
	Normal	6	20	Total: 26
		Total: 19	Total: 49	Total: 68

Table VI: Diagnostic Accuracy and Agreement of Cytology Samples and Colposcopy-Directed Biopsy Results, Among Subjects Referred for Biopsy

The number of positive and negative Pap smear results by each collection method is shown in Table 7. For all of the 272 evaluable patients, a positive SelfPap® kit sample demonstrated an agreement with a positive clinician-obtained Pap on 22 patients. Conversely, negative SelfPap® kit samples were in agreement with negative clinician-obtained Pap smears on 237 patients. The SelfPap® kit demonstrated an agreement of 0.735 (95% CI, 0.513-0.956) Kappa statistic, whereas 0.61-0.80 is generally considered significant.

	Clinician-Pap (+)	Clinician-Pap (-)	Total
SelfPap ® (+)	22	8	30
SelfPap ® (-)	5	237	242
Total	27	245	272

Table VII: 2x2 Chart for SelfPap ® vs. Physician-Collected Pap Cytology Results

Sensitivity	0.80
Specificity	0.967
Likelihood ratio (+)	24.2
Likelihood ratio (-)	0.004
Positive Predictive Value	0.727
Negative Predictive Value	0.978

Table VIII: Statistical Calculations (for data in Table VII)

Table 8 demonstrates the statistical calculations from the data shown in Table 7. The negative predictive value of the SelfPap® was 0.978 while the positive predictive value was 0.727 in a population where an average of 10.0% of the participants had a positive test by either method. The positive likelihood ratio and the negative likelihood ratio were 24.2 and 0.04, respectively.

Major outcomes evaluated by patient questionnaires evaluated for the question of comfort, would the subject use the SelfPap® device again and would they refer this sampling method to a family member or friend (Table 1). For all study sites, patient feedback revealed that study subjects were comfortable using the SelfPap® kit, with 89% reporting they would use it again. Of all users, 96% stated that they would recommend it to their friends or family. Ninety-seven of the subjects (35%) experienced some degree of discomfort while using the SelfPap® kit. Of these, the majority (eighty-one, 83%) reported this as "moderate." None of the respondents classified their discomfort as "severe."

Adverse effects were reported by four respondents (1%). These included mild uterine cramping in two participants and inability to get the tube inside the vagina in another two participants. There was no excessive bleeding reported afterward and all subjects felt this was a relatively comfortable procedure.

Discussion

Since the introduction of the Papnicoulau (Pap) smear in the 1950s, cervical cancer rates have declined by more than 60% [2]. According to the U.S. National Institutes of Health, approximately 55 to 60 million Pap smears are performed annually [2,9]. Of these, approximately 3.5 million (6%) are abnormal and require medical follow-up [2,9]. However, many barriers exist to women accessing this screening test, including fear, privacy concerns, discomfort from the procedure, discomfort with male providers and in some areas a lack of access to medical personnel to administer this test.

There have been a number of self-sampling collection kit studies performed in Europe within the past five to ten years [11,12-21]. Cervicovaginal lavage, vaginal swabs made of cotton or Dacron, and brushes have been tested in Europe. Women who previously did not attend for their screening tests were willing to perform these tests in their own homes. The majority of these women found such devices "easy to use, timesaving, less embarrassing, and more comfortable [than speculum examinations]". Additionally, women felt "more relaxed doing it". If such an option was widely available for women, rates of cervical cancer screening could potentially increase, especially in areas where access to primary care is limited. Based upon study subject response, women should find this to be a potential satisfactory option for screening.

The SelfPap® kit is designed to be a screening tool for cervical cancer. Ideally, screening tests should have a high sensitivity and negative predictive value. When the positive likelihood ratio is greater than 5 or the negative likelihood ratio is less than 0.2, then they can be applied to the pre-test probability of

a patient having the disease tested for to estimate a post-test probability of the disease state existing. Given the incidence of dysplasia is comparable to the general population, a negative result from a SelfPap® smear would reduce the likelihood of cervical cancer to 0.004 due to the very low negative likelihood ratio, while positive tests would increase the likelihood from a population mean of 9.8% to 73% due to the high positive likelihood ratio. Thus the SelfPap® kit appears to be as effective as clinician-collected Pap smears for detecting cervical dysplasia. Based on study results, similar conclusions may be drawn regarding SelfPap®-collected samples' detection of HPV and lesions with the same sensitivity as clinician-collected samples.

Given that the SelfPap® kit demonstrated a significant concordance with the physician-collected samples, it can be considered an acceptable option for cervical cancer screening. Of note, women were not given any verbal instruction before using the SelfPap® kit. They were able to self-collect samples successfully by following the written instructions or by viewing the "How to Use" pictures if they were not literate. Additionally, a majority of women would use the kit again, demonstrating a level of comfort with the kit. Of the small number of subjects who were not comfortable using it, 96% stated that they would still recommend the sampling kit to a friend or family member, supporting the contention that the instructions were understandable.

The women who were enrolled at the study sites were self-scheduled appointments to cervical cancer screening clinics, and they were of varied age and racial makeup. As such, this offers applicability to any primary care clinic. However, it does not apply to many women who likely have difficulties with cervical cancer screening in the first place. In 2010, a study from the Netherlands specifically addressed women who were non-responders to their regular cervical cancer screening program in spite of two consecutive invitations [34]. They were invited to submit a self-collected cervicovaginal sample for HPV testing. That study not only had a better rate of response than a control group, but also yielded a significant amount of high-grade lesions. The subjects in the SelfPap® kit studies were not specifically enrolled in a cervical dysplasia program and had ages ranging from 18-64, a reason likely contributing to the lack of high-grade lesions discovered in this study.

Cervical cancer screening opportunities for women may be expanded with the SelfPap® kit. In agreement with the results of the SelfPap® kit studies, a study of self-sampling methods found that women are willing to do self-collection and also found dysplastic lesions in those samples [24]. Historically, lack of endocervical cells on the Pap smear was considered limiting. However, research demonstrated that the absence of endocervical cells is not predictive of the incidence of cervical cancer in the years after negative tests [35]. The acceptability of home testing and simplified cytology makes home screening for cervical cancer a feasible option and potentially lifesaving when traditional care is not available. The SelfPap® kit is a home test system that could promote early diagnosis and subsequent treatment of precancerous lesions of the cervix, which if left untreated, can lead to cervical cancer.

The relative low-cost of the SelfPap® kit may warrant consideration as a potential screening strategy for targeting populations of underserved women of low socioeconomic class where for who professional medical care is scarce and healthcare is limited.

Conclusions

The SelfPap® kit cervical cell self-collection method is a viable alternative to clinician-collected Pap smears. Subject comments and post-exam questionnaire analysis indicated that women were comfortable with and understood how to use the SelfPap® kit.

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Conflict of interest

There are no conflicts of interest or relationships for any authors reported for this study that may be deemed to influence the objectivity of the paper.

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