Research Article

Cancer Prevention Research

Uptake of Cervical Cancer Screening in Ethiopia by Self-Sampling HPV DNA Compared to Visual Inspection with Acetic Acid: A Cluster Randomized Trial

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Abstract

In Ethiopia, the standard method of cervical cancer screening is using Visual Inspection with Acetic Acid (VIA). Self-collection–based human papillomavirus (HPV) testing is assumed to improve the uptake of screening, especially for hard to reach populations. We investigated whether HPV DNA testing with the self-collection of cervical samples would be associated with increased uptake and adherence to procedures at the population level compared with VIA within defined rural population in Ethiopia. A total of 22 clusters (comprising 2,356 women ages 30–49 years) were randomized in two arms. Following the community mobilization, women of the clusters were invited to go either to the local health post for a self-collection–based HPV DNA testing (arm A) or Butajira Hospital for VIA screening (arm B). In the HPV arm, of the 1,213 sensitized women, 1,020 (84.1%) accessed the health post for self-sampling compared with the VIA arm, where 575 of 1,143 (50.5%) visited the hospital for VIA ($P < 0.0001$). Of those women who attended the VIA and HPV arms, 40% and 65.4% adhered to all procedures expected after screening, respectively. Out of women positive for high risk HPV, 122 (85%) attended VIA as a follow-up test. The trial demonstrated significantly higher levels of population-based uptake and adherence for self-collection HPV testing. Women were more receptive for VIA after their HPV testing result was positive. Self-collection HPV testing can be done at the local health facility and may significantly improve the uptake of cervical cancer screening in Ethiopia.

Introduction

Cervical cancer remains a major public health problem globally, with an estimated 570,000 new cases diagnosed and 311,000 deaths occurring annually with the large share of these cases and deaths occurring in low and middle income countries (1). In most developing countries, cervical cancer is the leading cause of cancer-related death among women (2, 3). In Ethiopia, cervical cancer is the second leading cause of morbidity and mortality from all cancers in women (4). In Ethiopia, almost all women with cancers present to healthcare facilities at advanced disease and poor prognosis (4). Cervical cancer can be prevented and even possibly cured if identified in its early stages, and this could be achieved in developed countries (5, 6). However, the risk of developing invasive cervical cancer continues to be higher in developing countries as the regions do not have well-organized prevention strategies (7, 8).

Currently, cervical cancer screening by visual inspection with acetic acid (VIA) and immediate treatment with cryotherapy is recommended by the World Health Organization (WHO) for low and middle income countries as this method requires trained nurses, few resources, and the results are available immediately (9–11). However, accessing VIA is difficult for many rural women as the service is only available at the district hospital level in very few places (12–14). Although VIA is accepted by the government in many low income countries, yet maintaining quality assurance, the invasiveness of a pelvic examination, and user variability of the test remain critical barriers (15).

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Cancer Prev Res 2019;12:609–16

doi: 10.1158/1940-6207.CAPR-19-0156

The detection of high risk human papillomavirus (hrHPV) in the cervix is a very sensitive method and has been recommended by the WHO in settings wherever technically and financially possible (9, 16, 17). This approach is found to be less examiner-dependent, reduces the burden on the healthcare system, enhances accuracy and efficiency, and reduces cultural barriers (10, 15, 18, 19). Moreover, a self-collected sample for HPV DNA testing was found to be acceptable and feasible by underserved women (20–23). Therefore, HPV test might be a future option in low and middle income countries.

In Ethiopia, screening with VIA followed by cryotherapy started in 2009 first for HIV-positive women in few selected hospitals (4, 11). Currently, the Federal Ministry of Health in Ethiopia has expanded the service to general health facilities, but the uptake of VIA remains low (24).

So far, few studies have been conducted in African settings to assess the uptake and acceptability of different screening approaches at a population-based level (15, 25). A study in sub-Saharan Africa reported a higher uptake of HPV-based cervical cancer screening than VIA in clinical settings (15). In Ethiopia, there is no evidence of the uptake and acceptability of self-sampling–based HPV testing as a primary cervical cancer screening method. Therefore, the objective of this study was to compare the uptake and adherence to procedures between HPV testing with the self-collection of cervical samples and using visual inspection with acetic acid by including all women residing within the predefined clusters.

Materials and Methods

Study design and population

A cluster-randomized trial was employed. This trial has been registered in clinical trial.gov (NCT03281135). We have used the Butajira Health and Demographic Surveillance Site population as a platform. It provides a well-defined number of women with their basic demographic features (26). The clustering process was performed using the existing health system of the country. According to the Ethiopian cervical cancer screening guideline, women ages between 30 and 49 years were targeted for screening in both arms (11). All women included in this study had never been screened before. We used a total of 22 clusters, each comprising 80 women as a minimum required sample. The clusters were divided equally between two arms: self-collected HPV testing and VIA. Women were excluded if they were pregnant, actively bleeding, had a previous hysterectomy, and refused to give consent before the screening.

Randomization

We followed a step-wise randomization process; we first divided a total of 10 villages or kebeles (the smallest administrative unit of the country, Ethiopia) into 22 clusters where proportionally four of the clusters belong to the urban setting. Finally, we generated 11 clusters for each arm, which contained the minimum of 80 targeted women in each cluster and a buffer zone between the clusters to control contamination of information. All clusters were linked with responsible community health workers. The randomization list was created by using a unique allocation ID. The randomization was also performed for each village separately, which means two clusters in each village were randomly allocated to one of two trial arms: the HPV arm or the VIA arm. The randomization was conducted using Research Randomizer Software (27).

Procedure and intervention

Community mobilization was conducted in each village using health extension workers (HEW) under the supervision of a facilitator. Targeted women were invited to attend the sensitization program in their vicinity. A trained team provided information on cervical cancer and screening during the community sensitization conducted in every cluster for the HPV and VIA arms separately. The sensitization was performed independently for each cluster using different tailored pretested sensitization materials. Accordingly, we sensitized and invited an equal number of women to either Butajira hospital for VIA arm where the service was available in the district or the primary health care unit at their vicinity for HPV self-sampling. In both arms, a reminder was given once through HEWs in the middle of the allocated screening period.

In the HPV self-sampling arm, women were offered an Evalyn Brush (Rovers) to collect a swab under active supervision by a trained health professional. Women collected samples in a private area in the health post. Samples were immediately placed in a plastic bag provided by the Evalyn Brush Company after giving a unique ID. Samples were stored and transported by the end of the week to the Molecular Laboratory of the Department of Microbiology, Immunology and Parasitology, College of Health Sciences, Addis Ababa University (Ethiopia) for DNA extraction. A DNA aliquot was sent to Charité Universitätsmedizin Berlin, Department of Gynecology (Germany) for HPV genotyping. The genotyping was performed using GP5+/GP6+ PCR with MPG-Luminex assay read out.

Training was provided to local health workers on post-screening counselling information and instructions. After receiving the results back, the health workers communicated results based on the counselling instruction in person at the health post where the specimens had been collected. Women who tested positive for hrHPV were cautiously counselled and appointed for further screening by VIA at Butajira Hospital. Women who tested positive for hrHPV and VIA were treated by cryotherapy.

In the VIA arm, women were appointed on any of 5 consecutive days given to visit the hospital. They could choose a convenient day to reduce the attrition rate. VIA screening was done for all women who visited the hospital

and were eligible for the procedure. A trained and certified nurse was responsible for performing the screening. All women who tested VIA positive were rescreened by a gynecologist for quality assurance. A WHO see-and-treat approach was implemented to screen-and-treat with cryotherapy for women who tested positive (16).

Data analysis

The primary analysis of the endpoint "adherence to procedure" was analyzed on the intention-to-treat principle (based on previous categorization) by comparing the number of women sensitized in the HPV self-sampling arm and the VIA at hospital arm. Descriptive analysis was carried out to calculate the uptake and characterize the sociodemographic characteristics of participants. Descriptive statistics were done to compare the two arms with different socio-demographic and economic factors. The χ^2 test was employed to compare the significance of the two screening approaches for the uptake of screening with the significance level of $P < 0.05$. Fisher exact test was used when the expected values are too low. Continuous variables such as age and waiting time were changed to categorical variables for ease of reporting.

Ethical consideration

Ethical approval was obtained from the Institutional Review Board of the College of Health Sciences, Addis Ababa University (Ethiopia) and Martin Luther University (Halle, Germany). Further approval was obtained from the National Research Ethics Review Committee for transferring samples to Germany using a material transfer agreement bilaterally signed between two institutions. The study is in line with the declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects. Oral consent was obtained from the women under the study for both screening and exit interviews. Screening was performed in a way in which privacy and confidentiality was maintained. Treatment was provided for women who were positive in both arms according to the national cervical cancer treatment guideline.

Results

The 22 clusters were divided in the HPV self-sampling arm or VIA arm. A total of 1,213 women from 11 clusters were sensitized for HPV self-sampling, of which 1,020 [84.1%; 95% confidence interval (CI), 81.95–86.07] attended the self-sampling (Fig. 1). Moreover, of the total women sensitized in the HPV arm, 794 (65.4%) adhered to all procedures of the study protocol. Of the 1,143 women sensitized to attend VIA in the hospital, 575 (50.5%; 95% CI, 47.41–53.2) attended the hospital. Of the total women sensitized in the VIA arm, 458 (40%) have adhered to all procedures of study protocol. There was a statistical significant difference in uptake and adherence to procedures between HPV self-sampling and VIA ($P < 0.0001$).

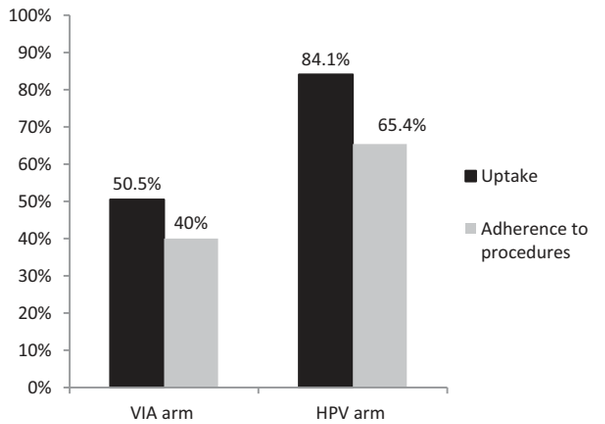

Figure 1.
Proportion of adherence to the uptake and procedures for women who participated in screening for cervical screening, Butajira, Ethiopia, 2018.

Study participant characteristics

Table 1 shows the demographic and reproductive characteristics of women according to their study arm. The majority of the study participants, 682 (81.7%) and 403 (86.9%) came from rural villages in the HPV self-sampling

Table 1. Sociodemographic characteristics of women who participated in screening for cervical cancer, Butajira, Ethiopia, 2018

Demographic characteristics	Total ($N = 1,299$) *n* (%)	Study arm: HPV self-sampling arm ($N = 835$) *n* (%)	Study arm: VIA arm ($N = 464$) *n* (%)
Residence			
Urban	214 (16.5)	153 (18.3)	61 (13.1)
Rural	1,085 (83.5)	682 (81.7)	403 (86.9)
Marital status			
Married	1,212 (93.3)	763 (0.2)	449 (96.8)
Single	2 (0.15)	2 (0.2)	—
Divorced	39 (3.0)	33 (4.0)	6 (1.3)
Widowed	36 (2.77)	28 (3.4)	8 (1.7)
Separated	10 (0.77)	9 (1.1)	1 (0.2)
Age category			
30–34	735 (56.6)	519 (62.2)	216 (46.6)
35–39	364 (28)	203 (24.3)	161 (34.7)
40–44	126 (9.7)	72 (8.6)	54 (11.6)
45–49	73 (5.6)	40 (4.8)	33 (7.1)
Educational status			
Illiterate	838 (64.5)	546 (65.4)	292 (62.9)
Primary level (1–8)	397 (30.5)	249 (29.8)	148 (31.9)
Secondary level and above (9–12)	64 (5.0)	40 (4.8)	24 (5.2)
Occupation			
House wife	995 (76.6)	686 (82.2)	309 (66.6)
Farmer	129 (9.9)	38 (4.6)	91 (19.6)
Merchant	143 (11)	83 (9.9)	60 (12.9)
Government employee	9 (0.7)	6 (0.7)	3 (0.6)
Daily laborer	20 (1.5)	19 (2.3)	1 (0.2)
Other	3 (0.2)	3 (0.4)	—
Husband education			
Illiterate	684 (52.6)	471 (56.4)	213 (45.9)
Primary level (1–8)	504 (38.8)	297 (35.6)	207 (44.6)
Secondary level (9–12)	111 (8.6)	67 (8.0)	44 (9.5)

Table 2. Service accessibility of women who participated in screening for cervical cancer, Butajira, Ethiopia, 2018

	Study arm	
	HPV self-sampling arm ($N = 835$)	VIA arm ($N = 464$)
Service accessibility	*n* (%)	*n* (%)
Means of travel to point of screening		
Foot	835 (100)	65 (14)
Horse cart	—	5 (1.1)
Car(Bajaj)	—	394 (84.9)
Distance to hospital		
<5 km	251 (26.1)	173 (23.8)
5–10 km	266 (27.7)	232 (31.9)
>10 km	444 (46.2)	323 (44.4)
Perceived difficulty of travel		
Yes	5 (0.6)	141 (30.4)
No	830 (99.4)	323 (69.6)
Mean (SD) of waiting time in minutes at point of screening	4.5 (2)	36 (12)

and VIA arms, respectively. Age distributions were similar in both arms; the majority of participants were between the age of 30 and 39. The mean (± SD) age at first pregnancy of the HPV arm and VIA arm was 18.4 (±4.8) and 18.6 (±4.6), respectively. Most of the participants were illiterate and housewives by occupation. Moreover, the majority of the participant's husbands were illiterate and farmers by occupation. Furthermore, we compared the service accessibility between two arms. All women in the HPV arm travelled to the point of care on foot while the majority of participants 394 (85%) travelled to the hospital using a car in the VIA arm. The majority of women, 323 (44.4%), who came for VIA screening were from furthest places where the distance was greater than 10 km from the hospital. While participants rated for perceived difficulty of travelling to the point of care, the majority responded that they did not perceive difficulty travelling to either of the health facilities. However, about one third of the participants in the VIA arm reported that travelling to hospital was difficult, while very few participants reported similarly in the HPV arm. The mean waiting time at the point of care before receiving the service of HPV arm and VIA arm was 4.5 and 36 minutes, respectively (Table 2).

HPV DNA testing arm

Of the total 721 women who were screened, there were 171 (19.2%) reported to have a too low cell count to detect any HPV type and required rescreening. Following the recommendation to rescreen women with a low cell count, of the 171, 73 (42.7%) were willing to provide a second self-collected sample, 76 (44.4) refused to resample, and 22 (13%) were not accessible during two consecutive follow-ups. According to the guidelines for cervical cancer screening, those who were found to be positive for hrHPV had to go for further screening or examination, in this case VIA examination. Accordingly, of all women who were positive for a single or multiple HPV infection, 122 (85%) attended VIA examination and 22 (15%) did not attend the point of care. Of the HPV-positive women who underwent VIA, 10 were VIA positive and consequently treated with cryotherapy (Fig. 2).

VIA arm

Of the 466 women screened by VIA, 22 (4.7%) were positive; 15 (3.2%) examinations were inconclusive, because the squamo-columnar junction zone (SCJZ) was not adequately visible. Two women refused the procedure after counselling. As part of the quality assurance, we rescreened all women found to be positive or inconclusive by a well-trained gynecologist. Accordingly, of the 22 women found positive by trained nurses, 11 (50%) were found to be positive by reexamination, 6 (27.3%) were negative, and 5 (22.7%) did not attend their appointment. Of the women who were positive on rescreening, 8 women received cryotherapy, and 1 was highly suspicious for cervical cancer and therefore referred for hysterectomy at the Butajira General Hospital. Cryotherapy was postponed for 1 woman due to pregnancy and 1 woman refused the cryotherapy treatment (Fig. 3).

Discussion

In this randomized trial, we compared the uptake and adherence of procedures for cervical cancer screening between self-sampled HPV testing with VIA in a population-based setting in Ethiopia. By using the lowest administrative unit in the community, including local health extension workers to invite the women, and selecting the unique IDs of 80 women in each cluster, we assured targeting a random population sample. Reducing the current burden of cervical cancer can only be achieved through a high uptake of cervical cancer screening by the targeted population (19). This study demonstrated higher uptake and adherence of HPV-based screening than of VIA, the standard method in Ethiopia. About 84% of sensitized women from the HPV arm attended screening, while only 50.5% attended VIA. Of those women attended screening in both arms, 65.4% and 40% adhered to all procedures expected after screening in the HPV and VIA arm, respectively. The improvement of screening uptake through self-sampled HPV-based testing has been reported by several studies. Self-sampling avoids multiple barriers associated with VIA, such as, taboo related with medical vaginal examination, fear of pain, long travel to the point of care, and long waiting time at health facilities (19, 28).

Study findings highlighted that the HPV triage eventually showed an increased uptake of VIA in this population. Accordingly, 85% of the women positive for hrHPVs underwent VIA screening. Similarly, studies

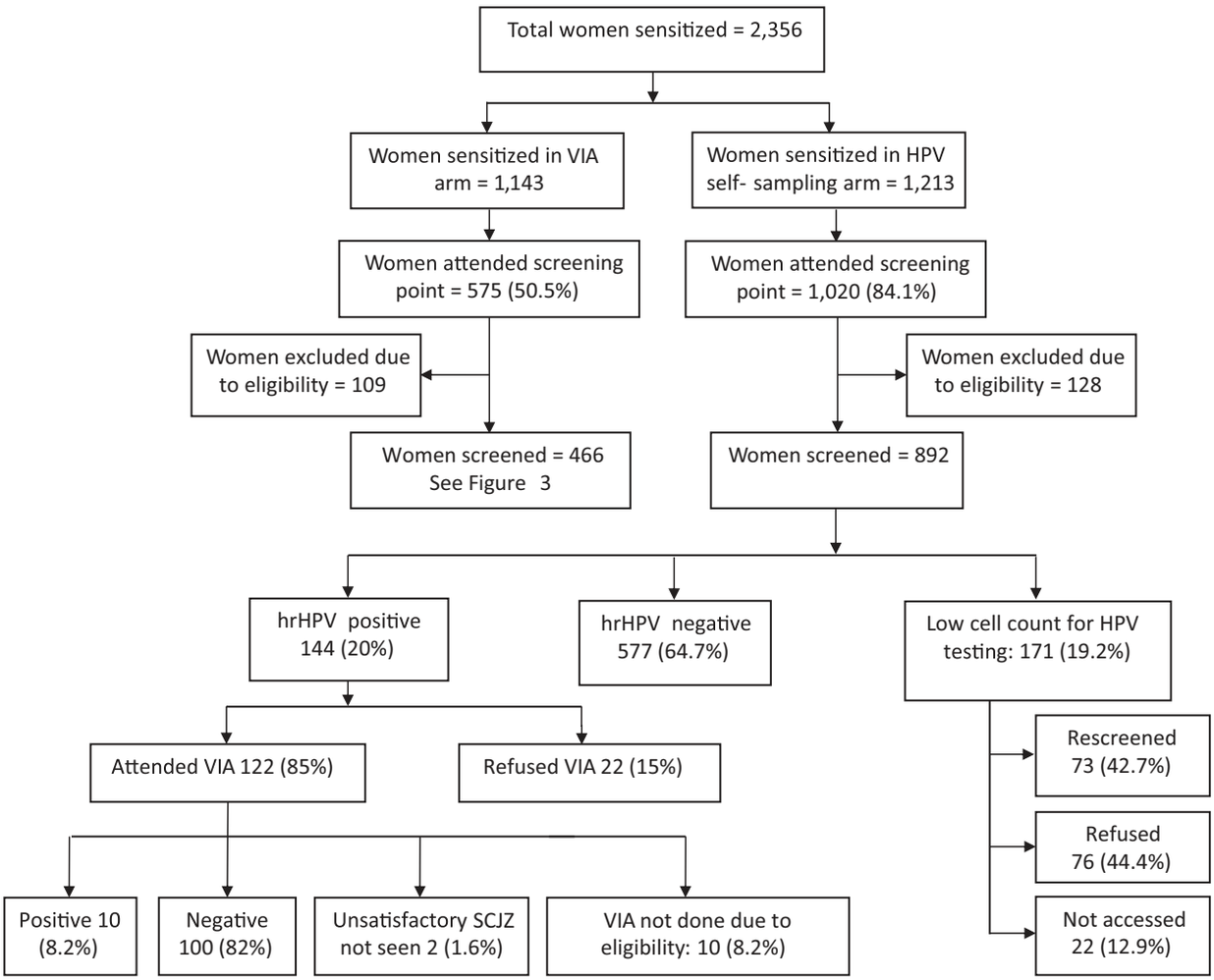

Figure 2.
Study trial flow chart and screening adherence outcomes for women who participated in HPV arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

conducted elsewhere reported that the majority of women who tested HPV positive will more likely comply with the subsequent medical advice (19). Among the women positive for hrHPV in the HPV arm, only 10 (8.2%) were positive in the triage test, VIA in this case. About 171 (19.2%) of women did not perform the sample collection properly. As a result, these samples were inadequate for the detection of HPV infection. In the VIA arm, a lack of consistency in interpreting the result by different providers has been a critical challenge in this study. Of the women who attended VIA screening, 22 (4.7%) of women were first identified as VIA positive or inconclusive by a trained nurse. However, only half of the women were found to be positive for VIA during the verification by an experienced gynecologist. Similarly, the subjective variability has been identified as one of the pitfalls of the VIA screening (16, 29, 30). In both arms, the majority of VIA-positive patients were treated by cryotherapy at the point of care; otherwise, they were sent to the gynecologist for further investigation and treatment at the district hospital.

Despite various advantages of the screening test used, maintaining a higher coverage of screening among targeted individuals must be assured. To improve the coverage of screening, the service must be accessible, with a short waiting time and simple protocol to comply with. Regarding the accessibility of both screening approaches, the HPV test was offered in the women's vicinity (accessible on foot), while women randomized to the VIA arm had to travel (mainly motor-vehicle) to undergo the screening, which may have contributed to the lower uptake and adherence to screening procedures. Women did not report any perceived difficulties in accessing the HPV testing, whereas 30% of the women

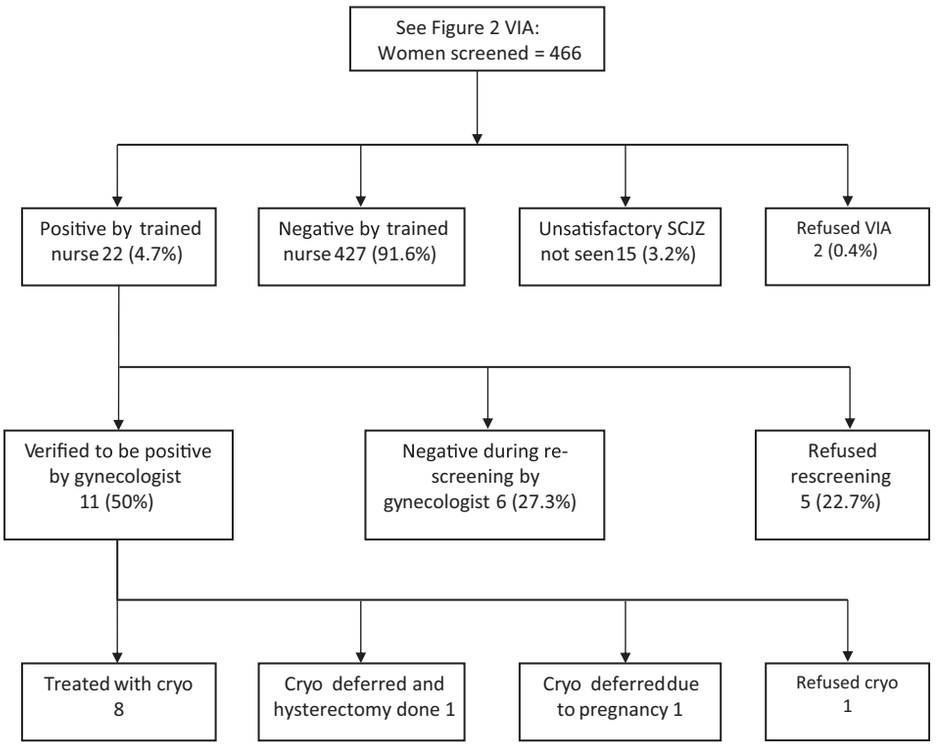

Figure 3.
Study trial flow chart and screening adherence outcomes for women who participated in VIA arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

reported difficulties reaching the VIA and a long waiting time as an additional barrier. Although the HPV testing for cervical cancer screening had a better uptake by the eligible women in this study, there have been several challenges to providing HPV-based cervical cancer screening. Because HPV-based sampling requires a strict working protocol, there needs to be an adequate health and laboratory structure in place or a point of care test can be considered after the development of new tests.

The lack of a point-of-care test in the HPV arm in our study may have led to delays in disclosing the results. In addition, organizing follow-up is another critical problem of HPV-based screening. Moreover, laboratory procedures to process the results require trained health personnel, several machines, and numerous consumables. Hence, full scale up of the HPV-based screening might be difficult in countries where having constrained health system.

This study has limitations. We are aware that the distance to the VIA service was rather far in our setup, so providing a VIA service closer to the population would possibly increase the uptake. There were additional charges of travel to the place at which VIA screening was done. Moreover, this study did not consider costing analysis to compare the feasibility of HPV-based screening over the conventional screening approach.

Conclusion

With proper and rigorous community sensitization, self-sampled HPV testing is feasible, resulting in the high uptake of screening for cervical cancer in Ethiopia. The study demonstrated that women who tested positive for HPV were more likely to go for follow-up screening. Regardless of the better uptake of HPV testing, to scale-up HPV-based screening in Ethiopia, the capacity of the health system must be properly evaluated and strengthened by assuring the presence of a point of care to efficiently process the collected samples.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Gizaw, T. Abebe, A. Worku, A. Addissie, E.J. Kantelhardt

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Gizaw, B. Teka, F. Ruddies, T. Abebe, A.M. Kaufmann, A. Worku

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Gizaw, T. Abebe, A.M. Kaufmann, A. Worku, A. Wienke, A. Jemal, A. Addissie, E.J. Kantelhardt

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Acknowledgments

Funding for this research was provided by Else Kröner-Fresenius-Stiftung, Germany with grant number 2017_HA03.

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Received March 16, 2019; revised May 23, 2019; accepted July 16, 2019; published first July 23, 2019.

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