Research Article

Cancer Prevention Research

Participation in Cervical Screening by Self-collection, Pap, or a Choice of Either in Brazil

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Abstract

Most cervical cancers occur in women who do not participate in cervical-cancer screening. We therefore evaluated adherence to screening for clinic-based Pap testing, self-collected sampling for HPV testing, and choice of the 2 among 483 unscreened/underscreened women in Brazil. Three public Basic Health Units (BHU) were each randomly assigned to three arms: (i) Pap testing at the BHU ($N = 160$), (ii) "Self&HPV" (self-collection for HPV testing) ($N = 161$), and (iii) "Choice" between self-collection and HPV testing and Pap test at the local BHU ($N = 162$). The theory-based (PEN-3 and Health Belief Model) intervention in all three arms was implemented by trained Community Health Workers (CHW) at participants' home. With the first invitation, 60.0% in the Pap arm, 95.1% [154 of 161 (95.7%) who selected Self&HPV and 0 of 1 (0.0%) who selected Pap] in the Choice arm, and 100% in the Self&HPV arm completed screening. By the second invitation to choose a method of screening in the Choice arm, 100% completed screening. After three invitations, 75.0% of women in the Pap arm completed screening. Adherence to screening differed by study arm ($P < 0.001$). In conclusion, Self&HPV testing is a promising strategy for unscreened/underscreened women who are recalcitrant or unable to undergo clinic-based cervical screening to complement the screening modality used in the general population. In Brazil, where Pap testing is recommended for routine cervical screening, training CHWs in behavior change strategies and offering Self&HPV or Choice could greatly improve screening population coverage by reaching the unscreened/underscreened populations.

Background

Cervical cancer is a highly preventable cancer and mostly occurs in women who do not participate in cervical-cancer screening (1–3). Pap (cytology) testing-based cervical-cancer screening programs have been responsible for the decline in the cervical cancer burden in the United States and other developed countries (4, 5). However, despite the fact that cytology screening programs are widely available, accessible, and at no cost to women living in Brazil through the public health system, some women do not fully take part in these programs primarily due to intrapersonal barriers such as lack of perceived need, symptoms, knowledge, physician recommendation as well as embarrassment, competing priorities, and illiteracy (6–9). Even when structural barriers are minimized in a socialized medicine context, intrapersonal barriers persist. Therefore, alternative patient-centered strategies that complement the ongoing cervical-cancer screening programs must be considered for women who are not reached by these traditional approaches.

Self-collection of cervicovaginal specimens for human papillomavirus (HPV) testing is a promising strategy for increasing screening, particularly if delivered by trusted members of the community such as Community Health Workers (CHW). Self-collection can be done at a convenient location (e.g., home, workplace, and church) and time without using limiting resources such as clinics and clinicians, or requiring a pelvic exam, all of which may prevent some women from seeking screening. Moreover, self-collection engages women to take greater responsibility for their health.

A meta-analysis (10) showed that HPV testing of self-collected cervicovaginal specimens is very sensitive for cervical precancer and cancer; when a validated polymerase chain reaction (PCR)–based assay is used, the performance of HPV testing of self-collected cervicovaginal specimens is equivalent to HPV testing of a provider-collected specimen. Another meta-analysis concluded that self-collection can increase screening in populations not participating in

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routine screening; sending kits to nonparticipants can increase participation by approximately 10%, although active engagement through door-to-door recruitment can increase participation by ~40% (10).

Most studies of self-collection in low- and middle-income countries (LMIC) have not evaluated actual patient preferences, as measured by screening adherence. Rather, studies in LMICs have had enrolled, consenting women undergo self-collection with or without also getting a provider-collected specimen and then relied on questionnaires and interviews to understand the acceptability/patient preferences for self-collection (11–14). As an exception, in a randomized trial of almost 6,000 women in Argentina, women offered self-collected sampling were 4-fold more likely to complete screening compared with those who were offered clinic-based provider-collected sampling for cytology (86% vs. 20%, respectively; ref. 15). In a feasibility study in the Mississippi Delta, a low-resource setting in the United States, women were approximately twice as likely to choose and almost twice as likely to complete their self-collected sampling for HPV testing compared with provider-collected sampling for cytology, for an almost 4-fold overall effect (16).

To our knowledge, no study has compared the adherence to screening for clinic-based, provider-collected sampling for screening (e.g., cytology), self-collected sampling for HPV testing, and choice of the two in any setting. We therefore conducted a trial of these screening strategies among 483 women aged 25 to 64 years in Maringá, Brazil, who had not been screened in 4 or more years to assess adherence to screening through a participatory, theory-based, culturally relevant intervention delivered by trained CHWs. Our primary goal was to understand women's preferences and adherence across these modalities (Pap only, self-collected sampling for HPV testing, and choice between Pap and self-collected sampling for HPV testing), which will inform strategies to be implemented in response to the World Health Organization call to eliminate cervical cancer (https://www.who.int/reproductive health/call-to-action-elimination-cervical-cancer/en/).

Ethics approval

The research protocol was approved by the Institutional Review Boards of all involved academic institutions (Albert Einstein College of Medicine, Bronx, NY; Universidade Estadual de Maringá, Maringá, Paraná, Brazil; Universidade Estadual de Londrina, Londrina, Paraná, Brazil; and University of Alabama at Birmingham, Birmingham, AL) and Maringá Municipal Health Department (Maringá, Brazil). All participants completed informed, written consent.

Materials and Methods

Geographic setting

The town of Maringá is located in the northeast of the State of Paraná in the south of Brazil. The town has 29 public basic health units (BHU), and each BHU has five groups of health care professionals (including CHWs) that provide health care to individuals and families within a geographic area. Each group was responsible for approximately 4,000 individuals. Three BHUs (one BHU per arm) were chosen due to the estimated population served and comparable cervical cancer incidence rates. Women were recruited to participate from March to October 2016.

Sampling

Women between ages of 25 and 64 years were recruited because this was the recommended screening age by the Brazilian Cancer Institute (17), and the median age of women with cervical precancer is late 20s and early 30s years (18). Within each of BHUs (and prior to randomization), CHWs and clinical staff generated a list of women who were registered in the BHU and had not been screened within the past 4 years despite its multiple efforts to do so. These lists were distributed among the CHWs for a home visit inviting them to participate in the study.

Intervention development

The PEN-3 and Health Belief Models (PEN-3/HBM) guided intervention development and implementation because the ultimate goal was to promote behavior change—participation in cervical-cancer screening. Detailed description of these behavior change models is provided elsewhere (19). Intervention mapping was the methodological framework that guided intervention development following the five steps proposed by Bartholomew and colleagues (20): (i) delineate proximal program objectives, which is described above; (ii) select theory-based intervention methods and strategies—extensive formative assessments were conducted at a BHU not included in trial. These included focus groups with women who were current with their cervical-cancer screening, focus groups with unscreened/underscreened women, and qualitative interviews with CHWs to identify barriers and facilitators to cervical-cancer screening and their input toward intervention strategies. Findings were organized to be consistent with the behavior change theoretical framework (PEN-3/HBM) and proposed objectives/outcomes; (iii) develop a program plan—during this phase, intervention materials/strategies were developed and pretested among unscreened/underscreened women, health care professionals, and CHWs at the same BHU where the formative assessments were conducted; (iv) plan for adoption in implementation—the actual implementation began with CHW capacity building. Because the goal of the study was to examine the effectiveness of the three screening modalities, all CHWs involved in the study received the same training in cervical cancer/HPV knowledge, protection of human subjects in research, and behavior change skills. Then, CHWs at each BHU received specific training on the intervention assigned to that particular BHU to avoid contamination (21); and (v) create

evaluation plans and instruments—during this phase, our assessment measures and standard operations procedures manual were finalized (20).

Intervention arms

The intervention in all three arms was implemented by CHWs at participants' home. Once eligibility and willingness to participate were determined, participants completed the consenting procedures and a short interviewer-administered questionnaire (on demographics, health care utilization, family history of cancer, and cervical cancer perceived risk and perceived severity) and then received a brief educational intervention in the context of the PEN-3/HBM. Although CHWs had an educational brochure with key messages to guide the session, this was an interactive session in which CHWs engaged a participant in an informal conversation in order to tailor the discussion with each participant to address structural, intra/interpersonal barriers or gaps in knowledge and reinforce motivators/facilitators that were relevant for each woman.

The educational session for all three arms was identical except for HOW women were to get screened. Participants in the Pap arm were only provided with a Pap test appointment at the local BHU. Participants in the self-collection for the HPV testing (Self&HPV) arm were only provided with the option of self-collection. Participants in the Choice arm were given both options (Self&HPV or Pap test at the local BHU).

Participants in the Self&HPV arm or those in the Choice arm who choose self-collection received a self-collection kit. CHWs provided details on how to collect the sampling. The self-collection kit for this study consisted of "Just for ME" self-collection kit (Preventive Oncology International), which included a self-collection device, written and diagrammatic instructions for self-collection, FTA Elute Card, and self-sealing cardboard carrier. Participants had the option to engage in self-collection during the CHW visit or arrange for a day/time for the CHW to return to gather the sample.

Participants in all three arms were given 15 days to comply with screening. Those who did not comply were contacted either by a phone call or in-person reminder and given another 15-day window to complete the intervention. Women assigned to the Pap arm were given an additional opportunity to get screened. That is, two additional Pap appointments were scheduled for them after the first invitation to be screened at the BHU. Those who did not participate after the two 15-day periods (self-collection) or missed three Pap appointments were categorized as a failure to comply and counted against the main endpoint of the study, participation. Women in the Choice arm were given a chance to change their choice during the second visit.

All participants who had normal results regardless of screening method received a follow-up visit from the CHW with the results and a message to continue with regular check-ups at the BHU and follow provider's recommendation for future screening. Participants who had an abnormal Pap or were positive for high-risk HPV also received a follow-up visit from the CHW with a scheduled colposcopy with a gynecologist.

HPV testing

The POI sampler is a modified, validated version of the Qiagen cervical sampler as many studies have used this device for self-collection (10, 15, 22, 23). The modifications were to lengthen the handle for ease of use for self-collection and to lengthen the soft collection bristles to increase the cellularity of the specimen collected. We selected this sampler because its similarities to the Qiagen cervical sampler would predict at least comparable performance. The FTA Elute Cards were used for specimen transport instead of a liquid-based cytology medium, which are commonly used with high-risk HPV tests. The reasons for using the FTA are that they are dry and therefore not prone to leakage and spilling, the collection membrane is impregnated with proprietary denaturant, rendering any pathogens (e.g., HIV) inactive while preserving and stabilizing nucleic acids, and the card changes color when the sample is applied to it, giving the woman instant feedback that she has done the procedure correctly. Used FTA cards were hand delivered to one of the investigators through weekly visits with the CHWs, who logged them and then mailed the cards to a certified laboratory to be tested for high-risk HPV.

The FTA cards were processed as follows: (i) punched between one and four 3-mm punches using a Harris 3-mm micropunch (WB100038) or a Harris 3-mm Uni-Core (WB100039) from the center of a dried specimen sample and place the disks into a sterile 1.5-mL microcentrifuge tube; (ii) washed the punch(es) by adding 1 mL of room temperature sterile water to the tube and vortex for 3×5 seconds (i.e., 15 seconds in total) to; (iii) using a sterile pipette, decant the wash from the tube; (iv) using sterile forceps or a pipette tip, transferred the punch (es) to a clean, sterile 1.5-mL microcentrifuge tube; (v) pipetted 60 μL of sterile water into each tube, ensuring that the punch(es) are completely immersed in the sterile water by centrifuging the tubes for 10 seconds at 10,000 rpm in a microcentrifuge; (vi) transferred the tubes to a heating block and heated at 98°C for 30 minutes; (vii) removed the tube from the block and mixed by vortexing for 60 seconds, (viii) clarified eluate by centrifugation of the tubes at 10,000 rpm for 30 seconds in a microcentrifuge, (ix) transferred eluate to a separate sterile 0.5 mL microfuge tube, and (x) stored the eluate at 4°C for a week or −20°C for more than a week before being used for HPV testing.

Extracted specimens (2–5 μL of the eluted DNA) were tested for high-risk HPV DNA using the cobas HPV test (Roche Molecular Systems) run on the fully automated

cobas 4800 testing platform. The cobas HPV test is a DNA test for high-risk HPV, and the results are reported in three separate channels: HPV16 individually, HPV18 individually, and a pool of 12 other high-risk HPV genotypes [11 definite high-risk, cancer-associated, HPV types (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) plus one possibly HPV genotype (HPV66)]. A fourth channel measures β-globin for specimen adequacy. Inadequate specimens were retested and, if testing was adequate, were the basis of clinical management. If still inadequate, results were treated as positive for patient safety purposes.

Pap testing

Women assigned to or having chosen Pap testing had conventional Pap smears done. Cytologic interpretation was according to The Bethesda System (24). Women with atypical squamous cells of undetermined significance (ASC-US) or more severe cytologic interpretation (ASC-US+) were considered to have a positive Pap test and referred to colposcopy.

Statistical analyses

The *a priori* power analysis was prepared to demonstrate that the study had sufficient sample size for detecting proportion difference of cervical-cancer screening within 30 days among three cervical-cancer screening modality groups. The primary hypothesis was to detect, with 80% power, an increasing linear trend of screening rates over three groups with 98 participants per group and $\alpha = 0.05$ by performing a two-sided Cochran–Armitage test for trends in proportions based on the assumption 0.25, 0.35, and 0.45 cervical-cancer screening rates by Pap, Self&HPV, and Choice arms, respectively. The second hypothesis was to detect, with 80% power, the difference between the null-hypothesis proportion of 0.5 (50% of participants in the Choice arm choosing self-collection and HPV testing) and the alternative proportion of 0.65 with total 98 participants by performing two-sided exact binomial test with $\alpha = 0.05$.

Assigning a screening strategy for participants in a BHU, rather than each individual separately, has important consequences for sample-size estimation (25, 26). Participants in a neighborhood are likely to be heterogeneous, giving rise to a component of variation to consider (26). Because participants in three CHWs' microareas per BHU will be chosen for a cervical-cancer screening modality, the unadjusted calculated sample size must be further increased by an inflation factor to account for clustering. The inflation factor is given by the following equation: $IF = [1 + (m - 1)\, p]$, where m represents the number of participants per CHW's microarea, and p represents the intraclass correlation coefficient (ICC), the ratio of between-microarea variation and total variability. In this study, we assume ICC is 0.02 consistent with typical values of ICC in community-based studies (27). Calculating the inflation factor and adjusting the aforementioned sample size per group, the sample size to maintain 80% power, with an ICC of 0.02, was 161 per cervical-cancer screening modality group. If ICC was weaker than we expected, there would be greater power to detect the same difference size or the same power to detect smaller difference size in the proportions between the study arms.

Data on sociodemographics, knowledge of cancer, cervical cancer, and HPV, and healthcare utilization were tested for statistical differences between arms using Fisher exact test for categorical data and Kruskal–Wallis for continuous data. Completion of screening or screening and colposcopy was compared between study arms using Fisher exact test. The overall high-risk HPV prevalence was compared between those women who completed self-collection in the Choice and Self&HPV arms, crudely using Fisher exact test and adjusting for age group (25–29, 30–39, 40–49, 50–59, and 60–64 years) distribution using logistic regression. Among those who completed self-collection in the Choice or Self&HPV arms, the combined overall and age-group–specific high-risk HPV prevalence with binomial exact 95% confidence intervals (95% CI) were calculated. Fisher exact test was used to test for determinants of testing high-risk HPV positive. A nonparametric test of trend was used to assess trends across categorical variables (28). STATA version 15.1 (STATA) was used for analyses. P values were two-sided and P values less than 0.05 were considered significant.

Results

One hundred sixty women assigned to Pap were offered an appointment to get Pap testing, 162 women assigned to "choice" were offered a choice of self-collection or an appointment for Pap testing, and 161 women assigned to Self&HPV were offered self-collection. Age distributions (mean; median; interquartile range) for women in the Pap arm (45.3; 45; 37–56 years), Choice arm (45.8; 48; 36–55 years), and Self&HPV arm (47.7; 49; 40–56.5 years) were not significantly different ($P = 0.1$), although women in the Self&HPV arm tended to be slightly older.

The data on self-reported sociodemographics, knowledge of cancer, cervical cancer, and HPV, and healthcare utilization are shown in Table 1. There were no differences by study arm in marital status ($P = 0.4$), race ($P = 0.3$), parity ($P = 0.6$), and whether they were working or not ($P = 0.1$). There was a significant difference by study arm in the level of education ($P = 0.001$), with women randomized to the Pap arm tending to be the least educated and those to the Self&HPV arm tending to be the most educated.

There were (marginal) differences across the groups with regard to perception of the seriousness of cervical cancer ($P = 0.06$) and having heard of HPV ($P = 0.04$). Women in the Self&HPV arm were more likely than those in the Pap and Choice arms to report that they never have routine exams (39.8% vs. 22.5% and 21.0%, respectively,

Table 1. Sociodemographics, knowledge of cancer, cervical cancer, and HPV, and healthcare utilization for the three cervical screening arms of the trial, Pap, Choice [of Pap or self-collection and high-risk HPV testing (Self&HPV)], or Self&HPV

	Pap arm		Choice arm		Self&HPV arm		Total		
	N	%col	*N*	%col	*N*	%col	*N*	%col	*P*[a]
Sociodemographics									
Marital status									
Single	22	13.8%	17	10.5%	23	14.3%	62	12.8%	0.4
Married/living together	110	68.8%	108	66.7%	108	67.1%	326	67.5%	
Separated/divorced	23	14.4%	20	12.3%	19	11.8%	62	12.8%	
Widowed	5	3.1%	16	9.9%	10	6.2%	31	6.4%	
Missing	0	0.0%	1	0.6%	1	0.6%	2	0.4%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Race/ethnicity									
Black	15	9.4%	15	9.3%	10	6.2%	40	8.3%	0.3
White	100	62.5%	84	51.9%	102	63.4%	286	59.2%	
Mixed	43	26.9%	58	35.8%	44	27.3%	145	30.0%	
Other/Asian/Indigenous/missing	2	1.3%	5	3.1%	5	3.1%	12	2.5%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Parity									
0 Children	14	8.8%	14	8.6%	19	11.8%	47	9.7%	0.6
1–2 Children	78	48.8%	82	50.6%	77	47.8%	237	49.1%	
3–7 Children	61	38.1%	53	32.7%	59	36.6%	173	35.8%	
Missing	7	4.4%	13	8.0%	6	3.7%	26	5.4%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Education									
Did not finish middle school	65	40.6%	61	37.7%	62	38.5%	188	38.9%	**0.001**
Finished middle school	35	21.9%	38	23.5%	32	19.9%	105	21.7%	
Finished high school	48	30.0%	63	38.9%	66	41.0%	177	36.6%	
Missing	12	7.5%	0	0.0%	1	0.6%	13	2.7%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Work									
Not working	99	61.9%	83	51.2%	83	51.6%	265	54.9%	0.1
Working	61	38.1%	78	48.1%	77	47.8%	216	44.7%	
Missing	0	0.0%	1	0.6%	1	0.6%	2	0.4%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Cancer related variables									
Do you have a family history of cancer?									
Yes	88	55.0%	77	47.5%	95	59.0%	260	53.8%	0.2
No	66	41.3%	82	50.6%	65	40.4%	213	44.1%	
Don't know/uncertain	3	1.9%	2	1.2%	1	0.6%	6	1.2%	
Missing	3	1.9%	1	0.6%	0	0.0%	4	0.8%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Are you at risk for cervical cancer?									
Yes	92	57.5%	93	57.4%	85	52.8%	270	55.9%	0.6
No	49	30.6%	55	34.0%	54	33.5%	158	32.7%	
Don't know/uncertain	18	11.3%	14	8.6%	22	13.7%	54	11.2%	
Missing	1	0.6%	0	0.0%	0	0.0%	1	0.2%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
How serious is cervical cancer?									
Not	0	0.0%	2	1.2%	0	0.0%	2	0.4%	0.06
Somewhat	6	3.8%	0	0.0%	3	1.9%	9	1.9%	
Serious	78	48.8%	65	40.1%	74	46.0%	217	44.9%	
Extremely serious	67	41.9%	90	55.6%	79	49.1%	236	48.9%	
Don't know/uncertain	8	5.0%	4	2.5%	4	2.5%	16	3.3%	
Missing	1	0.6%	1	0.6%	1	0.6	3	0.6%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Have you heard of HPV?									
Yes	115	71.9%	135	83.3%	125	77.6%	375	77.6%	**0.04**
No	44	27.5%	24	14.8%	32	19.9%	100	20.7%	
Don't know/uncertain	1	0.6%	3	1.9%	2	1.2%	6	1.2%	
Missing	0	0.0%	0	0.0%	2	1.2%	2	0.4%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Healthcare utilization									
Visits the doctor when sick?									
Never	10	6.3%	10	6.2%	11	6.8%	31	6.4%	0.8
Sometimes	83	51.9%	95	58.6%	96	59.6%	274	56.7%	
Only with an appointment	17	10.6%	15	9.3%	13	8.1%	45	9.3%	
Always	33	20.6%	31	19.1%	32	19.9%	96	19.9%	
Never sick	17	10.6%	11	6.8%	9	5.6%	37	7.7%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	

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Table 1. Sociodemographics, knowledge of cancer, cervical cancer, and HPV, and healthcare utilization for the three cervical screening arms of the trial, Pap, Choice [of Pap or self-collection and high-risk HPV testing (Self&HPV)], or Self&HPV (Cont'd)

	Pap arm		Choice arm		Self&HPV arm		Total		
	N	%col	*N*	%col	*N*	%col	*N*	%col	*P*[a]
Gets routine exams									
Never	36	22.5%	34	21.0%	64	39.8%	134	27.7%	**0.004**
Every 4 or more years	26	16.3%	34	21.0%	21	13.0%	81	16.8%	
Every 2 to 3 years	27	16.9%	27	16.7%	17	10.6%	71	14.7%	
Every year or more frequently	71	44.4%	67	41.4%	59	36.6%	197	40.8%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	
Healthcare utilization									
Uses basic health unit	42	26.3%	45	27.8%	55	34.2%	142	29.4%	0.3
Uses private clinic	139	86.9%	134	82.7%	123	76.4%	396	82.0%	0.05
Uses urgent care	85	53.1%	44	27.2%	89	55.3%	218	45.1%	<**0.001**
Uses hospital	144	90.0%	152	93.8%	144	89.4%	440	91.1%	0.3
Last mammography exam[b]									
1 Year or sooner	12	20.7%	10	14.3%	6	8.2%	28	13.8%	0.2
2–3 Years	9	15.5%	13	18.6%	17	23.3%	39	19.2%	
4 Years or longer	19	32.8%	35	50.0%	36	49.3%	90	44.3%	
Never	18	31.0%	12	17.1%	14	19.2%	44	21.7%	
Don't know/uncertain/missing	0	0.0%	0	0.0%	0	0.0%	2	1.0%	
Total	58	100.0%	70	100.0%	73	100.0%	203	100.0%	
When did you have your last Pap?[c]									
4 Years	68	42.5%	73	45.1%	52	32.3%	193	40.0%	<**0.001**
5 Years	21	13.1%	38	23.5%	26	16.1%	85	17.6%	
>5 Years	59	36.9%	41	25.3%	62	38.5%	162	33.5%	
Never	12	7.5%	9	5.6%	13	8.1%	34	7.0%	
Don't know/uncertain	0	0.0%	0	0.0%	8	5.0%	8	1.7%	
Missing	0	0.0%	1	0.6%	0	0.0%	1	0.2%	
Total	160	100.0%	162	100.0%	161	100.0%	483	100.0%	

[a]Two-sided, Fisher exact test; bolded values highlight statistical significance ($P < 0.05$).
[b]Among women ages 50 and older.
[c]Women had undergone screening in <4 years were ineligible for the study.

$P = 0.004$). Women in the Pap and Self&HPV arms reported that they were more likely than those in the Choice arm to report using Urgent Care health facilities (53.1% and 55.3% vs. 27.2%, respectively, $P < 0.001$). There were differences in when women reported last having a Pap test ($P < 0.001$), but there were no clear trends, i.e., the percentage of women reported never having a Pap was similar across study arms (7.5% for Pap arm, 5.9% for Choice, and 8.1% for Self&HPV).

Figure 1 shows the consort diagram for each arm, and Table 2 shows the cumulative adherence with screening and colposcopy by round of intervention and study arm. With the first invitation to participate, 60.0% completed screening in the Pap arm, 95.1% completed screening in Choice [154 of 161 (95.7%) who selected Self&HPV completed screening and 0 of 1 (0.0%) who selected Pap completed screening], and 100% completed screening in the Self&HPV arm. By the second invitation to choose a method of screening in the Choice arm, 100% completed screening. After three invitations, 75.0% of women in the Pap arm completed screening. Thus, adherence to screening was differed by study arm ($P < 0.001$). Of those who either chose or were assigned self-collection, 94.7% of them completed their self-collection on the same CHW visit at which they were given the self-collection kit.

Fifteen of 17 (88.2%) high-risk HPV-positive women who selected self-collection in the Choice arm and 15 of 18 (83.3%) high-risk HPV-positive women in the Self&HPV arm underwent colposcopy; surprisingly, none of the women who underwent Pap testing had an abnormal Pap and required colposcopy. Thus, adherence to screening and colposcopy differed by study arm (75% for the Pap arm, 98.8% for the Choice arm, and 98.1% for the Self&HPV arm; $P < 0.001$). Greater education attainment was associated with increased adherence in the Pap arm ($P_{trend} = 0.002$); no other factors were related.

There was no difference in crude high-risk HPV prevalence (11.0% and 11.3%, respectively, $P = 0.5$) or the age-adjusted high-risk HPV prevalence using logistic regression ($P = 0.8$) between women who chose self-collection and those assigned to it. Among the high-risk HPV positives, there was no difference in the high-risk HPV category, although those who self-collected in the Self&HPV arm were nonsignificantly more likely to have HPV16 or HPV18 than those choosing self-collection in the Choice arm ($P = 0.09$). Age was the only significant determinant of high-risk HPV prevalence. As shown in Fig. 2, high-risk HPV prevalence decreased with older age groups ($P_{trend} = 0.02$).

Discussion

To our knowledge, this was the first community-based clinical trial to offer Pap versus self-collection versus choice of either to women who were not adherent to cervical screening in a middle-income country. The adherence to

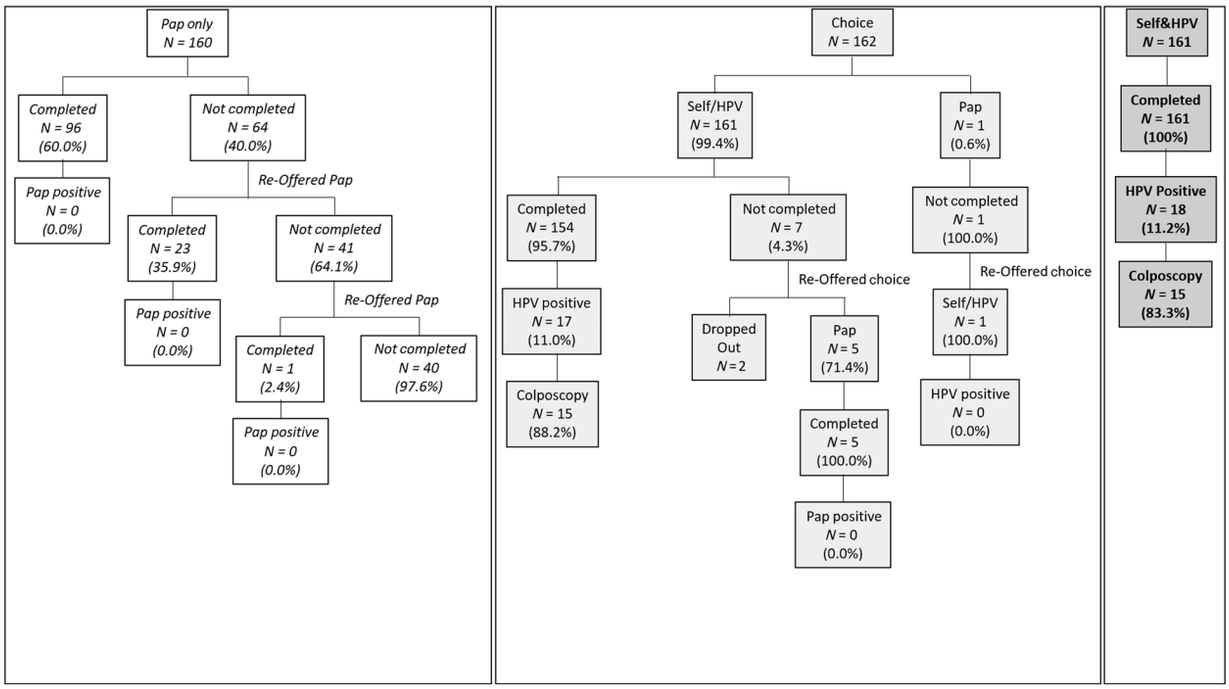

Figure 1.
Consort diagrams for the three cervical screening arms of the trial: Pap, Choice [of Pap or self-collection and high-risk HPV testing (Self&HPV)], or Self&HPV.

the two different screening modalities, Pap or Self&HPV, and in the case of the Choice arm, actual preference for one or the other modality was assessed. Overwhelmingly, women preferred, and were more likely to adhere to, self-collection and HPV testing than Pap.

We noted that the adherence in the Pap arm was much higher than expected and more than a previous experience in the Mississippi Delta region of the United States (16). This greater-than-expected participation may be attributed to two major factors. First, the health care system in Brazil includes decentralized primary care services (BHU) and CHWs are an integral part of the health care teams. Therefore, Brazil already has trained CHWs and community members were used to their presence, but they have not been fully engaged in cervical-cancer screening programs beyond referrals to BHU. In fact, CHWs indicated that they unsuccessfully had tried multiple times to engage some of the participants in cervical-cancer screening prior to the start of the study. The capacity building equipped them with behavior change strategies as evidenced by the significant pre- and post-training changes in perceived skills to promote behavior change and motivate women to be screened (21). This supports our work and others' that CHWs can be actively involved in behavior change if provided with appropriate training and supervision (29–34).

Second, structural barriers were removed as participants were given set appointments, with date and time, compared with routine practice in other settings in which women simply are required to show up at the clinic and wait their turn for cervical screening. As described above, CHWs were equipped to address intrapersonal barriers. As a consequence of the high participation rates overall, whether there were any multiplicative effects of offering choice versus self-collection only could not be assessed. That is, whether offering a choice was more effective than offered sequentially, as would be predicted by the participation in each modality individually (%Participation [choice] > %Participation [Self&HPV] + ((1 − %Participation [Self&HPV]) × %Participation [Pap]) could not be measured.

Table 2. Adherence to cervical screening and cervical screening and colposcopy for the three cervical screening arms of the trial, Pap, Choice [of Pap or self-collection and high-risk HPV testing (Self&HPV)], or Self&HPV

	Study arm					
	Pap only ($n = 160$)		Choice ($n = 162$)		Self&HPV ($n = 161$)	
Number of interventions	Completion of screening	Completion of screening and colposcopy	Completion of screening	Completion of screening and colposcopy	Completion of screening	Completion of screening and colposcopy
First	60.0%	60.0%	95.7%	93.8%	100.0%	98.1%
Second	74.4%	74.4%	100.0%	98.8%		
Third	75.0%	75.0%				

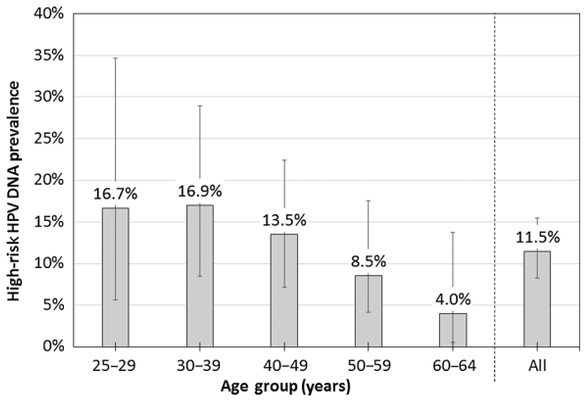

Figure 2.

High-risk HPV prevalence, with 95% confidence intervals shown as bars, stratified by age group and for all women who underwent self-collection and high-risk HPV testing (Self&HPV) in the Choice or Self&HPV arm.

Despite the better-than-expected participation in the Pap arm, it took three rounds of invitation to achieve 75% participation in the cervical screening in this previously nonadherent population. By comparison, nearly 100% of women participated and completed care through colposcopic evaluation with one round of invitation via assignment or choice to screen by Self&HPV. Among those who were high-risk HPV positive ($n = 35$), a high percentage complied with colposcopy (85.7%).

There was also better participation in the Choice arm (95.7%) and a stronger preference for self-collection (99.4%) of the Brazilian women in this study compared with a study of unscreened/underscreened women living in the Mississippi Delta (66.4% and 64.7%, respectively; ref. 16). Comparatively, in an individual-based randomized trial of education versus patient navigation versus choice of Pap versus self-collection conducted in unscreened/underscreened women living in Southern Florida, women assigned to the Choice arm had a 77.3% overall participation and 64.3% chose self-collection (35). The higher preference for self-collection in our study may be attributed to convenience of being recruited at home where they could get their own sampling (94.7% did it on the same day). In contrast, in the study by Carrasquillo and colleagues (35), participants were recruited at community venues (e.g., stores, community centers) in which it may have been harder to engage in self-collection for HPV testing at the time of recruitment.

Comparisons of this study with other studies of high-risk HPV detection using clinical HPV tests in the general population are often confounded by age of the populations studied. Nevertheless, the age-group–specific high-risk HPV prevalence in this study was greater than a high-risk HPV prevalence in more than 5,000 women living in Rio de Janeiro (36) and similar to high-risk HPV prevalence in more than 3,000 women attending routine screening in Campinas, São Paulo, and Porto Alegre, Brazil (37) as detected by Hybrid Capture 2 (Qiagen). Two studies using careHPV (Qiagen) found a slightly higher high-risk HPV prevalence in a somewhat younger population (38) and a slightly lower high-risk HPV prevalence in a comparably aged population (39) than observed in this study. Other studies using research PCR-based assays reported lower or comparable high-risk HPV prevalence in younger populations or higher HPV prevalence in much younger populations than observed in this study (40–42). Given that HPV prevalence is correlated with cervical cancer risk (43), it is inferred from these studies that this study population was at least similar and likely higher risk than the general population of mid-adult women living in Brazil.

Although the prevalence of high-risk HPV in the two comparable populations was ~11%, none of the women who underwent Pap screening had equivocal or definitive cytologic abnormalities. This is worrisome as it was reasonable to expect that approximately half of high-risk HPV infections will have concurrent cytologic abnormalities (ASC-US+), and high-risk HPV-negative ASC-US is a common result. That is, we expect a similar (unmeasured) HPV prevalence in the Pap arm and therefore at least 5% to 6% of women (~6–7 women) in the Pap arm should have had ASC-US+ cytology (44–47). This may be the result of underperforming Pap testing, as has been observed in many places in Brazil (48).

There were several limitations to this study. First, individuals or small clusters of women to each arm were not randomly assigned, which would have achieved better balance of the characteristics of women between arms. Individual randomization was not used because of concerns regarding contamination across arms. Small clusters of women were not randomized because of the logistical challenges of expanding the number of clinics to keep fidelity between clusters. As a result, there were notable differences in sociodemographics, knowledge, and healthcare utilization between groups of women assigned to the different study arms, but these were relatively small compared with the differences in adherence for those in the Pap arm versus the Choice and Self&HPV arms. Notably, there was no pattern in the difference between study arms, i.e., women in the Choice and Self&HPV arms were not more similar to each other than with the Pap arm. Still, differences in adherence may have been influenced by composition of the populations.

Second, the sample size was not sufficient to examine carefully adherence to colposcopy or treatment, or the diagnostic yield of cervical precancer and cancer, by study arm. Such a study would require at least an order of magnitude larger enrollment to address these issues. Yet adherence to the clinical management of screen-positives is critical for the success of the screening program, i.e., screening without management and treatment has little or no cervical-cancer prevention benefits. Future research,

using large screening trials or implementation, need to examine adherence to management algorithms, and cost-effective strategies to improve it, to optimize the effectiveness and cost-effectiveness of screening algorithms.

In conclusion, this study found that unscreened/underscreened women living in Brazil had a strong preference for self-collection and HPV testing as demonstrated by their choice of self-collection in the Choice arm and near-perfect adherence to it and their perfect adherence to self-collection in the Self&HPV arm. Global recommendations for HPV testing aside (49), Self&HPV testing should be offered to unscreened/underscreened women who are recalcitrant or unable to undergo clinic-based cervical screening regardless of the screening modality used in the general population. In Brazil, where Pap testing is recommended for routine cervical screening, training CHWs in behavior change strategies and offering Self&HPV or Choice could greatly improve screening population coverage by reaching the unscreened/underscreened populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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