original reports

Cluster Randomized Trial to Facilitate Breast Cancer Early Diagnosis in a Rural District of Rwanda

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abstract

PURPOSE Feasible and effective strategies are needed to facilitate earlier diagnosis of breast cancer in low-income countries. The goal of this study was to examine the impact of health worker breast health training on health care utilization, patient diagnoses, and cancer stage in a rural Rwandan district.

METHODS We conducted a cluster randomized trial of a training intervention at 12 of the 19 health centers (HCs) in Burera District, Rwanda, in 2 phases. We evaluated the trainings' impact on the volume of patient visits for breast concerns using difference-in-difference models. We used generalized estimating equations to evaluate incidence of HC and hospital visits for breast concerns, biopsies, benign breast diagnoses, breast cancer, and early-stage disease in catchment areas served by intervention versus control HCs.

RESULTS From April 2015 to April 2017, 1,484 patients visited intervention HCs, and 308 visited control HCs for breast concerns. The intervention led to an increase of 4.7 visits/month for phase 1 HCs ($P = .001$) and 7.9 visits/month for phase 2 HCs ($P = .007$) compared with control HCs. The population served by intervention HCs had more hospital visits (115.1 *v* 20.5/100,000 person-years, $P < .001$) and biopsies (36.6 *v* 8.9/100,000 person-years, $P < .001$) and higher breast cancer incidence (6.9 *v* 3.3/100,000 person-years; $P = .28$). The incidence of early-stage breast cancer was 3.3 per 100,000 in intervention areas and 0.7 per 100,000 in control areas ($P = .048$).

CONCLUSION In this cluster randomized trial in rural Rwanda, the training of health workers and establishment of regular breast clinics were associated with increased numbers of patients who presented with breast concerns at health facilities, more breast biopsies, and a higher incidence of benign breast diagnoses and early-stage breast cancers.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Breast cancer incidence and mortality are rising in low-income countries, where patients often present with advanced-stage disease and outcomes are poor.[1] Population-based mammography screening is the only screening strategy demonstrated to reduce breast cancer mortality. However, the effectiveness of mammography has not been studied in low-income countries, where breast cancer incidence rates are lower, the population is younger, and high-quality treatment is less consistently available. Furthermore, population-based mammography screening is not yet feasible in low-income countries. Thus, there is growing interest in identifying novel strategies to detect breast cancer earlier in such settings. Screening clinical breast examination (CBE) may decrease stage at presentation.[2] However, experts in global breast health increasingly recommend the adoption of a phased implementation approach that initially focuses on establishing breast cancer treatment capacity and promoting early clinical diagnosis of symptomatic disease rather than on screening asymptomatic women.[3,4] An early diagnosis approach could target scarce resources to the highest-risk women while health system capacity is being developed. Specific interventions that target symptomatic women in a resource-limited setting have not been rigorously examined.

Rwanda is a low-income East African country with a predominantly rural population of 12 million. Rwanda's health care system comprises a robust network of lay community health workers (CHWs), primary care health centers (HCs) staffed by nurses, district hospitals, and provincial and national referral hospitals. The Butaro Cancer Center of Excellence (BCCOE) is Rwanda's first public cancer care facility to serve as a national cancer referral hospital.[5] BCCOE operates within the district hospital for Burera,

CONTEXT

Key Objective

We sought to understand the impact of a breast cancer early detection intervention for patients and the health care system in rural Rwanda. There is scarce evidence with regard to feasible and effective strategies to diagnose breast cancer earlier in low-income settings. This cluster randomized trial investigated an approach to earlier diagnosis among women with breast symptoms in contrast to screening asymptomatic women.

Knowledge Generated

The training of health workers and establishment of regular breast clinics were associated with increased numbers of patients who presented with breast concerns at health centers, increased hospital referrals, more breast biopsies, and a higher incidence of benign breast diagnoses and early-stage breast cancers among the population served by intervention health centers.

Relevance

Building provider and health system capacity to care for women with breast symptoms is a promising initial strategy to promote earlier diagnosis of breast cancer in resource-limited settings. Programs must ensure access to timely, affordable, and high-quality treatment of all patients diagnosed with cancer.

a mountainous rural district of 372,000 inhabitants. Breast cancer is the most common cancer treated at BCCOE; approximately three quarters of patients are diagnosed with stage III or IV disease.[6]

Prior research at BCCOE demonstrated that patients with breast cancer experienced long delays both before presentation at an HC and between their first presentation and ultimate diagnosis.[7] Both types of delay increase the likelihood of advanced stage disease at diagnosis. We developed a health facility–level intervention in Burera District to train CHWs, HC nurses, and hospital clinicians in strategies to reduce delays at each stage of a symptomatic patient's pathway to diagnosis. We previously described the training and reported its impact on health workers' knowledge and clinical skills.[8] The goal of the current analysis was to assess the impact of this early diagnosis intervention at 2 years for both health care facilities and patients to determine the benefit for patients and the feasibility of a national scale-up for the health care system. Specifically, we sought to examine the intervention's impact on the volume of patients with breast concerns at HCs and the hospital, on biopsy procedures required, and the incidence of breast cancer and benign disease. We also performed an exploratory analysis of the impact on cancer stage.

METHODS

Intervention

Burera District has 19 HCs that serve communities that are socioeconomically and ethnically similar to one another (Appendix Table A1). Eighteen HCs were eligible for the study. We randomly assigned 12 HCs to receive a training intervention for all their nurses and all CHWs who serve their primary catchment areas (ie, their sectors). Seven HCs were randomly assigned to receive the intervention from April to May 2015 (phase 1), and an additional 5 HCs were randomly assigned to receive the intervention from November to December 2015 (phase 2). Six HCs did not receive the training and served as controls throughout the study period (see Appendix Fig A1).

As described previously,[8] the intervention consisted of instruction for CHWs in symptoms of breast cancer and messaging that community members should come to their local HC for any breast symptoms. HC nurses were taught about signs and symptoms of benign breast disease and cancer and how to perform a CBE and were provided with simple clinical algorithms for managing breast symptoms and examination findings, with an emphasis on findings that need urgent hospital-level evaluation. Nurses subsequently received ongoing mentorship and support from a hospital-based nurse-midwife trained in breast health. We also trained hospital clinicians in diagnostic breast ultrasound and ultrasound-guided core needle biopsy and launched weekly breast clinics in intervention HCs and the hospital.

The intervention study period was April 18, 2015, to April 17, 2017. To analyze changes in patient volume, we also examined HC registry data from October 1, 2014, to April 17, 2015.

Data Sources

To determine patient volume, number of referrals, and spectrum of diagnoses among patients who sought care at intervention and control HCs, we collected data from three sources: paper HC patient registries routinely used to record patient visits at intervention and control HCs, paper HC documentation forms for breast health visits developed for this project and used at intervention HCs, and paper and electronic district hospital and BCCOE medical records. We used patient identifiers to link patients across sources (see Appendix).

Key Variables and Outcomes

Intervention versus control HCs. For each HC, we identified the months between April 18, 2015, and April 17, 2017, that it served as an intervention HC and the months that it served as a control HC. HCs trained in April to May 2015 were considered intervention HCs for the whole study period. HCs trained in November to December 2015 were considered control HCs from April 18 to November 12, 2015, and intervention HCs from November 13, 2015, onward. HCs that never received the intervention were considered controls for the whole period.

HC visit volume. We reviewed all HC registries, where patients' names, birthdates, addresses, visit date, and reason for visit are listed. We documented all HC visits and the number of unique patients seen for breast concerns during the study and pre-intervention periods.

HC visit characteristics. Characteristics of patient visits at intervention HCs were abstracted from HC clinical documentation forms (see Appendix).

Patients evaluated at the hospital. The number of patients evaluated at the hospital for breast concerns was documented from oncology, outpatient, and emergency department records during the study period.

Hospital-level services and diagnoses. We abstracted hospital medical records to identify biopsies undergone and cancer and benign diagnoses made.

Breast cancer stage. We used medical records to assign breast cancer stage according to the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual,[9] the staging system used at BCCOE. If a chart did not clearly identify a patient's AJCC stage, we used clinical information in the record to assign an AJCC stage using BCCOE staging protocols. We reviewed all staging decisions with BCCOE clinicians. Because BCCOE protocols require that all patients with breast cancer be assessed for metastatic disease using chest x-ray and abdominal ultrasound, if these studies were not documented for a given patient, we initially classified the patient as having an unknown stage. In a sensitivity analysis, we assigned these patients to the stage that corresponded to their physical examination and/or treatment plan.

Analysis

HC visits. To compare changes in patient visits for breast concerns at intervention versus control HCs, we used a difference-in-differences model with HC as the unit of analysis. We compared the average monthly number of visits for breast concerns during the 6 months before the intervention with the average monthly visits for breast concerns during the 12 months after the intervention for phase 1 intervention HCs, phase 2 intervention HCs, and control HCs (the 6 HCs with no trainings). To calculate the incidence of HC visits for breast concerns, we used as the denominator the population of the primary sector served by each HC. We calculated person-years using each HC's catchment population and the length of time that the HC served as an intervention or control. We used generalized estimating equations to compare incidence between intervention and control areas, adjusting for clustering by HC.

Health services received and cancer incidence. We used generalized estimating equations to compare clinical services received, incident cancers, and incident early-stage cancers in areas served by intervention versus control HCs.

Ethics

Ethical approval for this study was obtained from the Rwanda National Ethics Committee and the Partners Human Research Committee. Health workers who participated in the trainings provided informed consent.

RESULTS

HC Patient Volume

There were 276,282 person-years served by intervention HCs during the study period compared with 302,856 served by control HCs. Overall, on the basis of health registry data from April 2015 to April 2017, 1,486 unique patients visited intervention HCs for breast concerns (537.1 patients/100,000 person-years) *v* 315 patients (104.0 patients/100,000 person-years) who visited control HCs ($P < .001$; Table 1). The mean age of these patients was 30.5 years at intervention HCs and 29.6 years at control HCs. According to registry records, 19.8% of patients with breast concerns at intervention HCs were referred to BCCOE for further evaluation *v* 13.0% at control HCs.

Trends in mean monthly number of visits for breast concerns before and after the training periods are shown in Figure 1. The phase 1 and 2 trainings were associated with immediate 4- and 7-fold increases in HC visits for breast concerns in the first month, respectively. At 12 months, after the phase 1 and 2 interventions, the mean number of visits was still 3- and 4-fold higher than baseline at 6.7 visits (range, 4.6-9.8 visits) and 11.1 visits (range, 5.9-19.8 visits) per month, respectively. In control HCs, the mean visits per month changed from 2.1 to 1.9 12 months after intervention phase 1 and 1.6 to 1.8 12 months after intervention phase 2. This led to a difference-in-differences result of 4.7 visits/month for phase 1 HCs ($P = .001$) and 7.9 for phase 2 HCs ($P = .007$).

Patient Characteristics

Nine hundred seventy-four unique patients had visits with clinical documentation forms completed at intervention HCs during the study period (Table 2). Patients' mean age was 31.4 years, and 44.3% were pregnant or breastfeeding. Thirty patients (3.1%) were noted on the forms to have come for screening, but 20 of these also had a symptom noted. Thus, we considered only the remaining 10 patients (1.0%) to have come for screening. The most

TABLE 1. Patients Seen and Documented Referrals Made on the Basis of Data From Intervention and Control HC Registries: April 18, 2015, to April 17, 2017

Variable	Intervention HCs	Control HCs	*P**
Person-years in catchment areas	276,282	302,856	
No. of patients seen at HCs for breast complaints	1,486	315	
Incidence of HC visits for breast concerns, per 100,000 person-years	537.6	104.0	< .001
Mean age, years (SD)	30.5 (11.7)	29.6 (11.6)	
Documented referral to BCCOE, No. (%)	294 (19.8)	41 (13.0)	

NOTE. Patients seen at an intervention and a control HC (n = 23) are counted in both intervention HC and control HC groups. Patients with a documented referral are those who are identified in the HC registries as having been referred to the hospital on at least 1 of their HC visits.

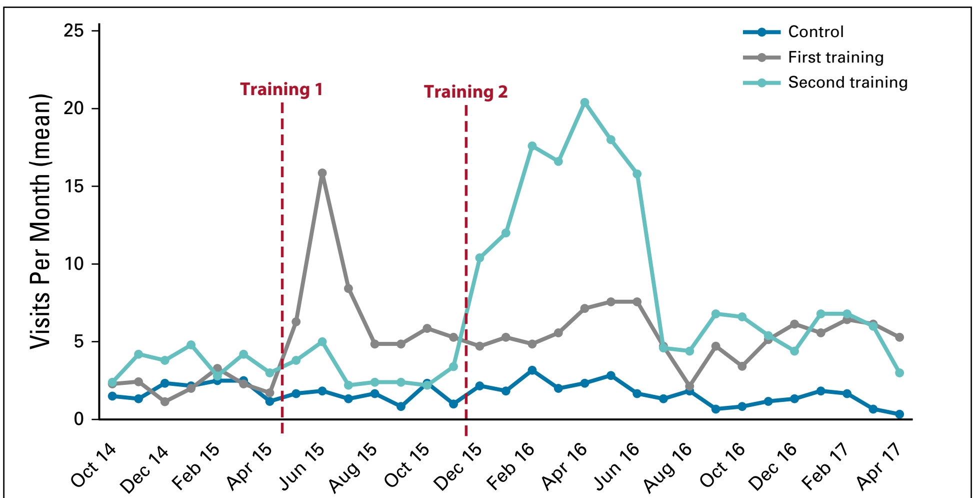
Abbreviations: BCCOE, Butaro Cancer Center of Excellence; HC, health center; SD, standard deviation.

*Generalized linear models adjusting for clustering by HC.

common symptom was breast pain (60.7% of patients) or a mass (26.0%). In their final impressions, nurses documented that 23.6% of patients had breast pain only with no abnormality on examination, 20.9% had a mass, and 13.3% had infections. Nurse impressions were missing for 27.1% of patients. Most patients (54.1%) reported having heard about breast cancer from a CHW. Nurses discharged 18.7% of patients, referred 22.8% to BCCOE, and recommended HC follow-up for 49.1%. Management plans were not documented for 9.4% of patients.

Hospital-Level Services, Diagnoses, and Cancer Stage

Overall, 318 patients referred by intervention HCs were seen at BCCOE during the study period *v* 62 from control HCs (Table 3). The incidence of hospital visits for breast concerns was higher among the population served by intervention versus control HCs (115.1 *v* 20.5 visits/100,000 person-years; $P < .001$; Table 4). Among patients referred from intervention HCs, 101 (31.8%) underwent biopsies *v* 27 (43.5%) of those from control HCs. The incidence of breast biopsies was higher among the population from intervention regions compared with control regions (36.6 *v* 8.9 biopsies/100,000 person-years; $P < .001$). Two hundred seventy-three patients (85.8%) referred from intervention HCs and 51 (82.3%) from control HCs were diagnosed with benign conditions. Among patients referred from intervention HCs, 19 (6.0%) were diagnosed with breast cancer, while 10 (16.1%) from control HCs were diagnosed with breast cancer. The incidence of breast cancer was 6.9/100,000 person-years in



Health Centers	No. of Visits Per Month During 6 Months Before Training, Mean (range)	No. of Visits Per Month During 12 Months After Training, Mean (range)	Difference in Means	Difference-in-Differences	*P*
Intervention, phase 1	2.2 (0.0-4.3)	6.7 (4.6-9.8)	4.5	4.7	.001
Control, phase 1	2.1 (1.0-3.2)	1.9 (1.1-2.8)	–0.2		
Intervention, phase 2	3.0 (1.2-5.3)	11.1 (5.9-19.8)	8.1	7.9	.007
Control, phase 2	1.6 (0.3-3.0)	1.8 (0.9-2.9)	0.2		

FIG 1. Monthly visits for breast concerns before and after the trainings at intervention versus control health centers.

TABLE 2. Characteristics of Patients With Breast Clinic Documentation Forms Completed at Intervention HCs After the Launch of Trainings: April 18, 2015, to April 17, 2017

Characteristic	No. (%)
No. of patients	974
Mean age, years (SD)	31.4 (11.9)
Sex	
Female	931 (95.6)
Male	35 (3.6)
Unspecified	9 (0.8)
Pregnant	59 (6.0)
Breastfeeding	373 (38.3)
Presence of breast symptoms	
None	10 (1.0)
Unknown	16 (1.6)
Symptom present	
Mass	253 (26.0)
Pain	591 (60.7)
Other	40 (4.1)
Type not specified	64 (6.6)
Heard about breast cancer from a CHW?	
No	430 (44.1)
Yes, through an educational session	356 (36.6)
Yes, through individual contact	176 (18.1)
Not documented	12 (1.2)
Nurse impression at initial visit	
Normal breast	80 (8.2)
Breast pain only	230 (23.6)
Breast infection	130 (13.3)
Breast mass	204 (20.9)
Other	66 (6.8)
Missing	264 (27.1)
Initial documented management	
Discharge	182 (18.7)
Follow-up at HC	478 (49.1)
Referral to BCCOE	222 (22.8)
Missing	92 (9.4)

Abbreviations: BCCOE, Butaro Cancer Center of Excellence; CHW, community health worker; HC, health center; SD, standard deviation.

intervention areas *v* 3.3/100,000 person-years in control areas; this was not statistically significantly different (*P* = .28; Table 4). The mean age of the 29 patients with breast cancer was 54 years (standard deviation, 15.7 years). Three were breastfeeding at diagnosis (data not shown).

Among patients from intervention HCs diagnosed with breast cancer, 9 (47.4%) had stage I or II disease (Table 3). One patient had a physical examination suggestive of T3N1 (stage III) disease but no documented imaging to exclude distant metastases as required by BCCOE protocols; she was lost to follow-up before initiating treatment, so for our main analysis she was classified as unknown stage. Among the patients with breast cancer from control HCs, 2 (20%) were diagnosed with early-stage disease. A third patient had T2N0 (stage II) early-stage disease on physical examination and no positive lymph nodes on her surgical pathology report, so she received treatment consistent with BCCOE's protocols for early-stage disease. However, she had no documented imaging to exclude distant metastases as required by BCCOE protocols, so for our primary analysis, she was classified as unknown stage. In our primary analysis, the incidence of early-stage breast cancer was 3.3 per 100,000 in intervention areas and 0.7 per 100,000 in control areas (*P* = .048; Table 4). In our sensitivity analysis, incidence of early-stage disease was 3.3/100,000 person-years in intervention areas *v* 1.0/100,000 person-years in control areas (*P* = .11).

Twenty-six patients (8.2%) from intervention HCs and 1 patient (1.6%) from a control HC did not have documented diagnoses to explain their symptoms (Table 4). Among the patients from intervention HCs, 5 had a biopsy recommended that was not subsequently done, and 2 patients who underwent an initial biopsy did not undergo a recommended second biopsy. Sixteen patients were recommended to have a follow-up clinical or radiologic evaluation, which was not done. Eight of these patients declined to return because of symptom resolution. The remainder could not be reached and were considered lost to follow-up. All patients who lacked diagnostic resolution were contacted by phone by hospital staff 3-6 times.

DISCUSSION

In this cluster randomized trial of a breast cancer early diagnosis intervention in rural Rwanda, the training of CHWs, HC nurses, and hospital staff and establishment of regular breast clinics were associated with increased numbers of patients presenting with breast concerns at HCs and the hospital, more breast biopsies, and a higher incidence of benign breast diagnoses and early-stage breast cancers in the population served by intervention HCs. The provider trainings focused on education, evaluation, triage, and referral of symptomatic women, and the majority of women seen had breast symptoms.

These findings have implications for Rwanda and other low-resource rural settings that seek to implement early detection strategies. First, the volume of patients presenting to HCs for breast concerns increased sharply initially after our CHW and HC trainings and then decreased to a steady rate of 7-11 patients/month, which was still higher than baseline. Although this steady-state volume was modest, staffing adjustments were still required.[8] Countries that are planning educational campaigns in the community or with health providers should prepare to meet an increased demand both initially and longer term. The modest

TABLE 3. Breast Health Services Provided and Diagnoses Made Among Patients Referred From Intervention *v* Control HCs and Evaluated at BCCOE: April 18, 2015, to April 17, 2017

Variable	Referred From Intervention HCs, No. (%)	Referred From Control HCs, No. (%)
No. of patients seen at BCCOE for breast complaint, with identifiable referral from HC	318	62
Mean patient age, years (SD)	33.6 (13.8)	35.0 (16.5)
Breast biopsies	101 (31.8)	27 (43.5)
Diagnoses		
Breast cancer	19 (6.0)	10 (16.1)
Benign*	273 (85.8)	51 (82.3)
Unknown	26 (8.2)	1 (1.6)
Reasons for unknown diagnosis		
Biopsy recommended but not done	5 (19.2)	0
Declined further care	2 (40.0)	0
Patient contacted but not reached	3 (60.0)	0
Biopsy done but report not available	1 (3.8)	0
Biopsy inconclusive and repeat biopsy not done	2 (7.7)	0
Patient contacted but not reached	2 (100.0)	0
Clinical/radiologic follow-up recommended but not done	16 (61.5)	0
Symptoms resolved	8 (50.0)	0
Patient contacted but not reached	8 (50.0)	0
Other/unknown reason	2 (7.7)	1
Breast cancer stage		
I or II	9 (47.3)	2 (20)
III	5 (26.3)	4 (40)
IV	4 (21.1)	3 (30)
Unknown	1 (5.3)	1 (10)

Abbreviations: BCCOE, Butaro Cancer Center of Excellence; HC, health center; SD, standard deviation.
*Clinically, radiologically, or pathologically confirmed benign conditions, including normal breast tissue.

postintervention patient volume likely reflects our focus on reaching symptomatic women. It may also reflect the fact that Burera District's population is more aware of breast cancer than other districts because of BCCOE's proximity, which has resulted in a higher pre-intervention number of visits.

Our findings also have implications for the demand for hospital-level breast diagnostic services as early detection efforts emerge. There was a higher rate of biopsies among the population served by intervention HCs than by control HCs. During the project, we trained BCCOE clinicians in diagnostic breast ultrasound and ultrasound-guided core

TABLE 4. Incidence of BCCOE Visits, Biopsies, Cancer, or Benign Diagnoses and Early-Stage Breast Cancer Among the Population Served by Intervention *v* Control HCs

Service or Outcome	Intervention HCs	Control HCs	*P**
Person-years in catchment areas	276,282	302,856	NA
Incidence of BCCOE visits for breast concerns, per 100,000 person-years	115.1	20.5	< .001
Incidence of breast biopsies, incidence, per 100,000 person-years	36.6	8.9	< .001
Incidence of breast cancer, per 100,000 person-years	6.9	3.3	.28
Incidence of stage I or II breast cancer, per 100,000 person-years	3.3	0.7	.048
Incidence of benign disease, per 100,000 person-years	97.4	16.8	< .001

Abbreviations: BCCOE, Butaro Cancer Center of Excellence; HC, health center; NA, not applicable.
*Generalized linear models adjusting for clustering by HC.

needle biopsy; core needle biopsy needles and pathology services were available onsite. Health systems that are developing early detection programs must plan for increased biopsy demand and determine the role of diagnostic imaging, clinical algorithms to determine which patients will undergo biopsy, where and how biopsies will occur, where pathology will be reviewed, and how results will be shared.

More than 80% of intervention and control HC patients evaluated at the hospital were ultimately diagnosed with benign breast disease, but the incidence of benign disease was significantly higher among areas served by intervention HCs. The high proportion of benign breast concerns is surely related in part to the young age (mean, 31.4 years) of patients seen at intervention HCs; furthermore, approximately one half were pregnant or breastfeeding and may have had lactation- or pregnancy-related breast concerns. Although breast cancer in young, pregnant, and breastfeeding women is a pressing concern in Rwanda and the rest of sub-Saharan Africa,[10] breast cancer is still much more common in older women. In our study, the patients with breast cancer had a mean age of 54.3 years, 10% were breastfeeding, and none were pregnant. Thus, efforts to target older women should be an important component of early diagnosis programs. Of note, an even higher incidence of benign disease would be expected to result from a program focused on screening asymptomatic women. Algorithms to guide the management of women with suspected or confirmed benign breast conditions are also important for early detection programs. We anticipate that our experience can help to refine such algorithms in Rwanda.

Encouragingly, this intervention seemed to facilitate earlier-stage breast cancer diagnoses. This presumably occurred through CHWs' community interactions and nurses' prompt referrals of patients with concerning examination findings. Approximately one half of patients from intervention HCs were still diagnosed with stage III or IV disease, however, which suggests that many patients still presented late with symptoms. The intervention may have facilitated care for women with prevalent late-stage disease that had been clinically apparent for some time. Over time, we would expect to see enhanced downstaging as women come earlier after symptom onset and more incident cancers are diagnosed. However, diagnosing earlier-stage breast cancer will not reduce breast cancer mortality unless access to timely and effective treatment is ensured.

Although we noted a trend toward an increased incidence of breast cancer in intervention catchment areas, this was not significant, likely because of the relatively small numbers of cancers diagnosed. Additional research will be needed to examine rates of cancer diagnoses over time to determine whether early diagnosis efforts reduce the number of undiagnosed cases in the country.

Our study had several strengths. Our partnership with public health facilities allowed us to design and implement an intervention that could be integrated into routine health services. Our randomized design allowed us to isolate the impact of the training intervention on clinical care.

Our study also has several limitations. First, we relied on clinical documentation that was not always complete. We found that some patients identified in intervention HC registries or the hospital did not have clinical documentation forms completed at intervention HCs. This made it challenging to identify rates of loss to follow-up at the HC level; for example, we could not ascertain whether patients were instructed to return for follow-up at HCs but did not return. We also could not determine whether there were patients who were referred to the hospital by HCs but did not arrive because the numbers seen at the district hospital were actually higher than those documented as referred by the HCs.

An additional limitation is that our experience may not be generalizable to other districts in Rwanda or areas outside Rwanda. We previously found that patients from Burera District already experienced shorter system delays, presumably because of increased patient or provider awareness of breast cancer and cancer treatment availability in this district.[7] In other areas of Rwanda, a similar intervention could have a greater impact. At the same time, implementation might be more challenging with providers in other areas if they have less cancer awareness. In addition, interventions in areas farther from a cancer center may require even more attention to ensuring timely follow-up and access to diagnostic and treatment services. However, comparable capacity-building efforts in Zambia and other countries have demonstrated the feasibility of building breast cancer diagnostic capacity at the primary, secondary, and tertiary levels in other resource-limited settings.[11]

We faced several challenges in implementing our intervention. Some patients evaluated at the hospital did not achieve diagnostic resolution, although this occurred for < 10% of patients. Reassuringly, approximately one half had declined further follow-up because their initial symptom resolved. However, 13 patients were lost to follow-up despite multiple documented phone calls by hospital clinicians. The fact that this occurred even with close tracking of patients and even when patients lived within the hospital's own district suggests the utility of dedicated staff, such as patient navigators, to support patients on their pathway through the medical system. In addition, ensuring that patients diagnosed with breast cancer successfully initiate and are retained in care is critical to realize the potential benefit of early detection programs. We are working now with Rwanda's Ministry of Health to expand the early detection intervention to other districts, and we are including patient navigation services to monitor and address loss to follow-up.

In summary, over a 2-year period, an intensive breast cancer early detection training project that targeted three levels of Rwanda's health care system increased the volume of patients who seek care at HCs for breast concerns and increased hospital referrals, biopsies, benign diagnoses, and early-stage cancer diagnoses in intervention regions. Our findings suggest that building provider and health system capacity to care for women with breast symptoms is a promising initial strategy to promote earlier detection of breast cancer in resource-limited settings. Building feasible documentation systems that allow tracking of patients through diagnosis and initiation and completion of cancer treatment and engaging older and higher-risk women are critical challenges to address. Additional research is needed to understand providers' perspectives, program costs, and the impact on other health services. Future analyses will investigate how well the intervention is sustained and explore the longer-term impact on patient outcomes.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

Methods

Health center eligibility. We excluded Butaro health center (HC) from randomization because it is located next to the hospital and often provides referrals for patients who come to the hospital from other regions but lack a referral from their own local facility. We were concerned that patients from Butaro HC would not necessarily represent the geographic area that surrounds the HC, unlike other HCs.

Randomization. To randomize HCs, we used random number generation with Excel (Microsoft Corporation, Redmond, WA) in 2 phases.

Data sources. We used patient identifiers to link various data sources for patients, including paper HC registries, HC clinical documentation forms, and hospital medical records. When all components of names, birthdates, and addresses were not identical, we required at least 3 patient identifiers to be identical (eg, last name, year of birth, and village of residence) to determine that records in different sources corresponded to the same patient.

Classifying intervention versus control HCs. As described in the article, for each HC, we identified the months between April 18, 2015, and April 17, 2017, that it served as an intervention HC and the months that it served as a control HC. For patients evaluated at the hospital, because we could not always determine the date of a patient's referral from an HC, we identified patients as being referred from an intervention HC if some nurses from their referring HC had already received the intervention at the time of the hospital visit.

Assigning HC visit characteristics. Visit dates were frequently missing on the clinical documentation forms, so when we were able to locate a patient in the HC registries, we identified first visit dates using the registry information. When a patient's visit date could not be identified from the HC documentation form or registry (n = 114; 10.5% of patients with visit dates during our study period and completed HC clinical documentation forms), she was excluded from our descriptive analysis of patient characteristics. When the same patient had more than one clinical documentation form completed (eg, for repeat visits), we used the information from the patient's first visit. On the clinical forms, nurses documented whether patients were coming for screening (no symptoms) or because of symptoms, and we identified patients' chief symptoms. If a patient was noted as coming for screening (no symptoms) and a symptom was checked, we considered the patient to have a symptom.

Additional Sensitivity Analyses

We analyzed whether the intervention led to a shift in patients coming from outside the intervention HCs' catchment areas to seek services at intervention HCs. We examined the addresses of patients with breast concerns recorded in the HC registries and categorized patients as residing within an HC's primary geographic sector or not. To examine whether there was a change in the proportion of patients coming from outside each sector's primary geographic sector after the intervention, we used χ^2 tests to compare the proportion of patients with breast concerns coming from each HC's primary sector before versus after the intervention. We found that $> 80\%$ of patients who received care at the intervention and control HCs were from the HCs' primary sectors (Appendix Table A2). After the trainings, there was a nonstatistically significant increase in the proportion of patients who came from the intervention HCs' main sectors.

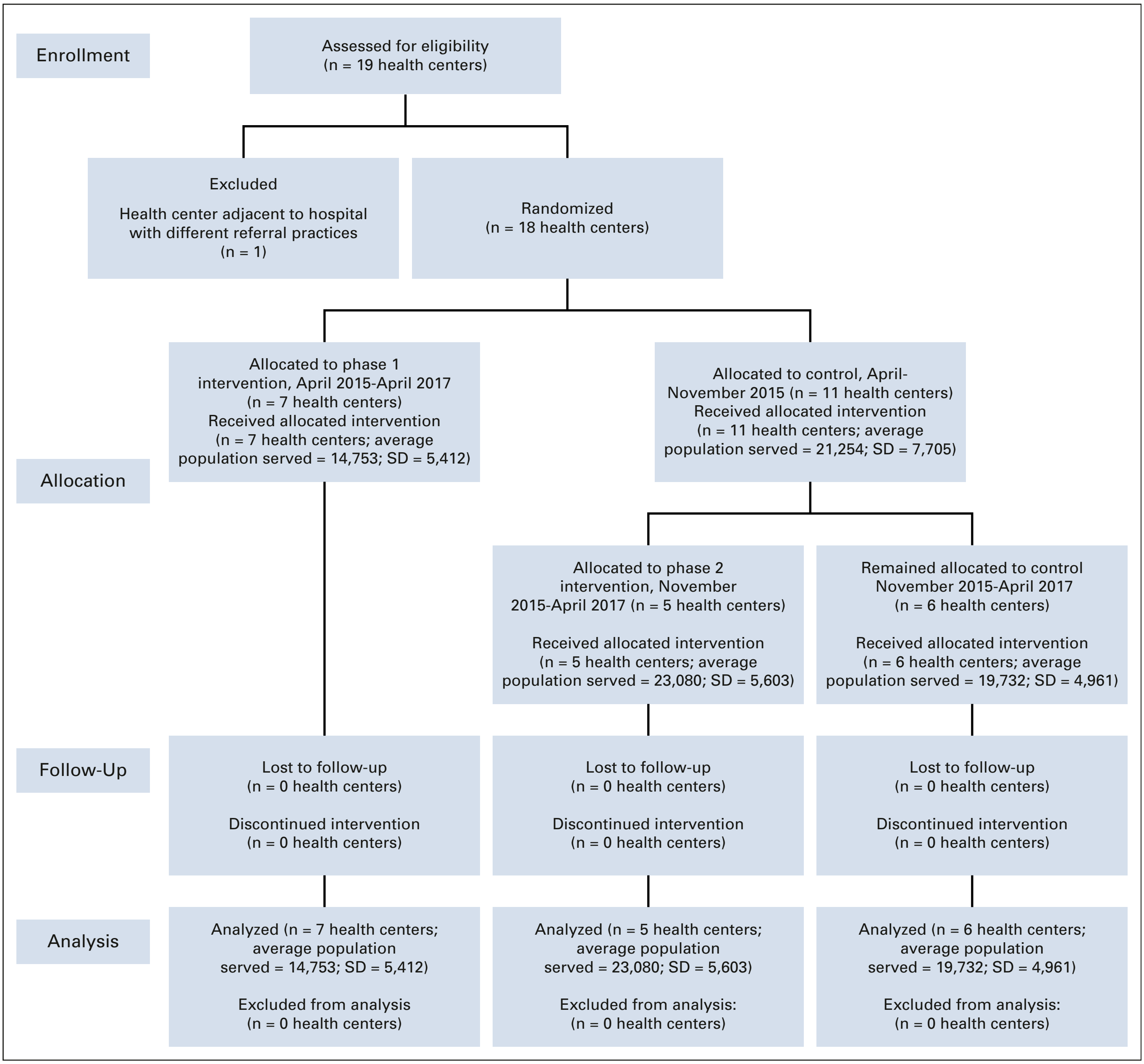

FIG A1. CONSORT diagram. SD, standard deviation. Reproduced with permission from Campbell et al: BMJ 345:e5661, 2012.

TABLE A1. Number of HC Nurses and Patients Served by Eligible HCs

HC	Nurses, 2015	Patients Served
Phase 1		
Kinoni	12	6,178
Kirambo	10	20,326
Kivuye	8	8,244
Ntaruka	10	13,183
Nyamugali	12	19,985
Rugarama	10	26,533
Rusasa	6	8,824
Phase 2		
Bungwe	11	16,324
Cyanika	10	41,564
Kinyababa	8	22,984
Mucaca	11	20,404
Ndongozi	5	14,124
Control		
Gahunga	6	28,326
Gatebe	8	18,293
Gitare	8	21,303
Ruhombo	9	11,480
Ruhunde	7	18,756
Rwerere	6	20,231

Abbreviations: HC, health center.

TABLE A2. Patients With Breast Concerns Who Came to Intervention and Control HCs From Inside *v* Outside the Sector Catchment Area Before Versus After HC Trainings: October 2014 to April 2017

Study HC	Pre-Intervention	Postintervention	*P**
All intervention HCs			
Patients from HC's main sector	507 (80.2)	1,484 (81.1)	.65
Patients from outside HC's main sector	125 (19.8)	347 (19.0)	
Control HCs			
Patients from HC's main sector	259 (84.1)	NA	
Patients from outside HC's main sector	49 (15.9)	NA	

Abbreviations: HC, health center; NA, not applicable.

*The χ^2 analysis compared the proportion of patients who came from within an HC's main sector before versus after the intervention.