The Value Chain for Breast Cancer in Botswana

The Value Chain for Breast Cancer Care in Botswana

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Abstract

Breast cancer is the leading cancer killer of women globally, with an estimated 22.2 million cases in Africa alone by 2030. However, the mortality to incidence ratio is much higher in low and middle income countries (LMICs), including Africa, relative to high income countries (HICs). The value chain for breast cancer, meaning all the essential steps required to improve outcomes, is long and complex. In order to effect positive change for breast cancer in LMICs, understanding this value chain and improving each component must be achieved to elevate the standard of care. This value chain consists of education and awareness, screening, evaluation for suspected cancer, multimodality treatment, and long-term follow-up. This thesis presents work in 3 of these domains: screening, evaluation for suspected cancer, and long-term follow-up. Regarding screening, we analyzed the outcomes from a cohort of over 6000 women who were screened using clinical breast exams regarding number of cancers diagnosed, time to diagnosis, and the burden of diagnostic testing performed. For evaluation of suspected cancer, we conducted a landscape analysis to get feedback from key stakeholders regarding a novel diagnostic device for breast cancer and evaluated feasibility of using the device for people with varying degrees of lab skill. Lastly, we evaluated long-term effects of HIV status on change in quality of life among women surviving at least 18 months. Each of these projects contributes to a critical component of the value chain for breast cancer in Botswana. The diagnostic portion of the value chain, screening through definitive diagnosis, could be substantially improved in terms of quality and timeliness by efforts presented here.

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Glossary

FNA = Fine needle aspiration biopsy

JOHB = Journey of Hope Botswana

MoHW = Botswana Ministry of Health and Wellness

PMH = Princess Marina Hospital

GPH = Gaborone Private Hospital

BPH = Bokamoso Private Hospital

NRH = Nyangabwe Referral Hospital

SLH = Scottish Livingstone Hospital

NHL = National Health Lab

LMIC = Low or Middle Income Country

HIC = High Income Country

IHC = Immunohistochemistry

IQR = Inter-quartile range

HER2 = Human epidermal growth factor receptor 2

ER = Estrogen receptor

PR = Progesterone Receptor

NGO = Non-governmental organization

CBE = Clinical Breast Exam

HIV = Human Immunodeficiency Virus

DCIS = Ductal Carcinoma In-Situ

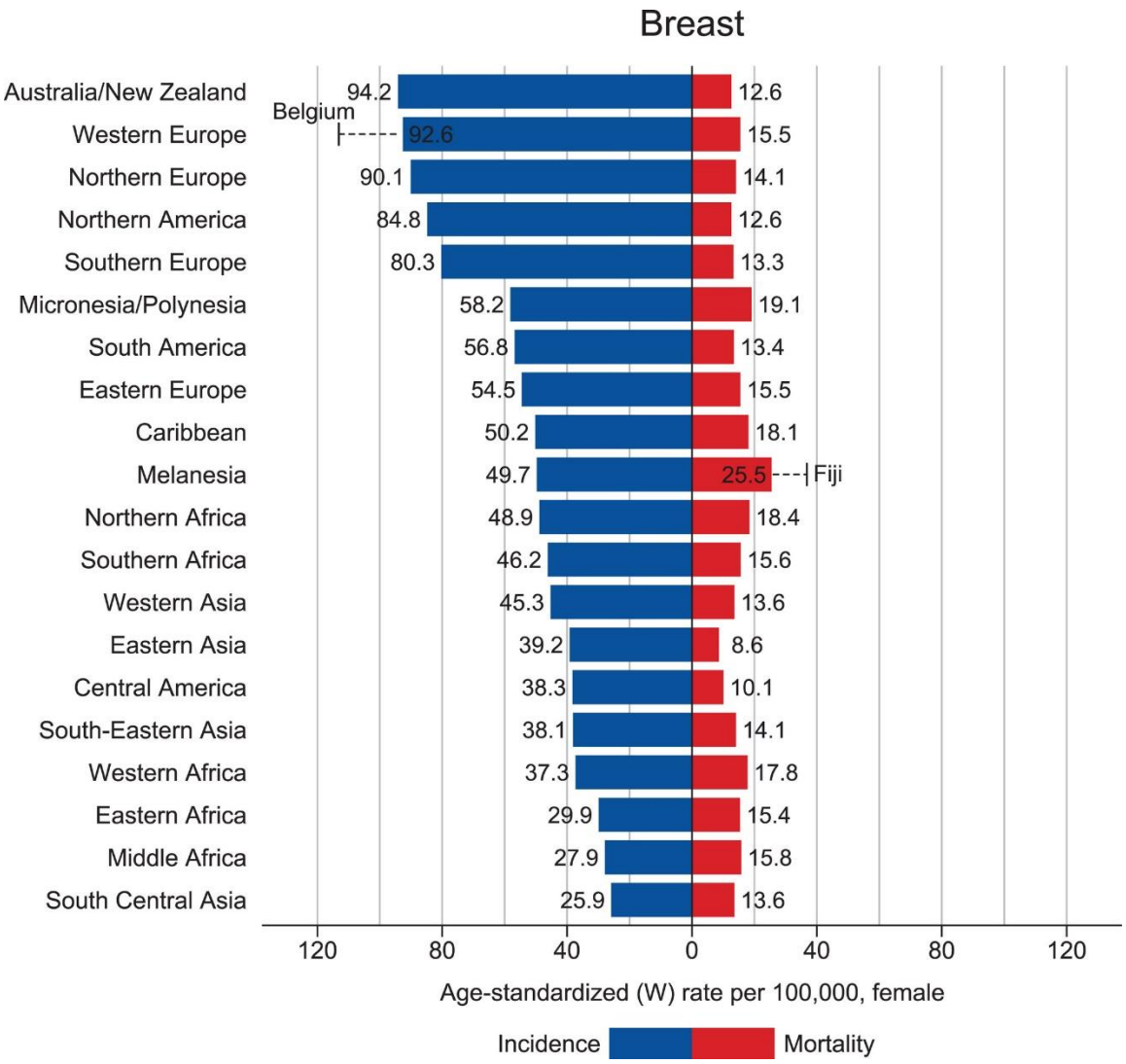
ASR = Age Standardized Rate

Chapter 1: Introduction

Cancer incidence and mortality continues to rise globally, with the highest proportion of new cases arising in low and middle income countries (LMICs). It is anticipated that by 2030 the majority of cancers will be originating in LMICs, where the current health system infrastructure is unprepared to meet the need. In Africa alone, one study estimates that cases will increase to 22.2 million by 2030, nearly doubling the incidence of 12.7 million in 2008.[1–3]

Breast cancer specifically is the leading cancer among women worldwide and across the continent of Africa, both in incidence and mortality. Based on Globocan 2018, the highest incidence of breast cancer is in the Australia/New Zealand region (ASR 94.2 per 100,000), while the Southern African region where this work was done has an incidence of only 46.2 per 100,000.[4] However, the mortality in these regions tell a very different story, with that of Southern Africa exceeding that of Australia/New Zealand (15.6 vs 12.6 per 100,000), as shown in Figure 1.2. The incidence-to-mortality ratios are 7.48 and 2.96 for Southern Africa and Australia/New Zealand, respectively, demonstrating that women who develop cancer in Southern Africa are much more likely to die from it. In order to understand the root causes of this striking difference, we must both understand the context where this study is being carried out, and the value chain required to improve the outcomes of patients with breast cancer.

Figure 1.1: Incidence and Mortality from Breast Cancer by WHO Region, GLOBOCAN 2018 [4]

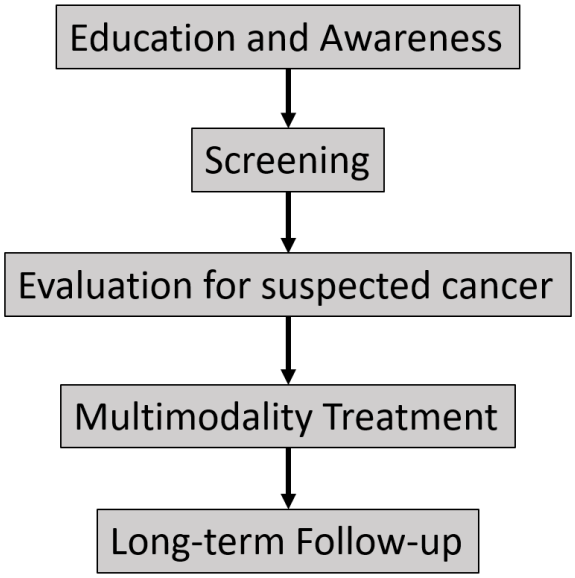


The clinical value chain begins at the general education and medical literacy among the population (Figure 1.2). This is the basis for women coming forward when they notice symptoms, as well as seeking out screening, both of which are critical for decreasing the average stage at presentation for a population. The next step is screening for breast cancer among asymptomatic women. Once breast cancer is suspected, either based on patient symptoms or positive screening, it is critical to

acquire a definitive diagnosis quickly so that treatment can begin. This cascade is likely to involve more imaging tests, like mammogram and ultrasound, fine needle aspiration biopsy, and core or excisional biopsy, which is currently the gold standard for diagnosis. Tissue samples will then need to be analyzed with microscopy and immunohistochemistry (IHC) by a skilled pathologist to achieve a definitive diagnosis. Following diagnosis, patients will require follow-up with a multidisciplinary oncology team to determine and implement a treatment plan, potentially involving a combination of surgery, chemotherapy, and radiation therapy. Treatment courses are often long and complex. Surgeries range from a simple lumpectomy, removal of the lump with negative margins, to modified radical mastectomies with lymph node dissection in cases where the tumor is larger and/or has spread locally. Radiation plays a role in preventing local recurrence both as standard practice after lumpectomy or to a mastectomy bed in cases where residual cancer is suspected. Chemotherapy typically involves multiple drugs and varies based upon the receptor status and stage of the cancer at diagnosis. It may be administered before or after other interventions to shrink or eliminate disease at the primary site or distant sites of metastasis. Women are then monitored long-term for recurrence so that it can be dealt with should further intervention be necessary. Long-term function and quality of life of women surviving breast cancer is a very important factor, particularly for diseases with favorable prognosis, and should be monitored and supported by the health system as well. Effectiveness of this entire value chain is required in order to improve breast cancer outcomes of mortality and quality of life. For example, an improvement in diagnostic capacity can only improve mortality if the

downstream interventions are also present. Similarly, an incremental improvement in available treatments will be of some benefit, but if patients are presenting at a late stage then developing mechanisms to decrease cancer stage at presentation may have a greater impact on outcomes.

Figure 1.2: Abbreviated Value Chain for Breast Cancer



Setting

This thesis will focus on Botswana, a middle-income country located in Southern Africa between South Africa to the south, Namibia to the west and north, Zimbabwe to the east, and Zambia to the north-east. Botswana is 224,610 square miles, approximately the size of Texas, and has a population of 2.2 million people. The population is over 80% rural. The two largest population centers, Gaborone and Francistown, have populations of 250,000 and 70,000 respectively.[5] Botswana became a protectorate of the British crown in 1885 to prevent invasion from South Africa and diplomatically achieved independence in 1966 under leadership of their first president,

Sir Seretse Khama.[6,7] The dominant ethnic group in the country is the Tswana (~80%), but a number of other smaller ethnic and language groups are present as well, including the Kalanga (11%) and Basarwa (3%). Non-black ethnicities, including European, Indian, and Kgalagadi, compose 7% of the population.[8] Botswana has never suffered war, civil or with foreign powers. The economy has historically been predominantly based on diamonds, which were discovered in the early 1970s following their independence. Beef cattle and tourism compose the 2nd and 3rd largest industries. The government has been shown to be less corrupt than many other African nations, so these resources have been largely used toward the public good.[7] Botswana boasts free, universal education through college and universal healthcare coverage for citizens among other social programs.

Education and Awareness

In Botswana, women presenting with breast cancer often have limited knowledge of the disease before being diagnosed [9]. Some patients also report that even when they know something is wrong, they are not aware that their condition can be cured or life extended. Others are concerned about the morbidity of the therapy. This lack of understanding can lead to a delay in presentation to a clinic for evaluation, one contributor to late presentation. According to a study by Brown et. al., the median delay from symptom onset to first clinic visit was 29 days [IQR 0-185 days].

There are ongoing efforts in Botswana to improve education surrounding breast cancer. The Non-Communicable Disease Division of the Ministry of Health and Wellness

(MoHW) is broadly distributing posters and pamphlets into clinics which provide basic information about breast cancer and breast health and teach women how to conduct breast self-exams.

Some non-governmental organizations (NGOs) are also conducting large-scale efforts to improve education and awareness about breast cancer. Journey of Hope Botswana (JOHB) is a Botswana-based NGO founded by a breast cancer survivor for this purpose. Throughout the year they conduct media campaigns and host events to educate women about breast cancer and demonstrate self-breast exams. They also have a variety of written materials which are distributed to clinics and employers. Once a year they travel around the country in a large caravan of pink vehicles and motor bikes to host events in the town centers, an event called the Big Journey. They collaborate with local clinics and officials to recruit women from the area to the event.

Screening

In many high income countries (HICs), a positive mammogram screen is the dominant method by which women present for evaluation of suspected breast cancer [10,11]. However, in LMICs, there are often no wide-spread screening programs available, and if available, it may be with a less efficacious method than mammograms [12,13].

In Botswana, there are currently no nation-wide screening programs. The MOHW is currently implementing a small pilot program in one district with support of JHPEIGO, where all women age 35 and up will be screened at health centers by trained nurses. JOHB also conducts clinical breast exams both during small events and the large annual Big Journey.

Definitive Diagnosis

Following first presentation to a clinic for a breast complaint, whether based on screening or a symptom, women must be evaluated to obtain a definitive diagnosis. In high income countries, patients are typically evaluated first with ultrasound and/or a diagnostic mammogram depending on age. Often these tests will be sufficient to rule out malignant disease. However, in cases where they don't, a fine needle aspiration biopsy (FNA) or a larger biopsy (excisional or core) will be obtained for pathological evaluation. The gold standard is either a core biopsy, where a large needle is used to obtain a core of tissue, or excisional biopsy, where a piece of tissue is removed surgically. Pathology evaluation will involve staining with multiple reagents including immunohistochemistry for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).

In Botswana, limited resources often make evaluation with diagnostic mammogram or ultrasound challenging. For example, in order to obtain rapid diagnosis after positive screening, it was decided within the MOHW that for the pilot screening study in one district near the capital, imaging tests would be skipped and the next step after CBE screening in diagnostic work-up would be FNA at the National Health Lab (NHL), which has a weekly clinic dedicated to these procedures. If there is continued suspicion for cancer following FNA, core or excisional biopsies are obtained by general surgery and evaluated at NHL. There are a number of components to the delays at this stage. While FNAs occur at some district hospitals, only tertiary centers currently have the capacity to do core biopsies. Since the tertiary centers are only located in 2 cities in

the country, it is challenging for many patients from rural areas to obtain timely follow-up. They also may not always be referred appropriately based on their presenting signs and symptoms. Of note, in Botswana, the step between first clinic presentation and definitive diagnosis has been found to be the longest delay in care between symptom onset and treatment, with median delay 160 days [IQR 59-653].[14] This delay represents a substantial opportunity for improvement within the health system.

Treatment

Treatment for breast cancer depends upon the stage at which it was diagnosed, and patients with earlier stage cancers have substantially better outcomes than those with later stage cancers [2]. At the earliest stages, breast cancer is either treated with a modified radical mastectomy, which involves removing all breast tissue of the affected breast, or a lumpectomy followed by radiation. Either of these approaches may be accompanied by chemotherapy depending on the risk profile of the cancers. Later stages of breast cancer are not eligible for a lumpectomy, so patients undergo mastectomy with a lymph node dissection and may receive radiation to the tissue bed if there is concern for residual disease. Chemotherapy may be given before or after surgery and radiation in the setting of advanced disease, and involves multiple agents from multiple classes, including anthracyclines (doxorubicin or epirubicin), antimetabolites (capecitabine or gemcitabine), and taxanes (docetaxel or paclitaxel). The receptor status of the breast cancer also leads to several other important considerations. If the patient is positive for ER or PR, they should receive treatment with selective estrogen modifier medications, typically Tamoxifen or Raloxifene. When a

tumor is positive for HER2, patients should receive targeted antibody therapy with Trastuzumab.[15]

In Botswana, all three components of multimodality therapy are available. The treatment plan for public patients is decided in a multidisciplinary clinic between surgical and medical oncology teams. If surgery or chemotherapy are needed they will be done at a public tertiary center, and radiation is administered at a private hospital in the capital and paid for by the government. Surgical capacity for oncology is limited by OR space, anesthesia coverage, and competition from other surgical subspecialties or emergent cases. The surgeons who attend the multidisciplinary clinic typically council patients for a mastectomy. They are experienced in this procedure and recently recruited a surgical oncologist who is from Botswana but completed residency and fellowship in Canada, who significantly increases their capacity to do basic and complex oncology surgeries. Botswana has high compliance with the WHO essential medicines for cancer list, with medications stocked an average of 80% of the time.[16] Therefore, patients are usually able to access needed drugs with or without delay. The radiation oncology facility is composed of one linear accelerator and a brachytherapy suite. There is a greater emphasis on treating the high volume of patients with need for radiation than on intricate planning to minimize side-effects, meaning that 3D conformal therapy is typically used and advanced techniques such as Volumetric Modulated Arc Therapy (VMAT) or Intensity Modulated Radiation Therapy (IMRT) have not been implemented.

Long-term Follow-up/Quality of Life

While breast cancer is curable, especially when caught at early stages, it still requires long-term follow-up to monitor for recurrence or complications of therapies such as secondary cancers or functional limitations. These visits may begin with a frequency of 1-3 months immediately following therapy and eventually lengthen to about 1 year. Additionally, treatment should be optimized to minimize the limitations of quality of life following therapy, particularly for patients with favorable prognoses.

Project Overview

The following 3 projects were completed throughout a year spent in Gaborone, Botswana, and they each intersect with different components of the value chain. The first project is related to breast cancer screening in Botswana using clinical breast exams. The outcomes from a cohort of over 6000 women who were screened by JOHB is analyzed for number of breast cancers diagnosed, number needed to screen to diagnose one breast cancer, time to diagnosis, and burden of diagnostic testing performed. The second is related to the implementation and optimal use of a novel diagnostic device for breast cancer. We conducted a landscape analysis to get feedback from key stakeholders regarding whether they thought this device would be useful, and if so, what would be the optimal way to integrate it into the current system. We also tested feasibility of using the device for people with varying degrees of lab skill. Last, we tested what affects quality of life among women surviving breast cancer for at least 18 months, specifically whether there was an association between HIV and quality of life recovery following treatment.

Chapter 2: Impact of a Community-Based Clinical Breast Exam Screening Program in Botswana

Abstract:

OBJECTIVE: To guide efforts to reduce breast cancer mortality, we evaluated a clinical breast exam (CBE) screening program to determine prevalence of breast abnormalities, number needed to screen to detect breast cancer, and clinical resources required for these diagnoses in a middle-income African setting.

METHODS: We performed a retrospective review of records from a clinical breast exam screening program (2015-2018) that was conducted by Journey of Hope Botswana, a Botswana-based non-governmental organization (NGO). Screening events were held in communities throughout rural and peri-urban Botswana, with clinical breast exams performed by volunteer nurses or physicians. Individuals who screened positive were referred for further evaluation at a private tertiary facility and followed by the NGO until definitive diagnosis. Data were obtained from NGO records. Stage at presentation was compared with controls matched for age and district from a cohort of all women presenting to major oncology centers in Botswana.

RESULTS: Of 6120 screened women (50 men excluded), 357 (5.83%) were referred for further evaluation; 257 ultrasounds, 100 FNAs, 58 mammograms, and 31 biopsies were performed. In total, 6017 were determined to not have cancer, 78 were lost to follow-up (67 for ≤ 50 years and 11 for >50 years), and 11 were diagnosed with cancer (0 for ≤ 40 years, 5 for 41-50 years and 6 for >50 years). Overall breast cancer prevalence in the

screened population was calculated to be 18/10,000 (95%CI 8-29/10,000). Number needed to screen to detect one breast cancer was 237 (95% CI 1910 to 126) for women 41-50 years and 196 (95% CI 109 to 977) for women > 50 years. Number of diagnostic procedures per breast cancer detected was 17 for women 41-50 years and 14 for women >50 years. The median time to diagnosis for all women was 17 [1-24] days. Screening-detected tumors were not different than tumors presenting through standard care.

CONCLUSIONS: In a previously unscreened population, yield from community-based clinical breast exam screening was high and required relatively modest diagnostic resources. This strategy has the potential to reduce breast cancer mortality.

Background:

Breast cancer incidence and mortality is rising rapidly in sub-Saharan Africa.[2,3] With decreased mortality from infections and birth complications, deaths from breast cancer have nearly doubled in the past two decades in southern Africa.[4] Case fatality rates are high in Africa, in part due to the majority of women entering care with advanced stage cancer.[3,4,17,18] In response, countries and non-governmental organizations (NGOs) are seeking effective strategies to promote early detection of breast cancer.[13,19]

Breast cancer screening with clinical breast exams (CBEs) has been shown to reduce the stage at which cancer is diagnosed in cluster randomized control trials in India.[20,21] No study has yet shown mortality reduction through CBE, though other

studies have also demonstrated the potential for CBE and algorithm training to assist in increasing detection and decreasing stage of breast cancers.[19,22–24] However, due to its benefits in down-staging and possibility of reducing mortality, and the infeasibility of large-scale mammography screening in low and middle income countries (LMICs), a number of governments and non-profit organizations have proceeded to introduce CBE breast cancer screening programs in LMICs globally.[19] The World Health Organization (WHO) does not currently endorse any strategy of population breast cancer screening in LMICs, finding mammography not cost effective in that context.[25] However, the WHO suggests that CBE screening could be useful in settings it has is determined to be effective and sustainable and where appropriate treatment and diagnostic services are available.

Botswana, a middle-income country with a predominantly rural population, recently endorsed routine breast screening by CBE as part of the 2016 core primary care guidelines for women 40-69 years old.[26] With multimodality breast cancer treatment available free of charge for all citizens, it is possible that if CBE is effective at reducing stage at presentation, it could lead to a reduction in mortality. Also impeding efforts to plan and implement population-wide CBE screening in Botswana and other LMICs are the lack of estimates of prevalence of breast abnormalities, the number and costs of women requiring specialized follow-up testing and the number women who require cancer treatment.[25] Utilizing records from a large screening initiative by a Botswana-based NGO, we sought to determine screening uptake, prevalence of breast abnormalities, number needed to screen to detect breast cancer, and clinical resources

required to achieve these diagnoses. Secondary analyses included proportion of women completing diagnostic evaluation and time to diagnosis. Findings may inform planning of national CBE screening programming in Botswana and similar settings.

Methods:

We performed a retrospective review of records from a CBE-based breast cancer screening program that was conducted by a Botswana-based NGO, Journey of Hope Botswana (JOHB). Established in 2010, this organization's primary mission is to promote breast cancer awareness in the country through events and media campaigns.

Screening Event Structure

An annual community-based 'Big Ride' screening event has been conducted by JOHB since 2010, with 1000 to 2000 women screened each year. Supported by philanthropy from local businesses, JOHB volunteers convoy in pink vehicles to day-long screening events in 5 to 7 rural and peri-urban communities. Locations for screening events each year are chosen based on perceived need for breast cancer education, geographic proximity to one another, and support of local chiefs and clinical staff. See Figure 1 for a map demonstrating the towns visited during the years included in this analysis. In addition to the awareness raised by convoy of pink vehicles, pre-event sensitization is supported by community leaders, local clinic staff, and via social media. Attendance of screening events are also encouraged through creation of a festive environment and distribution of gifts including bras and t-shirts.

Annually, prior to screening events, nurses are trained to perform CBEs by a general practice physician using a combination of models and healthy patient volunteers. Single-day screening events were held inside local public clinics or outdoor tents. A volunteer nurse first evaluate patients. Patients with a detected breast abnormality on this exam are referred to an onsite general practitioner for additional evaluation and determination of diagnostic referral. Services at the events have expanded over time with introduction of onsite fine-needle aspiration in 2015 and breast ultrasound examination in 2018. The diagnostic algorithm was developed by a general practitioner and nurses from the NGO. Patients with breast abnormalities not determined to clearly be benign were referred to a private tertiary hospital located in the capital city, where they were evaluated by ultrasound with or without mammogram. If there was persistent concern for breast cancer after this evaluation, patients were further referred for a core breast biopsy. A few patients also received core biopsies by a physician directly at the event prior to other evaluations. For women needing further evaluation, JOHB covered costs for transportation, accommodation if necessary, and all testing. When breast cancer diagnoses were made, patients were referred to the public tertiary referral hospital in Gaborone for multimodality treatment, where services are provided free of charge for citizens. JOHB continued following up with patients throughout treatment, encouraging treatment completion and connecting them with other breast cancer patients and survivors. They did not cover costs of transportation or accommodations after diagnosis.

Data Collection

Records from screening events from 2015 to 2018 were abstracted from JOHB records and included in the analyses (28 community screening events). Patients' age was recorded in 10-year increments (≤ 20, 21-30, 31-40, 41-50, 51-60, and > 60 years). For referral outcomes, all information was confirmed by the physician who oversaw the events and follow-up. Dates of diagnostic test results were obtained directly from paper records maintained by JOHB. Cancer was defined as any biopsy-proven breast cancer or ductal carcinoma in situ (DCIS). Clinical tumor stage (T stage) was determined using NGO records of tumor dimensions from ultrasound or mammogram imaging. Nodal and distant metastasis (N and M stage) was determined based on symptom review, clinical exam, chest x-ray, and abdominal ultrasound. No patients were contacted directly for this study. The institutional review boards of the Botswana Ministry of Health and Wellness and the Harvard T.H. Chan School of Public Health approved the study and waived requirement for informed consent.

Follow-up costs were estimated based on the rates charged to patients or insurance by the private hospital for standard procedures, though tests were waived for the NGO as a donation. Costs of the screening events or patient navigation were not included. Community population for each town was estimated from measured population on 2011 census in Botswana assuming 3% annual growth and consistent age-sex distributions.

Stage Comparison Cohort

The T-stage at diagnosis through JOHB were compared with those enrolled in a prospective cohort study including all patients with biopsy proven cancers who present

to a public or private oncology referral center in Botswana. This cohort has been described in prior studies regarding other types of cancer in Botswana.[27,28] Patients from this cohort were matched in a 4:1 ratio to JOHB patients based on age and district of current residence.

Statistical Analysis

The primary analytic objectives were to determine screening uptake, proportions of screened women with a positive CBE and number needed to screen to detect one breast cancer. Endpoints were summarized in three age categories: 20-40, 41-50 and women >50 years. The binomial distribution was used to calculate 95% confidence intervals (95% CI) of assessed proportions. The Kaplan-Meier method was used to estimate time to final diagnosis and Greenwood's formula utilized to calculate 95% confidence intervals.[29] Comparisons of subgroups utilized Wilcoxon rank sum and Fisher's exact tests for continuous and categorical measures, respectively. All tests were two-tailed with a significance level of 0.05. Analysis was performed using R.[30]

Results:

Screening participation

A total of 6120 women and 50 men were screened with CBE during the single-day, community screening events, 2015 to 2018 (Table 2.1). About 11% of attendees came with a current or previous breast-related complaint, including pain, lumps, discharge, or rash, but the majority were asymptomatic. The median age of women screened was between 31 and 40 years. The screening event was able to reach 0.89% (95% CI 0.86%

to 0.92%) of 20 to 40 years, 1.63% (95% CI 1.54% to 1.73%) of 40 to 50 years, and 0.81% (95% CI 0.76% to 0.86%) of women older than 50 years residing in the catchment area. However, reach of the CBE screening was variable between communities and dependent on the community size (figure 2.1).

Figure 2.1: Map of Botswana with Locations of Screening Events: Dot size corresponds to the size of the village where screening took place and the shade corresponds to the percent of that population which was screened.

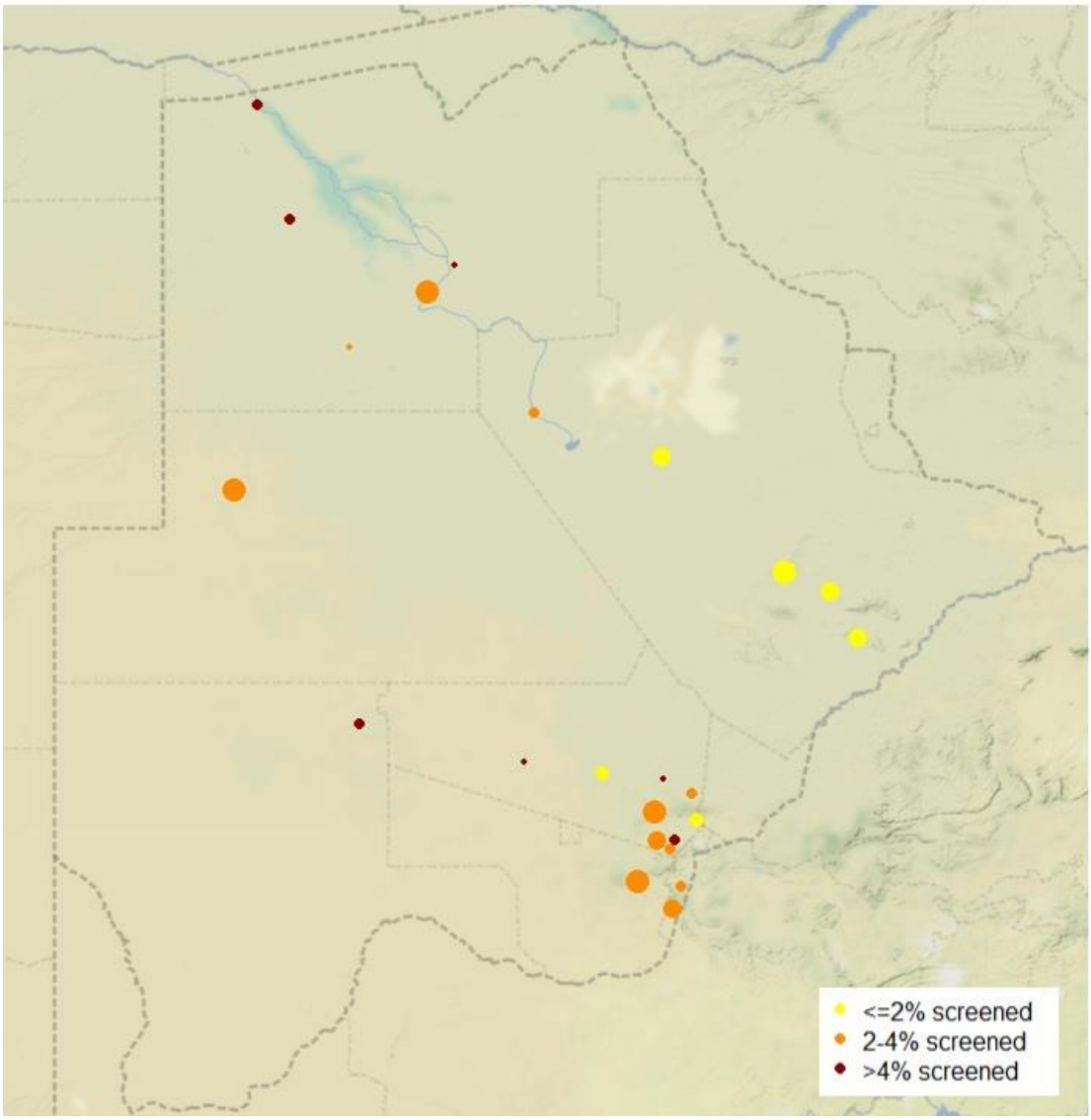


Table 2.1: Patient Characteristics for All Women Screened with CBE

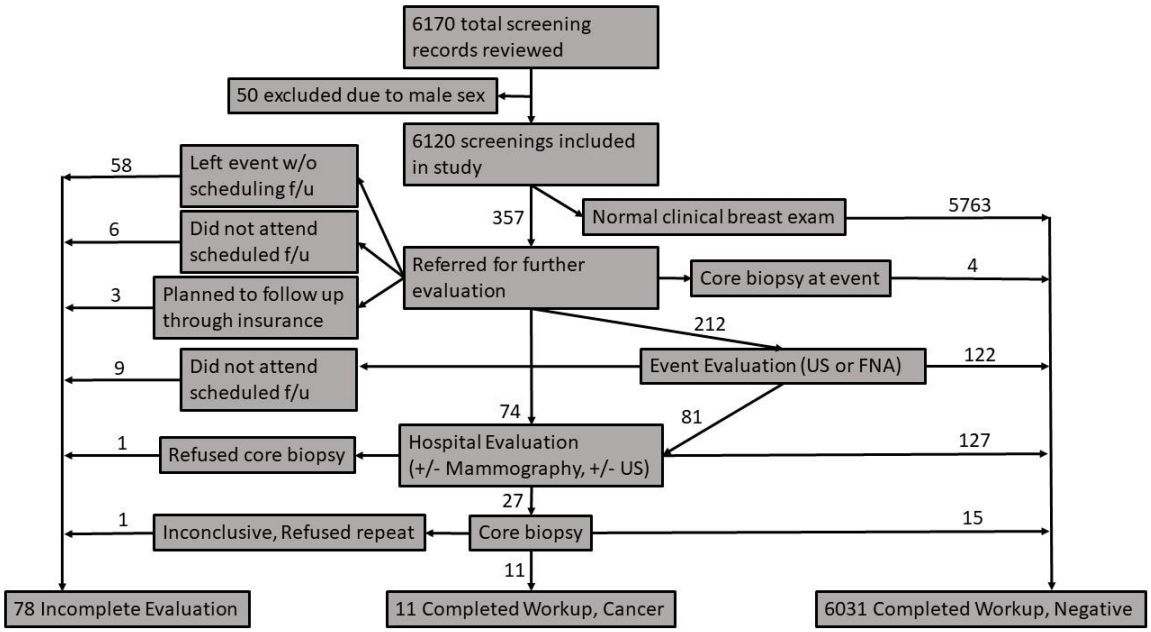
Age group	Women	Men
Total	6120	50
<21	335	3
21-30	1640	12
31-40	1782	11
41-50	1185	9
51-60	798	9
60+	379	6
Year		
2015	1243	1
2016	1229	34
2017	1497	7
2018	2151	8
Region		
Southern	721	6
South-East	508	28
Kweneng	1974	6
Central	692	2
Ngamiland	1390	5
Ghanzi	503	1
Kgalagadi	155	0
Kgatleng	177	2

Screening Results

Of the 6120 women screened, 6042 (98.5%) completed diagnostic evaluation and 78 (1.5%) were lost to follow-up before a final diagnosis secured. The majority of incomplete evaluations occurred because women did not enter the separate queue to see the physician and schedule follow-up at the event after screening exam (n = 58). Twenty-three (40%) of these women left a single event in a large town where lines were long and the NGO ran out of t-shirts for distribution. There was a non-significant trend toward younger women not scheduling evaluation at the event (p = 0.065). The remaining women who did not complete evaluation did not attend scheduled hospital follow-up (n = 17) or followed up through their own insurance and were not tracked by the NGO (n = 3), Figure 2.

A total of 357 (5.83%) women had a detectable abnormality during CBE requiring further evaluation (Table 2.2 and Figure 2.2). The 95% CI for referral was 5.83% [5.25%-6.42%] for all women. However, women under 40 years old were more likely to have an abnormality requiring referral than older women, p<0.01 (Table 2.2).

Figure 2.2: Pathway from Screening to Diagnosis or Loss to Follow-up: The results for all women screened were 6031 negative workups, 11 biopsy-proven cancers, and 78 incomplete evaluations. All arrows going left represent incomplete evaluations, arrows going right represent a completed negative diagnostic evaluation, and arrows down represent further evaluation and eventually a diagnosis of cancer. Women were sent straight to hospital evaluation if they were screened before advanced event evaluation was implemented or if an FNA could not be obtained on-site before ultrasound was available.



Of the 357 women with an abnormal CBE, 122 (34.2%) were able to complete evaluation without hospital referral (98 with ultrasound, 20 through FNA, and 4 through core needle biopsy). One-hundred forty-two (39.8%) women had cancer excluded after further evaluation at referral hospital (127 with ultrasounds and/or mammogram, 15 with core biopsy).

Eleven women were diagnosed with cancer, 6 women older than 50 years and 5 women between 41 and 50 years. Number needed to screen to detect one breast cancer was 237 (95% CI 126 to 1910) for women 41-50 years and 196 (95% CI 109 to 977) for women > 50 years. Ten of the eleven reported current or past breast symptoms. Undiagnosed cancer prevalence among all women was 0.18%, with women 41-50 having prevalence of 0.42%, and women 51+ had the highest prevalence at 0.51%.

No cancers were diagnosed in women under 40. Women diagnosed with cancer were older than women who were diagnosed with a benign condition ($p < 0.001$) or who received an incomplete evaluation due to loss to follow-up ($p < 0.001$). There were no significant differences between the ages of women who were diagnosed with a benign condition compared to those with an incomplete evaluation.

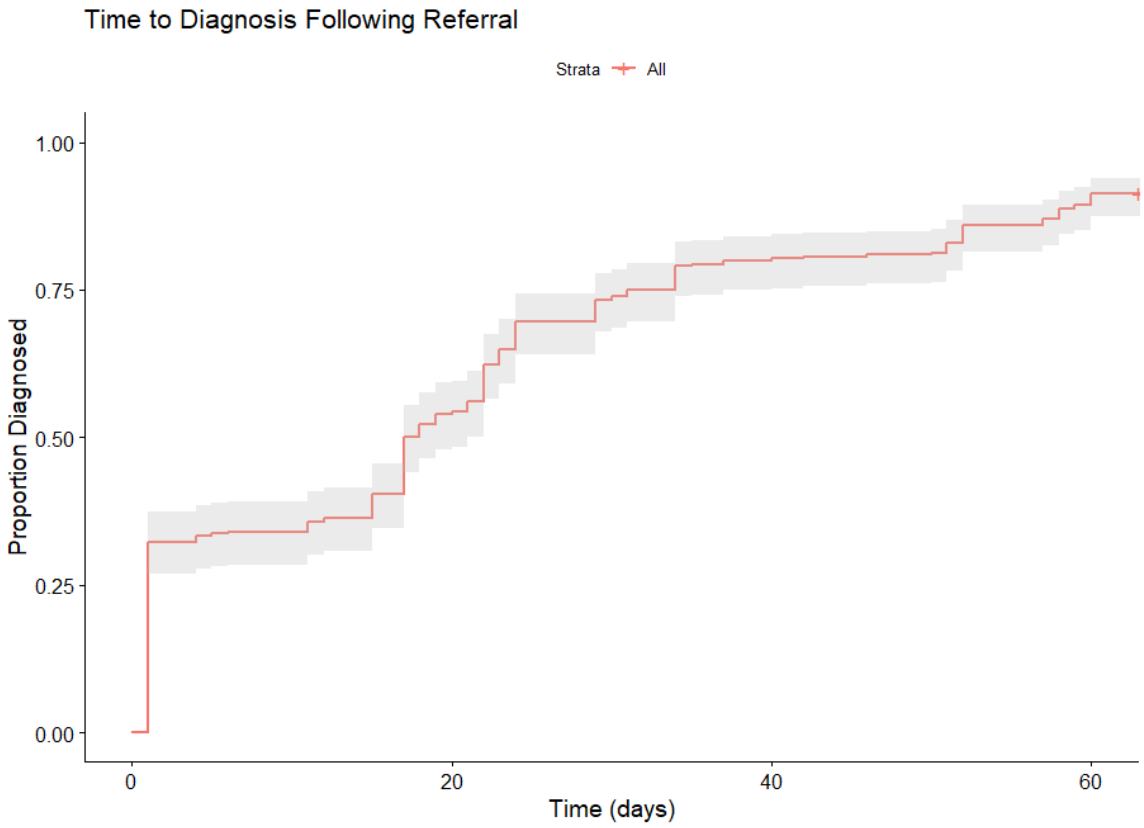
Table 2.2: Prevalence of Breast Abnormalities, Breast Cancer, and Resources Required

	Women total	<41	41-50	51+
n				
	6120	3757	1185	1177
Incidence of breast abnormality per 10,000				
	583 [525-642]	641 [563-720]	531 [404-660]	504 [369-640]
Number referred				
	357	242	63	52
Follow-up tests required				
FNA	100	68	13	19
Ultrasound	257	179	41	37
Mammography	58	21	19	18
Biopsy	31	11	10	10
Screening Outcome				
Negative	6017	3742	1177	1171
Positive	11	0	5	6
Incomplete	78	48	19	11
Undiagnosed Cancer Prevalence per 10,000				
	18	0	42	51
Cost per diagnosis (USD)				
	2206	Inf	1174	1017

Time to diagnosis

Median time to diagnosis was 17 [1-24] days for all women and 34 [19-44] days for women with biopsy-proven cancer (Figure 2.3). There were no significant differences in time to diagnosis between age groups of under 40, 41-50, and 50+. A total of 257 ultrasounds, 100 FNAs, 58 mammograms, and 31 biopsies were performed on the referred women (Table 2.2).

Figure 2.3: Kaplan-Myer Curve Representing Time to Diagnosis



Cost of follow-up testing

There was no per-unit costs for ultrasounds done at the event. The unit price of hospital ultrasound alone was $64, mammogram plus ultrasound package was $98, FNA reading was $33, and biopsy procedure and analysis was $285. The total costs of hospital follow-up for patients with breast abnormalities was $24261. This is a follow-up cost of $2206 per breast cancer diagnosed, excluding the costs of hosting the event and patient navigation. The follow-up cost per diagnosis for 41-50 was $1174 and for 51+ was $1017 (Table 2.2).

Cancer stage and outcomes

The number of women diagnosed with stage 0, 1, 2, and 4 disease were 1, 3, 5, and 2 respectively. Tumor stage was not significantly different than from the matched cohort (p = 0.54). Nine of these women received treatment. One declined treatment due to fear of complications, while the other initially declined because she and her family felt it was unnecessary, then was lost to follow-up. Most women had a favorable prognosis following their treatment course. See Table 2.3 for more detailed patient information.

Table 2.3: Clinical Details for Women Diagnosed with Breast Cancer

Age	Tumor Dimensions (cm)	metastatic eval	Clinical TNM Stage	recentor status (ER/PR/HER2)	grade	histology	Treatment	year	District
42	1.8 x 1.5	negative	T1cN0M0	unknown	unknown	unknown	treated in private sector	2015	d'kar
49	2.9 x 2.3	+ liver mets	T4NxM1	-/+/-	unknown	IDC	Surgery then passed away after 1 month	2015	Kang
72	1.5 x 1	negative	Tis (DCIS)	unknown	unknown	DCIS	Surgery	2015	Kang
61	3.03 x 2.92	negative	T2N0M0	-/-/+	2	IDC	refused	2016	kanye
62	8 x 8	negative	T3N0M0	unknown	unknown	unknown	chemo --> surgery --> radiation	2016	Otse
52	4.7 x 3.94	negative	T3N0M0	+/-/-	unknown	IDC	chemo --> refusing surgery	2017	maun
69	2.56 x 2.36	negative	T3N0M0	+/+/-	3	IDC	chemo --> surgery	2017	serowe
50	12.08 x 8.2	axillary LN +	T4N2M0	-/-/+	3	IDC	chemo --> surgery	2018	Molepolole
48	1.52 x 0.58	negative	T1cN0M0	-/+/-	2	IDC	chemo --> surgery	2018	molepolole
46	2.27 x 2.28	negative	T2N0M0	+/-/-	3	IDC	connected to care but delaying	2018	Kopong
55	1.53 x 1.39	negative	T1cN0M0	+/+/+	2	IDC	chemo --> surgery	2018	Molepolole

Discussion:

An NGO-led breast cancer screening initiative identified 11 breast cancers among a total of 6120 previously unscreened women in rural/periurban Botswana. Approximately 5% of women had breast abnormalities detected which required ultrasound, FNA, mammogram, or biopsy for diagnosis. A quarter of women with palpable abnormalities did not complete evaluation, with highest loss occurring with women not scheduling follow-up with a physician at the screening event. It is important to note that 10 of the 11 women who were diagnosed with cancer reported symptoms. Also, given that these populations were previously unscreened, yield from annual screening in a community would likely be substantially lower than what we report in this study.[31,32]

Relative to other studies investigating CBEs for breast cancer screening[20,22,23], we had a higher proportion of women referred for further evaluation based on CBE. Given that our study enrolled women from a younger age, and that younger women were more likely to be referred, this difference may attributable to a higher proportion of benign breast problems such as fibroadenomas in younger women. Our results for cancer prevalence were higher than that found in rural India[20], but similar to that described in Sudan[23] and China[24] when comparing similar age groups. Our rate is decreased by a large number of women younger than the enrollment criteria for some studies, which was restricted to women over the age of 35[20,22] or 30.[21] Of women who were scheduled for appointments, we had a higher rate of follow-up than comparable studies.[22,24] This high rate of follow-up is likely due to the support by JOHB provided to

referred individuals, including funding all testing, providing for transportation and accommodations when necessary, and persistent phone calls. Socioeconomic factors have been demonstrated to limit follow-up and linkage to care for individuals referred from community-based screening programs.[23,33,34] The inclusion of symptomatic women in our analysis may contribute to our higher proportion of breast abnormalities and breast cancers than comparable studies, though it should be representative of all comers in a community setting as in the cluster randomized control trials. Those with breast-related complaints may have been more likely to attend screening events than those without, and women were not asked about whether current or prior symptoms contributed to their motivation to come. It is also possible that the communities visited by the NGO were more convenient than those where events have not been held, and that unvisited communities have differing prevalence of breast abnormalities and breast cancer due to limited access to care.

Of note, 82% of incomplete follow-up in our study was due to not scheduling an appointment at a screening event. Over 93% of those who did schedule an appointment reached a final diagnosis, which is higher than comparable studies. Our estimates likely overstate the proportion of incomplete evaluations since it includes women who planned to receive evaluation in the private sector and other women who left events prior to scheduling an appointment may have taken their referral slip to a local public clinic themselves. Since 40% of women who did not schedule an appointment happened at one large event with long lines and where JOHB ran out of participation gifts. This highlights the importance of providing convenient screening services including

streamlining of processes such that a separate queue is not required to schedule an appointment to facilitate screening uptake and follow-up.

The average time to diagnosis in this study is substantially shorter than others published in studies conducted in Botswana. Brown and colleagues reported median time from first clinic visit to diagnosis for all cancers diagnosed between October 2010 to September 2014 to be 160 [59-653] days.[14] This substantial time difference is probably largely attributable to Journey of Hope patient support and advocacy and utilization of a private hospital with relatively short wait-times relative to public hospitals.

Despite being annual events, we are unable to assess down-staging of cancer because of the geographic variation; each year screening is performed in different towns which were not visited previously. Low screening coverage would also make such comparisons challenging. We would expect that for long-term evaluation of women with breast cancer, both the average number of cancers and cancer stage would decrease. This is because the number of cancers that are prevalent from before the screening interval will decrease, in which case only cancers which are incident over a recent time-scale would be detected.[31,32] Therefore, we anticipate that the detection rate of breast cancer using clinical breast exams found in this study is higher than what would be expected in a longitudinal CBE program.

Our overall follow-up cost per diagnosis was $2206 for diagnostic evaluation after CBE, though it was lower for older age groups. While this does not include cost of CBE screening itself or patient navigation, testing costs within the public system would

be less, and if community nurses or primary care doctors were trained to perform CBE, the unit cost per CBE would also be low. Unfortunately we cannot make direct comparisons with studies which tested cost per DALY saved.[35]

The stages at diagnosis were comparable for those diagnosed by JOHB compared to the country as a whole. Given that women were often symptomatic when they presented to JOHB, and that some women in the community setting never reach a tertiary center for diagnosis and treatment, it is not surprising that stage was comparable. A larger, longitudinal study in southern Africa may be needed to detect an association between breast cancer screening with CBE and stage at presentation or mortality.

The age of women screened should be based on the efficacy of screening to detect malignancy or pre-malignancy, with international guidelines targeting women older than 40 or 50 years. Our findings suggest that community-based CBE screening is most efficient for detecting cancers in women over the age of 40. Further study with a larger sample size is required to definitively determine the optimal age-range for breast cancer screening, particularly for LMICs with a higher proportion of early-onset, aggressive breast cancers.[36–38]

Conclusion:

This study adds to the limited evidence in the region regarding community-based CBE screening, using data from over 6000 women. Our findings, which are relevant to similar settings, characterize cancer prevalence in the screened population, number

needed to screen to diagnose one cancer, and resource needs for complete diagnostic evaluation. Our results suggest that screening with CBE may be a reasonable approach in some settings to detect breast cancer at an earlier stage and that is most effective for older women.

Chapter 3: Assessing Implementation and Feasibility of a Novel Point-of-Care Diagnostic Device for Cancer

Abstract:

OBJECTIVE: This project assesses the Botswana health system for optimal implementation of a novel point-of-care diagnostic device for lymphoma and breast cancer and determines the feasibility of device implementation into those settings.

METHODS: i) Landscape analysis through interviews with key stakeholders from clinics and primary and tertiary hospitals focused on referral pathways and barriers to care for cancer patients. An integrated literature review was also conducted regarding causes of diagnostic delays.

ii) Pilot half-day training was conducted with diverse health worker cadres including varied degrees of lab experience, randomized to either in-person demonstration or simulated remote training with only videos and written materials. Participants were assessed on sample preparation and device use.

RESULTS: i) In Botswana there is a long delay (median 160 days, mean 406 days) between first clinic presentation and cancer diagnosis, the longest delay of any step between symptom onset and treatment, in part because the majority of cancers originate in rural areas. This novel technology could reduce diagnostic times by enabling triage of patients from primary hospitals or rural clinics instead of requiring referral to tertiary centers. It could also reduce pathology bottlenecks at tertiary centers.

ii) After training, 12/12 lab scientists learned to prepare samples and use the device with in-person or remote training. Of those with intermediate lab background, 6/8 were successful, and 1/5 with no prior lab background succeeded. Most errors were due to basic lab techniques, with pipetting generally presenting the greatest challenge. Participants who received in-person training performed better than those given the training materials alone. All participants who did not conduct the protocol successfully were confident they could learn with 1-2 more days of training.
DISCUSSION: This study shows that inexpensive, rapid molecular testing devices for cancer have potential to decrease diagnostic delays in Botswana and other LMICs. Diverse cadres of health workers are able to prepare samples and operate the device, enabling decentralization and simplification of the diagnostic algorithm.

Background:

As previously discussed, the mortality to incidence ratio is much higher in LMICs than in HICs, and a late stage at presentation is one major contributing factor to these poorer outcomes. In addition to possibilities for screening, there are other major diagnostic steps following symptom onset prior to treatment. These delays can be broken down into a delay to seek care following symptom onset, the delay between seeking care and obtaining a definitive diagnosis, and the time between diagnosis and the start of treatment. In Botswana, the median times for these steps are 29 days, 160 days, and 69 days respectively; therefore, there are opportunities for interventions within the health system to improve time to treatment initiation (Figure 3.1).[14] The

largest opportunity for decreasing delay is between seeking care and a definitive diagnosis, raising the possibility for innovations within the healthcare system to address this need.

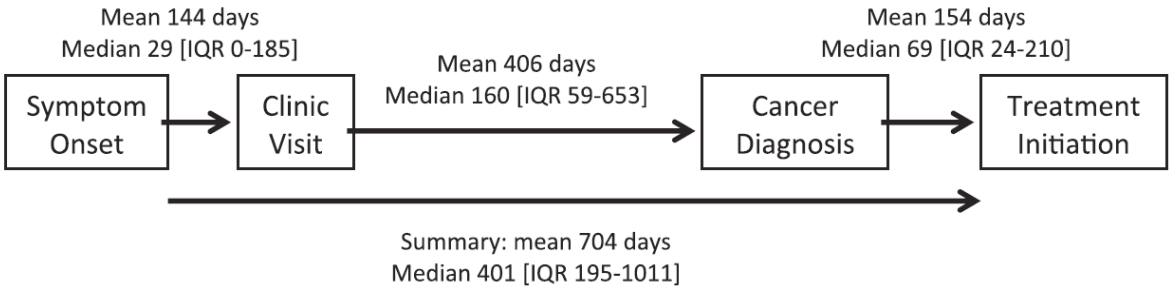


Figure 3.1: Delays in Cancer Care in Botswana (Brown et al)

There are a number of technical challenges in diagnosing breast cancer in LMICs. First, it is impossible to differentiate between a benign and malignant breast mass based on a clinical exam alone, requiring tools for advanced evaluation. In HICs, this typically involves advanced imaging technologies including a mammogram and/or an ultrasound followed by a biopsy and immunohistochemistry by a pathologist. For comparison, work-up from initial suspicion of breast cancer to definitive diagnosis takes 20 or 29 days for private and public hospitals respectively in a cohort of hospitals in the rural United States.[39]

However, in Botswana, access to those tests are severely restricted. The public mammogram is frequently broken, and the few private mammogram machines are expensive for government referrals and most volume is dedicated to private patients. Ultrasound machines are limited, as each major public hospital only has a few machines which are largely occupied with acute and in-patient needs. Therefore, in the public healthcare system, clinicians instead rely upon fine needle aspiration biopsies (FNAs) for

initial evaluation of breast cancer. Flow cytometry is available for other indications, particularly CD4+ counts in patients living with HIV, but is not used for breast cancer given a lack of trained professionals and difficulties in keeping sufficient stock of reagents. Without flow cytometry these samples are assessed by a pathologist using morphology alone, which has relatively low sensitivity and specificity for breast cancer. Frequently, FNAs do not result in a definitive diagnosis for the patient and contributes to a delay in diagnosis. The turn-around times for FNAs are typically 7-10 days if obtained at a central site, and longer at peripheral district or primary hospitals where transportation is needed.[40] Some clinicians can perform FNAs in their clinics while others refer to an FNA clinic at the district hospital or to one of the two referral centers. If either the FNA is positive for breast cancer or inconclusive with a concerning clinical story, a core or excisional biopsy will be performed by general surgery. Immunohistochemistry on these samples is either performed at the National Health Lab in Botswana or referred out to the private system, often including a shipment of the tissue sample to South Africa. The typical sign-out for pathology samples is 1-4 months; one study found a median time of 83 days from specimen collection to report for all cancer samples requiring analysis with immunohistochemistry.[40]

We are conducting a clinical trial of a novel diagnostic device called CytoPan, which we believe could offer a potential solution to some of these obstacles. The device uses multiple fluorescent channels to obtain information about the levels of hormone receptor markers (ER and PR), HER2, and a 'quad marker' based which is based on antibodies to 4 proteins (MUC1, EPCAM, EGFR, and HER2) which have a good sensitivity

for epithelial cancers.[41] It then uses a machine learning algorithm to differentiate cells and non-cellular debris. The percent of cells positive for each marker is used to determine whether the sample is positive or negative based on thresholds from historical patient data. This device could be used to obtain diagnoses from FNAs within one day without needing pathologists to read them. It is also small and relatively mobile so it could be used in near-to-care settings, and would cost ~$2000/device, much lower than the industry standard for flow cytometry or immunohistochemistry. The clinical trial testing the efficacy of this device relative to local and HIC gold-standards is ongoing and has enrolled over 120 patients.

We sought to understand how best this device could be utilized within the health system in Botswana, as well as the feasibility for its implementation based on the training required for successful use.

Methods:

Landscape analysis

We conducted a landscape analysis with a number of key stakeholders throughout Botswana. This included presentations followed by interactive sessions as well as individual meetings with institutional leadership of the 4 clinical sites at which the trial has been launched. Participants shared their thoughts about whether the device could provide benefit to the healthcare system, how it could be utilized most efficiently, as well as anticipated shortcomings and challenges.

Pilot Training Trial

Training materials were developed to provide an overview of the scientific background, general lab techniques, sample preparation, and device usage. They included a training video, pamphlet, and written protocol.

Participants were then enrolled in a pilot training trial and randomized to receive either all training materials with an in-person practical demonstration or simulated remote training with exclusively the training materials and no in-person demonstration. Those with a degree in the biological sciences and long-term work in a research lab were considered advanced lab background, those who were still students or had minimal exposure to diverse lab protocols in a clinical laboratory were considered intermediate lab background, and those who had never worked or studied in any lab environment were considered minimal lab background. Participants in the simulated remote training group were given time to practice in lab with access to all training materials. One hour was allocated for a written pre-test, watching the training video, and reviewing other written training materials. Approximately 3 hours was used for lab practice time. The remainder of training was for assessment only; participants were observed performing the protocol step by step for accuracy and time, in addition to a written post-test. Participants were allowed to skip incubation times which would have otherwise totaled 35 minutes. All reagent vials were labeled according to those needed in the protocol, but water was used for all liquid reagents. Cells and lyophilized (dried) antibodies were simulated with cell-sized plastic beads so that antibody rehydration and maintenance of the cell pellet could be assessed.

Errors were categorized into minor and major. Minor errors were those unlikely to change the result of the protocol, such as ≤ 10% volume pipette errors or minor variations in slide preparation. A participant who performs greater than 2 of these errors would be considered to have failed the protocol. Major errors were those considered likely to cause a failure of the protocol, including skipped steps, incorrect volume by >10%, major errors in slide preparation, disturbing the cell pellet before a wash, not mixing prior to an incubation, or incorrect reagent use.

Results:

Landscape Analysis

A total of over 200 people were presented to and asked for feedback. This group included students, residents, attending physicians, lab scientists or technicians, nurses, research scientists, heads of department, and institutional leadership. These clinical and lab professionals were from a range of institutions, including tertiary public referral centers, the national health lab, a district hospital, a university-based pathology residency training program, and an academic research lab.

The first proposed use of CytoPan was to have it available in rural areas where no pathologists are currently present. In this setting, a local clinician could obtain an FNA, and a local lab technician could perform the protocol and use the device to get a diagnosis. This could identify patients who are in need of urgent evaluation and ensure a rapid referral, avoiding the current paradigm where symptoms may need to worsen before a patient is sent or prioritizes reaching a tertiary center. District hospitals or

primary hospitals would be the best place for this to occur, as patient volume would likely be too low in health posts.

Second, even at tertiary centers, pathologists are overburdened. There are only 10 in the country, 8 in Gaborone and 2 in Francistown. Given the current vital role of FNAs in diagnosing cancer in an absence of advanced imaging modalities, this could also be used to reduce ques, triage patients needing further evaluation, and provide information for acutely ill patients needing immediate intervention. If the device proves to be accurate both for diagnosing breast cancer and sub-typing based on receptor status, it may allow treatment to start while awaiting a diagnosis with immunohistochemistry.

The stakeholders also discussed a number of challenges which must be addressed for the device to have the desired impact in the future. First, the device results depend on the ability to obtain high quality FNAs. While National Health Lab has a number of skilled clinicians who have done this procedure for years to decades, this is a challenge in more remote settings. The head of cytology for the National Health Lab is conducting trainings of medical officers and attending physicians throughout the country, and our group also conducted several FNA trainings to build capacity for FNAs outside the tertiary centers. Ultrasound guidance for all procedures is currently not possible given the resource constraints, but is available as needed for National Health Lab clinicians.

Another concern about the device is supply chains of the required reagents. For other reagents there are persistent concerns about supply. One key cause is that all

supplies must come through South Africa, and local suppliers often require months to obtain a particular reagent. The government healthcare system has many needs and a limited budget, so sometimes particular reagents will be deferred to later times such that they go out of stock. For protocols used for this device where multiple reagents are required to conduct the full assay, the probability that a reagent will stock out is higher than for more basic protocols.

Lastly, many stakeholders wondered about the maintenance fees and frequency required for the device. Unfortunately this information is not yet known for this device because it is still in the research phase and only have a few devices which are in existence, all of which are less than 2 years old.

Pilot Training Trial

We enrolled 25 participants in our pilot training trial, with the majority of them from the Botswana-Harvard Partnership. Years of lab experience ranged from 0 to 15 years. A total of 12 participants had advanced lab background, 8 had intermediate background, and 5 had minimal lab background.

Table 3.1 Protocol Success by Training Group and Lab Background

	high	intermediate	minimal or none
in-person	4/4	2/2	1/3
remote	8/8	4/6	0/2
total:	12/12	6/8	1/5

Of those with advanced lab background, the training materials and time were sufficient for 100% of them to conduct the protocol successfully (Table 3.1). Six of 8 participants with intermediate lab background did the protocol successfully, including 2/2 with in-person training and 4/6 with simulated remote training. One of 5 with

minimal background did the protocol successfully, with the one successful participant receiving in-person training.

Types of Errors:	Total #	% Total
skipped step	12	25.0
Incorrect pipette volume (>10%)	18	37.5
centrifuge	3	6.3
mixing error	1	2.1
other pipette error or multiple in 1 step	2	4.2
disturbed cell pellet	2	4.2
didn't take final sample from pellet	4	8.3
Slide error	2	4.2
wrong vial	4	8.3

Table 3.2: Error Summary

A total of 48 errors occurred (Table 3.2). The most common error which happened 18 times was of an incorrect pipette volume, typically due to incorrect placement of the decimal place leading to an error by a factor of 10. There were 12 errors of skipped step. Other errors were rarer, including 4 placements into the incorrect vial, 4 cases of taking sample from the solution instead of the concentrated cell pellet for slide preparation, and 3 centrifuge errors. All other errors occurred 2 times or less.

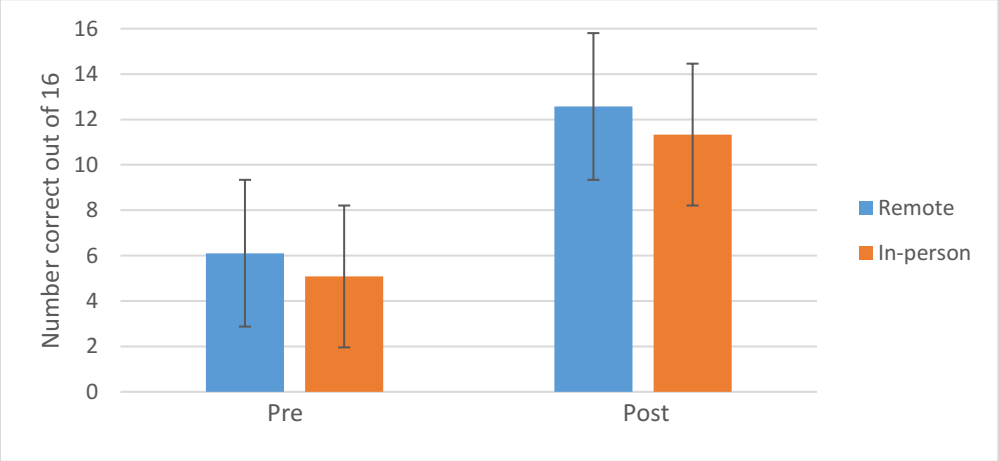


Figure 3.2: Pre- and Post-test Scores

Participants generally had a low understanding of cancer and the device before training, but training led to a significant improvement in understanding (Figure 3.2). Improvement between the pre- and post-tests were similar for in-person and simulated remote training groups.

The median and mean times to complete the protocol were 48 and 52 minutes respectively for all participants (Table 3.3). In person training had a lower median time (43 minutes) than simulated remote training (48 minutes), though in-person training participants had a longer mean time than simulated remote training (61 vs 48 minutes). Therefore, there were not substantial differences in protocol completion times between simulated-remote and in-person training.

Table 3.3: Time to Protocol Completion (excluding incubation times)

	total (min)	in-person (min)	remote (min)
mean	52	61	48
median	48	43	48

Discussion:

Our landscape analysis demonstrated that based on feedback from key stakeholders from a wide variety of roles and practice environments, this device has the potential to improve cancer diagnosis in Botswana. In rural areas, this device would serve as a triage mechanism for patients undergoing evaluation for a possible cancer diagnosis. Due to a lack of availability of advanced imaging, this device which uses only FNAs without need for ultrasound or mammogram could provide feedback nearer to a patient's home and more quickly than conventional methods.

Technologies are often not designed specifically for lower resourced contexts, despite the unique challenges often faced in those contexts.[42] Given the high rate of failure for new technologies being sent into LMIC contexts[43], creative approaches are required to ensure more involvement of local stakeholders throughout the implementation process. We implemented our landscape analysis throughout the trial design and writing of the IRB application in order to incorporate feedback and co-design key documents with local stakeholders. Additionally, since obtaining samples for this clinical trial requires integration into the health system's diagnostic pathway, subtleties of all involved institutions were discussed by relevant administrators, clinicians, and lab personnel, making the trial more likely to succeed. Feedback during implementation will also allow for iterative changes to the technology to be made, ultimately optimizing adaptation into an LMIC context. In our case, we standardized our collection buffer to be the same across protocols and decreased the number of separate slides per sample from three to one based on feedback from this analysis.

Additionally, a lack of training among healthcare professionals is also a substantial barrier to implementation of new technologies. In an evaluation by Engineering for World Health, it was found that a frequent cause for unused or broken technology was a lack of training, although local staff could be trained following the needs assessment.[43] However, without their staff in country, the technology would have remained unused or broken. This highlights that for our device to have an impact, it must be usable by staff with relatively low scientific and lab literacy, and training must be designed with the target population in mind. Such capacity can be difficult to find in

urban areas, and rural areas are even less likely to house individuals with advanced skillsets in those disciplines. We outlined steps more clearly and had both written and video training about basic lab techniques to assist those of minimal background.

Standards for implementing technologies into new contexts must be established in order to maximize the probability for success.[44] Of the many components required for technology implementation, training of local staff to use the technology and making them feel confident using it will be key to uptake of devices into clinical care. Robust mechanisms for evaluation and feedback of the training materials must be incorporated into the implementation strategies. In our study, by assessing our training materials alone or with in-person training, we could adapt and update the training materials based on the steps where the majority of people failed. Particularly for those with minimal lab training, we have expanded on our information about basic pipette techniques for future larger scale training efforts. We subsequently included several examples of setting pipettes of different volumes, since the position of the decimal point on the various pipettes was a persistent source of confusion for our participants without extensive lab expertise. Assessing and adapting training materials in this way, informed by observed practical of training participants, was well received by all participants and allowed the trainers to be certain about the efficacy of the training; this is an ideal way to test the feasibility of implementation of new technologies. We emphasize the importance of training materials, iterative updates, and practical assessment for other organizations trying to implement technology into a new setting.

Going forward, both projects will continue to evolve as the clinical trial is ongoing. Stakeholders are continuously engaged to improve the efficacy of the trial and prepare for potential integration of the device into the medical system following trial completion. A larger cohort of about 100 participants of intermediate lab skill (early university students in the lab sciences) will be trained to perform the protocol and use the device with the updated training materials. This will allow us to more statistical power regarding the differences between groups trained in person vs with training materials alone, and will seek to show non-inferiority as updated materials focus on areas where participants were most likely to fail in the pilot study.

Conclusion:

Based on a landscape analysis with over 200 stakeholders in Botswana, a novel point-of-care diagnostic device shows promise to decentralize cancer diagnosis to district and primary hospitals while off-loading some cases from overworked pathologists in tertiary centers. A pilot training study shows that the laboratory skills required to perform the protocol and use the device are low enough that there is possibility for successful use outside of urban areas and tertiary hospitals.

Chapter 4: The Association Between HIV and Quality of Life Among Women Surviving Breast Cancer

Abstract:

OBJECTIVE: Women living with HIV (WLHIV) experience decreased survival from breast cancer. We sought to determine whether WLHIV surviving breast cancer also experienced decreased post-treatment quality of life (QOL).

METHODS: We included women enrolled in Thabatse Cancer Cohort presenting from October 2010 to October 2019 at oncology centers in Botswana for initial treatment of breast cancer. QOL was measured quarterly using the SF-8, which includes a physical composite score (PCS) and a mental composite score (MCS). We assessed change in PCS and MCS from 3 (+/-3) months post-treatment to 18 (+/-3) months post-treatment. We performed multivariable linear regression to model the relationship between change in QOL and HIV, age, wealth, and cancer stage.

RESULTS: Of 638 women enrolled, 145 women died prior to 15 months post-treatment and 201 had not reached 15 months post-treatment. A total of 58 (9.1%) women missing QOL measurements at 3 or 18 months were excluded. Of the remaining 203 analyzed, 60 (25.6%) were WLHIV and 174 (74.4%) were HIV-uninfected. Over half (52%) had advanced stage (stage III/IV) and 84.6% received multimodality treatment with surgery and chemotherapy and/or radiation. Overall, PCS increased following treatment, + 2.04 (95%CI 0.98 - 3.11, $p < 0.001$), and MCS did not change significantly, + 0.60 (95%CI -0.67 – 1.87, $p = 0.24$). A significant association between HIV infection and improvement in PCS was observed, +2.92 (95%CI 0.41 – 5.35, p=0.021), though HIV was

not predictive of change in MCS, 1.25 (95%CI -1.73 – 4.30, p=0.41). In the secondary analyses of the components of the PCS, HIV was predictive of improved general health and bodily pain ($p<0.05$). No other covariates were significantly associated with MCS or PCS.

CONCLUSIONS: HIV infection is associated with a positive difference in a change of physical quality of life between 3 and 18 months following treatment for breast cancer and not associated with mental quality of life.

Background:

As the survival outcomes for women with breast cancer continue to improve, there has been increasing interest in identifying factors that determine the quality of life following treatment [45]. Prior studies have shown that breast cancer survivors may have similar general health scores with controls, but that there are increased restrictions in physical and social functioning as well as pain.[46] The surgery performed has also been shown to impact long-term quality of life, favoring breast conserving therapy over mastectomy.[47,48] In some cases, quality of life scores have been shown to predict survival and progression; one study demonstrated a positive correlation between a social well-being score with mortality and breast cancer recurrence [49]. A quantitative study in Nepal found that women undergoing chemotherapy had a poor quality of life, with age inversely related to quality of life, and family income plus education level predictive of better quality of life.[50] However, these investigations have never examined the association of HIV in the recovery of quality of life following cancer treatment.

In Botswana, a rural middle-income country of 2.2 million people in southern Africa with HIV seroprevalence of 23% among breast cancer patients, HIV has been shown to be an independent predictor of mortality even when controlled for stage and receptor status.[51] There were no differences in treatment practices between HIV positive and negative women to explain this variation. The majority of CD4 counts among women in this cohort was within the normal range and viral load suppressed, decreasing the likelihood that opportunistic infections or AIDS were the cause of this association. Given this finding, we hypothesized that there may also be an association between quality of life and HIV among women surviving breast cancer.

Methods:

Patient Population

The Thabatse Cancer Cohort is a prospective cohort study which enrolls all biopsy-proven cancer patients who present to one of the major referral centers in Botswana. Three of these centers are in the capital of Gaborone, including the public Princess Marina Hospital and both private hospitals, Gaborone Private Hospital and Bokamoso Private Hospital. The public hospital in Francistown, Nyangabwe Referral Hospital, was also included. We included women enrolled in Thabatse Cancer Cohort presenting from October 2010 to October 2019 during initial treatment of breast cancer. Women were excluded from our analysis if they died before 18 months post-treatment or had not yet reached 18 months of post-treatment follow-up.

Quality of Life Measurement

QOL was measured quarterly using the SF-8, a patient self-report tool which includes a physical composite score (PCS) and a mental composite score (MCS). The PCS is composed of general health, physical functioning, role physical, bodily pain, and vitality scores. The MCS is composed of social functioning, mental health, and role emotional scores. We assessed change in PCS and MCS from 3 months post-treatment to 18 months post-treatment to determine the change in quality of life over that period. We chose 3 months given that it was the first survey following the completion of treatment, and 18 months since it was sufficient time to be considered the new baseline following treatment without compromising sample size.

Statistical Analysis

A multivariate linear regression of the difference in difference in QoL scores was performed in R.[30] Exposures included age (defined as above or below 45 years old), stage, ER/PR status, wealth, treatment modalities received, and HIV status. The primary outcome was effect of HIV on change in PCS and MCS from baseline as determined using the 95% CI. In secondary analysis, a multivariate linear regression with the same exposures was also performed for each component variable of the composite scores.

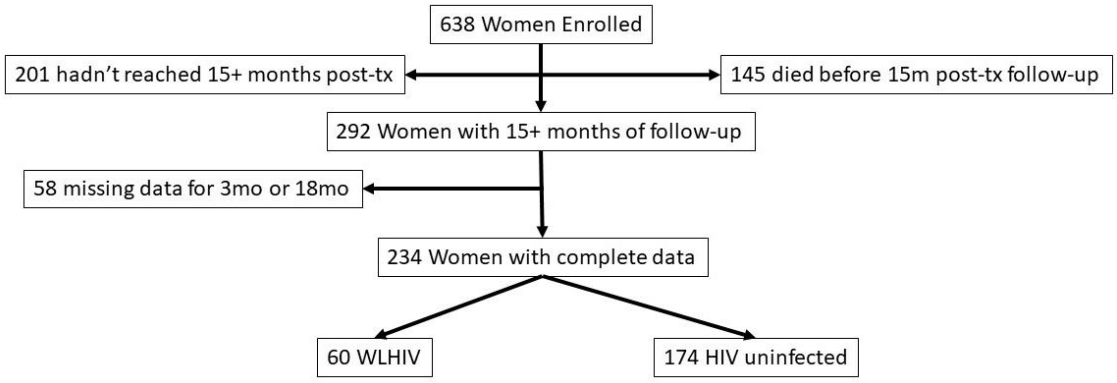
Results:

Patient Population

A total of 638 women were enrolled. One hundred forty-five died before 15 months of follow-up, and 201 had not yet reached 15 months of follow-up after the conclusion of treatment. Women lacking a quality of life measurement at one or both

survey times were also excluded, numbering 58 with approximately equal proportion of HIV infection as the remaining cohort. Of the remaining 234 analyzed, 60 (25.6%) were women living with HIV (WLHIV) and 174 (74.4%) were HIV-uninfected. See figure 4.1 for a schematic of women included in the study.

Figure 4.1: Patient Inclusion.



WLHIV were younger than women in the non-HIV-infected cohort ($p < 0.05$), and stage was not different overall. WLHIV were significantly less likely to get surgery and radiation, though there was no association with chemotherapy. Treatment differences in these modalities based on HIV status were not found among all eligible women enrolled, but only in the final cohorts.[51] There was a non-significant trend toward WLHIV being less wealthy. Among WLHIV, 42 had an undetectable viral load and 3 were unknown. The average CD4 count was 513. See Table 4.1 for other patient characteristics.

Table 4.1: Patient Demographics

	HIV+	HIV-	p-value
Total	60	174	
Age			0.091
<45	22	44	
>=45	38	130	
Stage			0.41
I	3	16	
II	19	58	
III	21	68	
IV	6	8	
Unknown	11	24	
Treatment			
Surgery	54	168	.047*
Chemotherapy	50	146	0.92
Radiation	26	104	.027*
Receptor Status			
ER or PR+	34	83	0.29
TNBC	7	24	0.84
Unknown or Other	19	67	0.63
Wealth			
mean	3.25	3.74	0.067
Viral Load			
<400 copies	53		
Unknown	7		
CD4+ Count			
	530		

Quality of Life Outcomes

Overall, Physical Composite Scores increased following treatment, +2.04 (95%CI 0.98 – 3.11), $p < 0.001$, while the Mental Composite Score was unchanged, +0.60 (95%CI -0.67 – 1.87), $p = 0.35$. In our primary outcome, a significant association between HIV infection and improved PCS was observed, +2.92 (95%CI 0.41 – 5.35, p=0.021). HIV was not predictive of change in MCS, 0.85 (95%CI -2.73 – 4.44, p=0.64). Two components analyzed in secondary analysis, general health and bodily pain, had significant

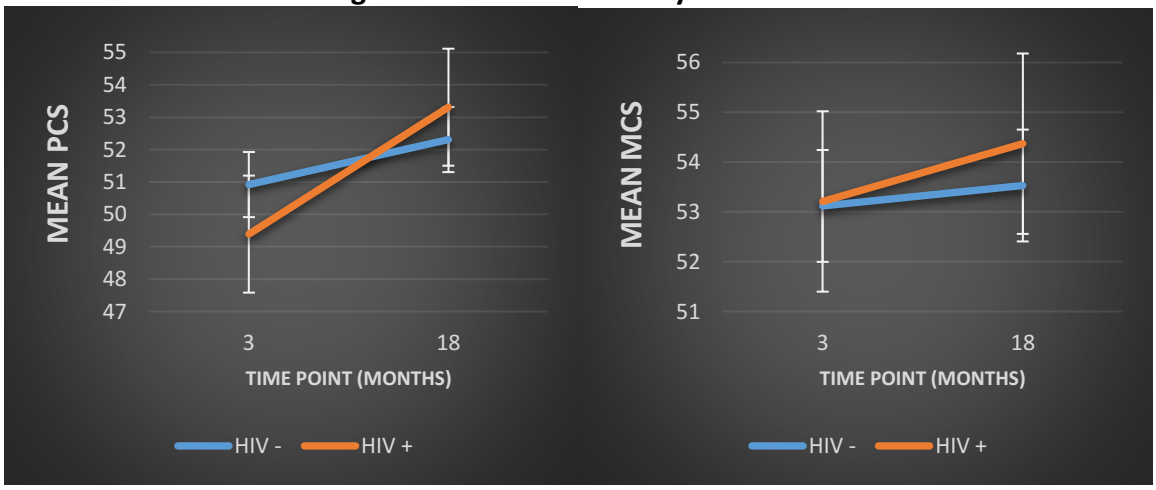
associations of 2.59 [0.06 – 5.12], p =0.045 and 3.35 [0.43 – 6.27], p = 0.026 respectively (Table 4.2). WLHIV had a lower PCS relative to HIV uninfected women at the 3 month timepoint and a greater PCS following treatment (figure 4.2). Physical functioning and vitality scores also had non-significant associations between HIV and higher PCS. No components of MCS demonstrated trends of association.

Table 4.2: Associations between Quality of Life Metrics and HIV

Metric	Estimated attributed change in linear model	P-value
PCS	**2.92 [0.41 - 5.35]**	**0.021***
General Health	2.59 [0.06 - 5.12]	0.045*
Physical Functioning	1.91 [-0.13 - 3.95]	0.067
Role Physical	1.43 [-0.96 - 3.82]	0.24
Bodily Pain	3.35 [0.43 - 6.27]	0.026*
Vitality	1.89 [-0.21 - 3.99]	0.08
MCS	**1.25 [-1.73 - 4.30]**	**0.41**
Social Functioning	1.6 [-1.01 - 4.21]	0.23
Mental Health	1.17 [-1.42 - 3.76]	0.37
Role Emotional	1.54 [-0.69 - 3.77]	0.18

Of the other variables included in the linear regression model, none were significantly associated with a decreased PCS or MCS.

Figure 4.2: PCS and MCS by HIV status



Discussion:

This study found a significant association between HIV infection and increased recovery of physical quality of life as measured by an SF-8 questionnaire between 3 and 18 months following treatment for breast cancer. Several sub-categories of physical quality of life also reached significance, but no significant associations were observed for mental quality of life. Changes in quality of life of 1 or less [52,53] as measured by the SF-8 have been considered clinically significant, indicating that our results with an estimated change in PCS of almost 3 are a clinically relevant effect size.

This positive change in the PCS reflects both the slightly lower baseline at 3 months and slightly higher overall value at 18 months. This may mean that WLHIV have a lower nadir of physical quality of life following treatment than their HIV-uninfected counterparts. However, it is encouraging that these women are able to regain that quality of life following treatment. This finding provides further support that HIV patients derive high benefits from treatment for breast cancer, including a good long-term quality of life. A study of quality of life among cervical cancer patients in an HIV-endemic population in South Africa undergoing chemoradiotherapy versus radiotherapy alone reported substantial improvement in both groups, indicating that HIV positive patients may also reap substantial benefit in QoL for another disease site [54]. However, they did not report a sub-analysis based on HIV-status so we cannot directly compare results.

While WLHIV in this cohort were shown to have increased mortality in this cohort,[51] this analysis only included the subset of women who survived to a minimum of

18 months. The selection of this cohort therefore excludes many patients who contributed to this increased mortality. The association between HIV and quality of life therefore is likely more positive in our cohort, as WLHIV who may have suffered a negative impact on quality of life are excluded due to early mortality. We elected to not include women who died as having a QoL of 0 in this analysis because any signal among surviving women would likely be masked by the large differences in mortality between the cohorts.

The survey tool used in this study, the SF-8, has been validated in one breast cancer cohort in the US as well as in a non-cancer-specific population in Uganda and in a low-income, diverse population in the US [55–57]. The SF-8 has not been formally validated for use among PLHIV, though a systematic review suggested that shorter versions of the validated SF-36 could be used when such a long questionnaire was burdensome.[58] Some key areas of health were left out of this survey form, including sexual health, financial struggles, and specific symptoms other than pain, which have been reported in other studies of quality of life among women surviving breast cancer [46,48]. While a more detailed survey tool or qualitative studies may be more likely to uncover more specific associations between symptoms that may be clinically actionable, the SF-8 allowed us to collect data on many patients over a long period of time.

Other studies have demonstrated equivalence of quality of life among people living with HIV (PLHIV) when they were connected with treatment greater than 5 years [59]. A large sample size was required to detect small differences in quality of life between HIV uninfected patients and those enrolled in treatment for HIV for <5 years [59]. Since

Botswana was among the first countries to initiate universal HIV treatment for its citizens in 2002, and implemented a "Treat All" strategy in 2016,[60] many patients have well-controlled HIV on long-term antiretroviral (ARV) therapy. This likely substantially increases the quality of life among WLHIV in Botswana compared to other nations in the region which have less ARV coverage.

Among women surviving breast cancer, quality of life among most physical and mental metrics has been shown to increase over time [61], which is consistent with our results. Of note, other studies have found that the greatest improvement is QoL is within 3 months of the conclusion of treatment, so our results may understate the true change in QoL between treatment end and 18 months [62]. However, given that these studies are based in the United States, patients were at a less advanced stage and were more likely to have less invasive interventions (e.g. breast conserving surgery vs mastectomy), which limits their generalizability into settings like Botswana.

Conclusion:

HIV infection is associated with a clinically meaningful and statistically significant positive difference in the change of physical quality of life between 3 and 18 months following treatment for breast cancer relative to HIV-uninfected women. Mental quality of life demonstrated minimal change between these time points, though investigations with more specific tools validated in the region would be more likely to yield an association.

Chapter 5: Conclusion

Implementing any medical intervention into a low or middle income country is challenging, and cancer provides a number of unique challenges due to the scientific complexity of education, diagnosis and treatment. In light of these complexities, the value chain is a helpful framework for understanding the entire continuum of how to best improve care, from education and screening to treatment and long-term follow-up.

This thesis has an emphasis on the diagnostic component of the value chain, with a goal of decreasing the stage at which cancers are diagnosed. The yield of a community-based education and screening initiative through an NGO was higher than similar studies in other LMICs, and used only modest resources. However, given that screening did not occur on an annual basis in consistent locations, more women were diagnosed than would be likely to occur in a single longitudinal program. However, clinical breast exams this may still provide an avenue to decrease the stage at which cancer is diagnosed in LMICs where mammograms and other forms of imaging are not available. The Cytopan diagnostic device has potential to decentralize cancer diagnosis to regions beyond where most pathologists and highly trained lab professionals work, typically in major cities. This decentralization will allow patients to avoid the typical delays due to transportation. Since Cytopan can provide a diagnosis within hours of sample collection, this can also be used to circumnavigate long delays sometimes associated with conventional pathology diagnosis given the limited number of pathologists in the country. We have shown that lab technicians from a range of lab backgrounds can learn to perform the protocol quickly and with high efficacy, a key

requisite for the technology to function outside of urban centers. According to our understanding of delays in cancer care in Botswana, improving the path to diagnosis following first clinic presentation is the greatest opportunity to shorten delays between first presentation to a clinic and the start of treatment.[14] Diagnosing patients faster and more efficiently is likely to decrease the stage at which patients start treatment, currently a weakness in the value chain. With multimodality treatment available without long delays, decreasing the stage at presentation may result in improved breast cancer outcomes.

In terms of long-term follow-up, we found that HIV infection was associated with an increased positive change in physical quality of life between 3 and 18 months relative to HIV uninfected women. This improvement is likely due to a lower nadir of quality of life among WLHIV during and immediately following treatment, as well as a return to a high baseline. This finding supports curative treatment for WLHIV, since they are able to regain a good quality of life even though they suffer from a higher mortality rate than their HIV uninfected counterparts. While treatment modalities used were not significantly associated with differences in physical or mental QoL, we anticipate that as cancer therapies become more robust in Botswana that there may be more emphasis on interventions historically associated with a higher post-treatment quality of life such as breast conserving surgery and modulated radiation therapies.

Much more work remains to be done surrounding breast cancer in LMICs, including Sub-Saharan Africa. The value chain model, considering education/awareness, screening, evaluation for suspected cancer, definitive diagnosis, multimodality

treatment, and long-term follow-up/quality of life, is a useful tool in identifying the most critical junctures and strategizing intervention in oncology systems.

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Bibliography

1. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *The Lancet Oncology*. 2012;13(8):790-801. doi:10.1016/S1470-2045(12)70211-5

2. Pace LE, Shulman LN. Breast Cancer in Sub-Saharan Africa: Challenges and Opportunities to Reduce Mortality. *The Oncologist*. 2016;21(6):739-744. doi:10.1634/theoncologist.2015-0429

3. Hashim D, Boffetta P, La Vecchia C, et al. The global decrease in cancer mortality: trends and disparities. *Ann Oncol*. 2016;27(5):926-933. doi:10.1093/annonc/mdw027

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;68(6):394-424. doi:10.3322/caac.21492

5. Statistics Botswana. 2011 Botswana Population and Housing Census. Statistics Botswana. http://www.statsbots.org.bw/sites/default/files/publications/national_statisticsreport.pdf. Published 2015. Accessed February 10, 2019.

6. Meredith M. *The Fortunes of Africa: A 5000-Year History of Wealth, Greed, and Endeavor*. London: Public Affairs; 2014.

7. Meredith M. *The State of Africa: A History Of Fifty Years Of Independence*. London: Free Press; Simon & Schuster; 2005.

8. CIA. CIA World Factbook. The World Factbook. https://www.cia.gov/library/publications/the-world-factbook/geos/bc.html. Published February 4, 2020. Accessed February 4, 2020.

9. Mbuka-Ongona D, Tumbo JM. Knowledge about breast cancer and reasons for late presentation by cancer patients seen at Princess Marina Hospital, Gaborone, Botswana. *African Journal of Primary Health Care & Family Medicine*. 2013;5(1). doi:10.4102/phcfm.v5i1.465

10. Fiorica JV. Breast Cancer Screening, Mammography, and Other Modalities: *Clinical Obstetrics and Gynecology*. 2016;59(4):688-709. doi:10.1097/GRF.0000000000000246

11. Malmgren JA, Atwood MK, Kaplan HG. Increase in mammography detected breast cancer over time at a community based regional cancer center: a longitudinal

cohort study 1990–2005. *BMC Cancer*. 2008;8(1):131. doi:10.1186/1471-2407-8-131

12. Béatrice L-S, Chiara S, Dana L, et al. Breast-Cancer Screening — Viewpoint of the IARC Working Group. *n engl j med*. 2015:6.

13. Gutnik LA, Matanje-Mwagomba B, Msosa V, et al. Breast Cancer Screening in Low- and Middle-Income Countries: A Perspective From Malawi. *Journal of Global Oncology*. 2016;2(1):4-8. doi:10.1200/JGO.2015.000430

14. Brown CA, Suneja G, Tapela N, et al. Predictors of Timely Access of Oncology Services and Advanced-Stage Cancer in an HIV-Endemic Setting. *The Oncologist*. 2016;21(6):731-738. doi:10.1634/theoncologist.2015-0387

15. National Comprehensive Cancer Network. Breast Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published February 5, 2020. Accessed February 7, 2020.

16. Martei YM, Chiyapo S, Grover S, et al. Availability of WHO Essential Medicines for Cancer Treatment in Botswana. *J Glob Oncol*. 2018;(4):1-8. doi:10.1200/JGO.17.00063

17. Vanderpuye V, Grover S, Hammad N, et al. An update on the management of breast cancer in Africa. *Infect Agents Cancer*. 2017;12(1):13. doi:10.1186/s13027-017-0124-y

18. Pace LE, Dusengimana J-MV, Hategekimana V, et al. Benign and Malignant Breast Disease at Rwanda's First Public Cancer Referral Center. *The Oncologist*. 2016;21(5):571-575. doi:10.1634/theoncologist.2015-0388

19. Pace LE, Dusengimana JMV, Shulman LN, et al. Cluster Randomized Trial to Facilitate Breast Cancer Early Diagnosis in a Rural District of Rwanda. *JGO*. 2019;(5):1-13. doi:10.1200/JGO.19.00209

20. Mittra I, Mishra GA, Singh S, et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: Methodology and interim results after three rounds of screening. *International Journal of Cancer*. 2009:NA-NA. doi:10.1002/ijc.24840

21. Sankaranarayanan R, Ramadas K, Thara S, et al. Clinical Breast Examination: Preliminary Results from a Cluster Randomized Controlled Trial in India. *JNCI Journal of the National Cancer Institute*. 2011;103(19):1476-1480. doi:10.1093/jnci/djr304

22. Pisani P, Parkin DM, Ngelangel C, et al. Outcome of screening by clinical examination of the breast in a trial in the Philippines. *International Journal of Cancer*. 2006;118(1):149-154. doi:10.1002/ijc.21343

23. Abuidris DO, Elsheikh A, Ali M, et al. Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study. *The Lancet Oncology*. 2013;14(4):363-370. doi:10.1016/S1470-2045(12)70583-1

24. Song Q-K, Wang X-L, Zhou X-N, et al. Breast Cancer Challenges and Screening in China: Lessons From Current Registry Data and Population Screening Studies. *The Oncologist*. 2015;20(7):773-779. doi:10.1634/theoncologist.2014-0351

25. *World Health Organization. Breast Cancer Early Diagnosis and Screening. Geneva: World Health Organization; 2018. Https://Www.Who.Int/Cancer/Prevention/Diagnosis-Screening/Breast-Cancer/En/. Accessed September 3, 2019.*

26. Tapela NM, Peluso MJ, Kohler RE, et al. A Step Toward Timely Referral and Early Diagnosis of Cancer: Implementation and Impact on Knowledge of a Primary Care-Based Training Program in Botswana. *Front Oncol*. 2018;8:187. doi:10.3389/fonc.2018.00187

27. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, et al. HIV Infection and Survival Among Women With Cervical Cancer. *JCO*. 2016;34(31):3749-3757. doi:10.1200/JCO.2016.67.9613

28. Milligan MG, Bigger E, Abramson JS, et al. Impact of HIV Infection on the Clinical Presentation and Survival of Non-Hodgkin Lymphoma: A Prospective Observational Study From Botswana. *J Glob Oncol*. 2018;(4):1-11. doi:10.1200/JGO.17.00084

29. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis.* Springer-Verlag New York; 2016. https://ggplot2.tidyverse.org.

30. *R Core Team (2017). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL Https://Www.R-Project.Org/.*

31. Ngoma T, Mandeli J, Holland JF. Downstaging cancer in rural Africa: Downstaging Cancer in Rural Africa. *International Journal of Cancer*. 2015;136(12):2875-2879. doi:10.1002/ijc.29348

32. Weigel S, Heindel W, Heidrich J, Heidinger O, Hense H. Reduction of Advanced Breast Cancer Stages at Subsequent Participation in Mammography Screening. *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren*. 2015;188(01):33-37. doi:10.1055/s-0041-107835

33. Austad K, Chary A, Xocop SM, et al. Barriers to Cervical Cancer Screening and the Cervical Cancer Care Continuum in Rural Guatemala: A Mixed-Method Analysis. *JGO*. 2018;(4):1-10. doi:10.1200/JGO.17.00228

34. Cunningham M, Thomson V, McKiever E, Dickinson LM, Furniss A, Allison MA. Infant, Maternal, and Hospital Factors' Role in Loss to Follow-up After Failed Newborn Hearing Screening. *Academic Pediatrics*. 2018;18(2):188-195. doi:10.1016/j.acap.2017.05.005

35. Zelle SG, Nyarko KM, Bosu WK, et al. Costs, effects and cost-effectiveness of breast cancer control in Ghana: Breast cancer control Ghana. *Tropical Medicine & International Health*. 2012;17(8):1031-1043. doi:10.1111/j.1365-3156.2012.03021.x

36. Darré T, Tchaou M, Folligan K, et al. Breast cancer cases of female patients under 35 years of age in Togo: A series of 158 cases. *mol clin onc*. October 2017. doi:10.3892/mco.2017.1461

37. Brinton LA, Figueroa JD, Awuah B, et al. Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast Cancer Research and Treatment*. 2014;144(3):467-478. doi:10.1007/s10549-014-2868-z

38. Sighoko D, Kamaté B, Traore C, et al. Breast cancer in pre-menopausal women in West Africa: Analysis of temporal trends and evaluation of risk factors associated with reproductive life. *The Breast*. 2013;22(5):828-835. doi:10.1016/j.breast.2013.02.011

39. Louis CJ, Clark JR, Hillemeier MM, Camacho F, Yao N, Anderson RT. The Effects of Hospital Characteristics on Delays in Breast Cancer Diagnosis in Appalachian Communities: A Population-Based Study: Breast Cancer Diagnosis Delays in Appalachia. *The Journal of Rural Health*. 2018;34:s91-s103. doi:10.1111/jrh.12226

40. Martei YM, Narasimhamurthy M, Prabhakar P, et al. Breast Cancer Pathology Turnaround Time in Botswana. *J Glob Oncol*. 2018;(4):1-7. doi:10.1200/JGO.17.00090

41. Haun JB, Castro CM, Wang R, et al. Micro-NMR for Rapid Molecular Analysis of Human Tumor Samples. *Science Translational Medicine*. 2011;3(71):71ra16-71ra16. doi:10.1126/scitranslmed.3002048

42. Caldwell A, Young A, Gomez-Marquez J, Olson KR. Global Health Technology 2.0. *IEEE Pulse*. 2011;2(4):63-67. doi:10.1109/MPUL.2011.941459

43. Malkin RA. Design of Health Care Technologies for the Developing World. *Annu Rev Biomed Eng*. 2007;9(1):567-587. doi:10.1146/annurev.bioeng.9.060906.151913

44. Nilsen P. Making sense of implementation theories, models and frameworks. *Implementation Science*. 2015;10(1). doi:10.1186/s13012-015-0242-0

45. Perry S, Kowalski TL, Chang C-H. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. *Health and Quality of Life Outcomes*. 2007;5(1):24. doi:10.1186/1477-7525-5-24

46. Koch L, Jansen L, Herrmann A, et al. Quality of life in long-term breast cancer survivors – a 10-year longitudinal population-based study. *Acta Oncologica*. 2013;52(6):1119-1128. doi:10.3109/0284186X.2013.774461

47. Sun Y, Kim S-W, Heo CY, et al. Comparison of Quality of Life Based on Surgical Technique in Patients with Breast Cancer. *Japanese Journal of Clinical Oncology*. 2014;44(1):22-27. doi:10.1093/jjco/hyt176

48. Tsai H-Y, Kuo RN-C, Chung K. Quality of life of breast cancer survivors following breast-conserving therapy versus mastectomy: a multicenter study in Taiwan. *Japanese Journal of Clinical Oncology*. 2017;47(10):909-918. doi:10.1093/jjco/hyx099

49. Epplein M, Zheng Y, Zheng W, et al. Quality of Life After Breast Cancer Diagnosis and Survival. *Journal of Clinical Oncology*. 2011;29(4):406-412. doi:10.1200/JCO.2010.30.6951

50. Bhandari S, Sriyuktasuth A, Pongthavornkamol K. Treatment-Related Quality of Life in Nepalese Women with Breast Cancer. *Asian Pac J Cancer Prev*. 2017;18(12). doi:10.22034/APJCP.2017.18.12.3365

51. Sadigh K, Scott Dryden-Peterson. HIV is Associated with Decreased Breast Cancer Survival: A Prospective Cohort Study. Oral presented at the: Conference on Retroviruses and Opportunistic Infections; March 4, 2019; Seattle, Washington. http://www.croiconference.org/sessions/hiv-associated-decreased-breast-cancer-survival-prospective-cohort-study.

52. Yost KJ, Haan MN, Levine RA, Gold EB. Comparing SF-36 scores across three groups of women with different health profiles. *Qual Life Res*. 2005;14(5):1251-1261. doi:10.1007/s11136-004-6673-8

53. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: A response. :9.

54. du Toit GC, Kidd M. Prospective Quality of Life Study of South African Women Undergoing Treatment for Advanced-stage Cervical Cancer. *Clinical Therapeutics*. 2015;37(10):2324-2331. doi:10.1016/j.clinthera.2015.08.018

55. Lefante JJ, Harmon GN, Ashby KM, Barnard D, Webber LS. Use of the SF-8 to assess health-related quality of life for a chronically ill, low-income population

participating in the Central Louisiana Medication Access Program (CMAP). *Qual Life Res*. 2005;14(3):665-673. doi:10.1007/s11136-004-0784-0

56. Mehnert A, Herschbach P, Berg P, Henrich G, Koch U. Progredienzangst bei Brustkrebspatientinnen - Validierung der Kurzform des Progredienzangstfragebogens PA-F-KF/ Fear of progression in breast cancer patients – validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). *Zeitschrift für Psychosomatische Medizin und Psychotherapie*. 2006;52(3):274-288. doi:10.13109/zptm.2006.52.3.274

57. Roberts B, Browne J, Ocaka K, Oyok T, Sondorp E. The reliability and validity of the SF-8 with a conflict-affected population in northern Uganda. *Health Qual Life Outcomes*. 2008;6(1):108. doi:10.1186/1477-7525-6-108

58. Emerge Consortium, Cooper V, Clatworthy J, Harding R, Whetham J. Measuring quality of life among people living with HIV: a systematic review of reviews. *Health Qual Life Outcomes*. 2017;15(1):220. doi:10.1186/s12955-017-0778-6

59. Thomas R, Burger R, Harper A, et al. Differences in health-related quality of life between HIV-positive and HIV-negative people in Zambia and South Africa: a cross-sectional baseline survey of the HPTN 071 (PopART) trial. *The Lancet Global Health*. 2017;5(11):e1133-e1141. doi:10.1016/S2214-109X(17)30367-4

60. Makhema J, Wirth KE, Pretorius Holme M, et al. Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana. *N Engl J Med*. 2019;381(3):230-242. doi:10.1056/NEJMoa1812281

61. Härtl K, Engel J, Herschbach P, Reinecker H, Sommer H, Friese K. Personality traits and psychosocial stress: quality of life over 2 years following breast cancer diagnosis and psychological impact factors. *Psycho-Oncology*. 2010;19(2):160-169. doi:10.1002/pon.1536

62. Deshields T, Tibbs T, Fan M-Y, Bayer L, Taylor M, Fisher E. Ending treatment: the course of emotional adjustment and quality of life among breast cancer survivors immediately following radiation therapy. *Support Care Cancer*. 2005;13(12):1018-1026. doi:10.1007/s00520-005-0801-z