Breast Cancer and Endocrine Therapy Adherence in Ethiopia: Diagnosis, Treatment, and Breast Nurse Intervention

Dissertation

for the degree of Doctor of Medical Science (Dr. rer. medic.)
for the specialty in Epidemiology

Submitted

of the Medical Faculty
of the Martin Luther University of Halle-Wittenberg

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Date of defense: 16.03.2023

Summary

The overall objective of this doctoral dissertation is to discuss how a breast nurse intervention improves adherence to endocrine therapy among breast cancer patients in Ethiopia, ultimately contributing to higher survival rates. This dissertation discusses five academic studies concerning breast nurse intervention, diagnosis, and systemic treatment. The first two studies dealt with patients' clinical profiles, the magnitude and associated factors of late-stage presentation, delays in diagnosis, and barriers to the early diagnosis of breast cancer. In our study, 72% of the patients presented at a late stage, and the median patient delay was four months. Patient- and health-system-related barriers were the main factors found to impede early diagnosis. The time to initiation of systemic therapy showed that in nearly half of the patients (47%), systemic therapy was not initiated in a timely manner. The study on adherence to tamoxifen therapy revealed that adherence and persistence to endocrine therapy were very low in the peripheral regions of the country. Access to systemic therapy was found to be very limited.

Thus, considering the barriers to adherence to endocrine therapy, survivorship care, and gaps in early diagnostics in the peripheral regions of Ethiopia, we implemented a breast nurse interventional study with the aim of improving adherence to endocrine therapy among breast cancer patients in peripheral hospitals. To our knowledge, this is the first cluster randomized intervention trial conducted in Ethiopia and Africa of its kind. The intervention was feasible; the study recruited 162 patients from eight clustered hospitals and divided them into two equal arms. During the 12-month period of our breast nurse intervention trial, the intervention group had significantly higher subjective levels of adherence (70%) than the control group (44.8%). Patients in the intervention group were four times more likely to self-report adherence than those in the control group (AOR = 4.05; 95% CI (1.17‑14.03)). The Medication possession ratio (MPR) was high in both the intervention and control groups (90% vs 79.3%, respectively, p = 0.302). However, persistence to therapy was found to be 91.2% in the intervention and 77.8% in the control group in a 12-month period (p = 0.010).

Since the breast nurse intervention in our study proved to be a feasible approach to improving adherence and persistence to endocrine therapy, extending it further and scaling it up to the whole continuum of breast cancer care should be considered. As part of a task-sharing approach, trained breast nurses following a hub-and-spoke model could facilitate not only adherence to treatment but also early detection screening measures at peripheral sites. Hence, the development of the professional capacity to offer comprehensive treatment without abandonment is highly recommended in line with the recent WHO Global Breast Cancer Initiative.

Referat

Das Ziel dieser Dissertation ist es, den Einsatz von *breast nurses* zur Verbesserung der Therapieadhärenz zur Einnahme von Tamoxifen zu untersuchen. Patientinnen mit Mammakarzinom in ländlichen Gebieten Äthiopiens wurden in die Interventionsstudie eingeschlossen. Im Rahmen dieser Dissertation wurden fünf wissenschaftliche Studien in Peer-Review Fachzeitschriften veröffentlicht, die sich mit Intervention, Diagnose und systemischer Therapie des Mammakarzinoms befassten. Der Fokus der ersten beiden Studien lag dabei auf dem klinischen Profil der Patientinnen, dem Stadium bei Diagnose, den Zeitintervallen sowie den Hindernissen. In unserer Studie stellten sich 72 % der Patientinnen in einem fortgeschrittenen Stadium der Erkrankung vor, die Zeit bis zum Therapiebeginn betrug im Median 4 Monate. Faktoren, die die Zeit zur Diagnose negativ beeinflussten, lagen dabei sowohl im Gesundheitssystem als auch auf Seite der Patientinnen. Die langen Zeiten bis zum Beginn systemischer Therapie und der Fakt, dass viele Patientinnen (47 %) angaben, Schwierigkeiten bei der zeitnahen Aufnahme der Therapie zu haben, zeigen den deutlich eingeschränkte Zugang zu onkologischer Therapie. Für endokrine Therapie (Tamoxifen) ergaben sich insbesondere im ländlichen Äthiopien Probleme mit der Therapieadhärenz und -persistenz.

In Anbetracht dieser Herausforderungen, sowie fehlender Nachsorge-Betreuung und Frühdiagnostik in der Peripherie haben wir eine Interventionsstudie mit *breast nurses* durchgeführt, um die Therapieadhärenz in der Primärversorgung zu verbessern. Unseres Wissens nach ist dies die erste Cluster-randomisierte Interventionsstudie, die in Äthiopien bzw. Afrika durchgeführt wurde. Die Intervention war machbar; es wurden 162 Patientinnen aus 8 Krankenhäusern in 2 Clustern rekrutiert. Während des 12-monatigen Zeitraums unserer Interventionsstudie verbesserte sich die subjektive Adhärenz im Vergleich zur Kontrollgruppe erheblich (70 % zu 44,8 %). In der Interventionsgruppe war die Wahrscheinlichkeit, dass die Patientinnen Therapieadhärenz berichten, viermal höher als in der Kontrollgruppe (AOR = 4, 05; 95% CI (1, 17-14, 03)). Die Medikamentenbesitzrate war in der Interventions- und in der Kontrollgruppe hoch (90 % gegenüber 79, 3 %, p = 0,302). Die Therapiepersistenz lag innerhalb von 12 Monaten in der Interventionsgruppe bei 91,2 %, in der Kontrollgruppe 77,8 % (p = 0,010).

Da sich der Einsatz von *breast nurses* in unserer Studie als durchführbar und wirksam zur Verbesserung der Adhärenz zur endokrinen Therapie von Patientinnen mit Mammakarzinom zeigte, empfehlen wir diesen Ansatz auszuweiten. Die Einrichtung eines "*Hub-and-Spoke*"-Modells, das geschultes Personal einbezieht, um auch die Peripherie zu erreichen, halten wir bei begrenzten Ressourcen im Gesundheitssystem für empfehlenswert. Die weitere Ausbildung von Fachkräften in diesem Sinne wird daher dringend empfohlen und steht im Einklang mit der *Global Breast Cancer Initiative* der Weltgesundheitsorganisation, die Maßnahmen und Ziele zur weltweiten Senkung der Mortalität des Mammakarzinoms formuliert hat.

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Abbreviations and Acronyms

ABC-DO: African Breast Cancer-Disparities in Outcomes

BC: Breast Cancer

BHGI: Breast Health Global Initiative

GBCI: Global Breast Cancer Initiative

LMICS: Low and Middle Income Countries

MPR: Medication Position Ratio

NCCP: National Cancer Control Plan

NCCN: National Cancer Center Network

SMAQ: Specific Medication Adherence Questioner

SSA: Sub Sharan Africa

WHO: World Health Organization

1. Introduction and Objectives

Globally, an estimated 19.3 million new cancer cases occurred in 2020, and the numbers are rapidly increasing worldwide, with a particularly large increase in transitioning countries (Sung et al. 2021). Cancer is a major cause of death, responsible for 10.0 million deaths annually worldwide. Breast cancer (BC) is now the cancer entity with the highest incidence and the fifth leading cause of death globally, with an estimated 2.3 million new cases (11.7%) and 685,000 (6.9%) deaths in 2020 (Sung et al. 2021). In Sub Sharan Africa (SSA), BC is the most common cancer entity, and its incidence varies across countries, with a five-year overall relative survival of 59% (Joko-Fru et al. 2020b). In Ethiopia, it is estimated that 16,133 (20.9%) cases and 9,061 (17.5%) deaths occurred in 2020 (Ferlay et al. 2020), and BC ranked as the cancer of highest incidence in the country. According to hospital records from the capital city, one- and two-year metastasis-free survival were 90.4% and 73.6%, respectively (Kantelhardt et al. 2014a), whereas the two-year overall survival was only 53% in rural Ethiopia. The majority of patients had an advanced stage of the disease (stages III and IV) and did not receive systemic therapy (Eber-Schulz et al. 2018).

The primary objective of the recent Global Breast Cancer Initiative (GBCI) by World Health Organization's (WHO) is to reduce global mortality from BC by increasing access to early diagnosis and prompt comprehensive cancer management (Anderson et al. 2021). Strategies to diagnose BC in the early stages when treatment is less complex and cost intensive are necessary, especially in resource-constrained settings. Patient outcomes could be improved, particularly in settings where BC is commonly diagnosed in advanced stages (Ginsburg et al. 2020). A systematic review in 2016 revealed that the proportion of advanced disease presentation was on average 74.7% (ranging from 30.3% to 100%) in the African region (Jedy-Agba et al. 2016). Data from population-based registries in SSA show that 64.9% of BC patients presented with late-stage disease, and 18.4% had metastasis at diagnosis (Joko-Fru et al. 2020a). Studies from Zimbabwe and Rwanda also revealed that 72% to 74% of BC patients presented at a late stage (Muchuweti et al. 2017, Pace et al. 2015). Patients who were diagnosed in an early stage (stage I or II) had a higher survival probability than those with late-stage disease in the SSA region (Joko-Fru et al. 2020a).

A multi-center study in Ethiopia also documented that 72.5% of patients were diagnosed at a late stage (Tesfaw et al. 2021) in the peripheral regions of the country; many of them had notable diagnostic delays. The time intervals between symptom recognition by the woman and first presentation to the health care system vary across countries and are unacceptably high in SSA (Espina et al. 2017). Favorably, the National Cancer Center Network (NCCN) Harmonized Guidelines for SSA have now been endorsed in six SSA countries, including Ethiopia, as national standards of care by the ministries of health or national cancer centers in the region (Koh et al. 2020). The guidelines give clear, resource-stratified directions on the diagnosis and management of BC and other cancer entities.

In 2010, the Breast Health Global Initiative (BHGI) outlined the key steps to developing BC treatment programs tailored to existing resources (Anderson et al. 2011). Nevertheless, one third of the BC-related deaths in SSA can be attributed to a lack of attention to early diagnosis and adequate treatment (McCormack et al. 2020). An assessment of the Global Landscape of Treatment Standards for BC found that the majority are not appropriate for the national or regional context (Trapani et al. 2021). The development of BC control programs is facing various challenges, mainly in low- and middle-income countries (LMICs) (Pace and Shulman 2016). WHO's GBCI attempts to guide comprehensive BC management in resource-restricted settings and indicates that women with BC require timely access to cancer treatment (Anderson et al. 2021).

Systemic treatment is an essential component of comprehensive BC management. Hormone therapy using Tamoxifen is one of the most affordable and the standard BC therapy option (Anderson et al. 2008b) (Mohamed and Elamin 2020), depending on hormone receptor status. The therapy is underutilized in most African settings, including Ethiopia (Kantelhardt et al. 2015). According to studies conducted in SSA, fewer than 20% of health facilities had aromatase inhibitors available, whereas the majority had tamoxifen (Vanderpuye et al. 2016). However, there is still a discrepancy between the availability of such therapies and the number of facilities that provide them. In addition to limited access and underutilization in rural settings, adherence to endocrine therapy is a significant problem in SSA that affects treatment outcomes. Evidence from Nigeria and South Africa showed 25% and 36% non-adherence to tamoxifen therapy among patients in one and three years period of follow-up (Oguntola et al. 2011, Du Plessis and Apffelstaedt 2015). In Ethiopia, the majority of BC patients have hormone-receptor-positive tumors (Kantelhardt et al. 2014b, Reibold et al. 2021) and would benefit from tamoxifen therapy. The Ethiopian National Cancer Control Plan (NCCP) issued in 2016 aimed to provide diagnostic procedures and treatment for another 30% of new cancer patients by 2020 (NCCP 2016). To this end, the Ethiopian Ministry of Health planned to train health care professionals on different levels of the health system in cancer diagnostics and treatment. However, a retrospective study in southern and southwestern Ethiopia (Tesfaw et al. 2021) found that only 13% of BC patients received tamoxifen therapy, and in some communities, none of the patients received hormonal therapy. A study from northern Ethiopia (Deressa et al. 2019) revealed that 22% of patients were given tamoxifen therapy, and 27% did not receive any hormonal therapy. The continuous survivorship care of cancer patients is strongly challenged, mainly in peripheral settings: our study found that adherence to tamoxifen therapy was only 52% after one year, and although the service was free of charge, almost 34% of patients discontinued therapy (Reibold et al. 2021). Studies have shown that non-adherence to endocrine therapy is a multifactorial problem associated with poor survival that requires target-oriented and sustainable interventions (Du Plessis and Apffelstaedt 2015, Sawesi et al. 2014). Recently, the GBCI has focused on training health care professionals to support compliance to comprehensive treatment of BC patients (Anderson et al. 2021). In the case of endocrine therapy for (BC) patients, few studies have recommended that the appointment of trained nurses would improve patients adherence to treatment (Doggrell 2011, Kelly and Agius 2006, Miaskowski et al. 2008).

Thus, we planned and implemented a breast nurse intervention in peripheral settings as an innovative and feasible approach to improving adherence to tamoxifen therapy. The study was conducted in eight peripheral hospitals, using a cluster randomized trial design. In addition to this large, interventional study, this dissertation includes data on patient's clinical profiles, including disease awareness, presentations to hospital, stage at diagnosis, delays and barriers to early diagnosis, treatment intervals, and level of adherence and persistence to tamoxifen therapy based on study findings. Our findings are discussed in the literature context to address the objectives covered in the dissertation.

The objectives of this dissertation are

- To assess the effect of a breast nurse intervention on adherence to tamoxifen therapy in patients with BC in the peripheral setting of Ethiopia
- To determine the socio-demographic and clinical profiles of BC patients
- To investigate the stage of disease at presentation and diagnostic delays among BC patients
- To explore barriers to early diagnosis among BC patients
- To assesses patient's awareness of the disease and therapy during follow-ups
- To describe the level of systemic treatment and barriers to its timely initiation among patients

This dissertation is based on five publications. Most importantly, it will discuss adherence and persistence to endocrine therapy and summarize the effect of a breast nurse intervention on adherence to endocrine therapy as part of a task-sharing model in peripheral settings in Ethiopia.

2. Synopsis of the Publications

This dissertation is based on the following five articles published in international peer reviewed journals, and the contribution to each of the studies is stated.

Publication 1: <u>**Sefonias Getachew**</u>, Adamu Addissie, Edom Siefe, Tariku Wakuma, Susanne Unverzagt, Ahmedin Jemal, Lesley Taylor, Andreas Wienke, Eva. J. Kantelhardt. Breast Nurse Intervention to Improve Adherence of Endocrine Therapy among Breast Cancer Patients in South Ethiopia. *The Oncologist* **27, no. 8 (2022): e650–e660.**

Contribution as an author:

I conceptualized and designed the study, developed the protocol and data collection forms, and organized the study procedures. I was responsible for data management. I wrote the original draft of the manuscript and actively managed all communication pertaining the publication.

Publication 2: <u>**Sefonias Getachew**</u>, Aragaw Tesfaw, Mirgissa Kaba, Andreas Wienke, Lesley Taylor, Eva J. Kantelhardt, and Adamu Addissie. Perceived Barriers to Early Diagnosis of Breast Cancer in South and Southwestern Ethiopia: a qualitative study. *BMC Women's Health* **20, no. 1 (2020): 1-8.**

Contribution as an author:

As the principal investigator, I was responsible for the conceptualization of ideas, formulation of the research questions, study design, and conducting the fieldwork. I supervised and was involved in the interviews during the study. I was also responsible for translating, transcribing, coding, and analyzing the data and later for compiling the results and developing, drafting, and publishing the manuscript.

Publication 3: Aragaw Tesfaw, **Sefonias Getachew**, Adamu Addissie, Ahmedin Jemal, Andreas Wienke, Lesley Taylor, and Eva Johanna Kantelhardt. Late-Stage Diagnosis and Associated Factors among Breast Cancer Patients in South and Southwest Ethiopia: A Multicenter Study. *Clinical Breast Cancer* **21, no. 1 (2021): e112-e119.**

Contribution as an author:

I was the principle investigator and supervisor responsible for the conceptualization of the idea, formulation of the research questions, and design of the study. I actively supervised the data collection, data analysis, development, and publication of the manuscript, together with other investigators.

Publication 4: Bethel Teshome, Josephin Trabitzsch, Tsion Afework, Adamu Addissie, Mirgissa Kaba, Eva Johanna Kantelhardt, and **Sefonias Getachew**. Perceived Barriers to Timely Treatment Initiation and Social Support Status among Women with Breast Cancer in Ethiopia. *PloS One* **16, no. 9 (2021): e0257163.**

Contribution as an author:

As supervisor of the first author, I took part in conceptualizing the idea, design, and methodology of the study. I advised and supervised the research work. I was responsible for validating the data analysis. I reviewed and improved the manuscript and approved it for publication.

Publication 5: Christian Felix Reibold, Wakuma Tariku, Pia Eber-Schulz, **Sefonias Getachew**, Adamu Addissie, Susanne Unverzagt, Andreas Wienke et al. Adherence to Newly Implemented Tamoxifen Therapy for Breast Cancer Patients in Rural Western Ethiopia. *Breast Care* **(2021): 1-7.**

Contribution as an author:

I was part of the study team, reviewed the protocol, and gave continuous feedback. I was involved in the methodological development of the study. I was actively involved in organizing the project and in the ethical approval process. I contributed to the interpretation of the study and critically revised the manuscript, including approval for publication.

3. Discussion
3.1. Stage and delay in the diagnosis of breast cancer

Stage at diagnosis

In low- and middle-income countries (LMICs), women with BC usually present with and are eventually diagnosed with late-stage disease (Jemal et al. 2011). The BHGI pioneered the first set of resource-stratified, evidence-based oncology clinical practice guidelines in 2005 to address the detection, diagnosis, and treatment of BC in LMICs (Anderson et al. 2006). During the 2018 Global Breast Cancer Summit, it was recommended that early diagnosis be strengthened through a triple-test evaluation before considering screening (Duggan et al. 2020). However, in 2020, in most of Sub-Saharan Africa (SSA), 64.9% of BC patients were diagnosed at a late stage (Stages III and IV), and 18.4% were metastatic at diagnosis. Our multi-center study in rural Ethiopia found that 72.5% of all patients were diagnosed with late-stage disease (Tesfaw et al. 2021) comparable to our study from Aira hospital in South West Ethiopia, which reported that 64% were diagnosed at a late stage (Reibold et al. 2021). A study conducted in the capital city Addis Ababa, where the National Cancer Center is located, revealed that 58.5% of patients were diagnosed at a late stage (Teshome et al. 2021). The lower proportion of late-stage diagnoses at the cancer center might be related to greater patient awareness and access to diagnostic services in the city than in rural areas.

We found that the proportion of late-stage diagnoses varied across patient pathways to care in our multicenter study. Patients with a referral history from other health facilities were more likely to present with an advanced disease stage (81.5%) than those without any referral history (67.9%). Similarly, the variation between patients with and without referral history existed across all delay intervals until diagnosis. Studies from cancer centers have found that navigation chains are divergent and usually involve three or four care nodes before reaching a referral hospital (Dye et al. 2010). Studies from Zimbabwe and Rwanda found that 72% to 74% of BC patients had late-stage diagnoses (Muchuweti et al. 2017, Pace et al. 2015). However, the evidence indicated that patients diagnosed at an early stage have higher survival probability than those diagnosed at a late stage (Joko-Fru et al. 2020a, Bleicher et al. 2016). Various factors affect the time to diagnosis among patients. As discussed in the next section, it has been suggested that settings with a high proportion of advanced-stage disease require strong efforts to promote early detection to improve therapy outcomes (Ginsburg et al. 2020).

Delay in diagnosis

Early BC diagnosis is difficult due to the time interval between the woman's recognition of symptoms and eventual presentation at a center with an adequate diagnostic service. In SSA, late presentation is unacceptably common compared to other regions (Espina et al. 2017). The NCCN harmonized guidelines for SSA recommend that patients be referred to centers that provide the highest level of care for a given clinical presentation (NCCN 2019). Evidence indicates that the

clinical stage and survival of BC patients is negatively affected if delays longer than three months occur between symptom discovery and initiation of treatment (Richards et al. 1999).

A review of 21 studies conducted in Africa found that the study-specific average times between symptom recognition and presentation to a health care provider ranged from less than one to four months in North Africa, whereas in SSA, it ranged from less than three to greater than six months (Espina et al. 2017). In most settings in SSA, a symptom duration of 8–12 months was identified, which represents a considerable delay between symptom onset and diagnosis. These long intervals have a profound negative effect on the probability of successful therapy and survival (Jedy-Agba et al. 2016). Our study in southern and southwestern Ethiopia found that the median patient delay was three months, and 76% of patients had a longer patient delay, whereas 26.9% had shorter patient delay. The median health system delay was almost one month, and the median total diagnostic delay was found to be almost six months (Tesfaw and Getachew et al. 2021), showing that the patient and overall diagnostic delay were unacceptably high. A review of these 21 studies identified that the main reported reasons for delays in BC patients' diagnostic work-up were related patient and health-system factors (Espina et al. 2017). In most African settings, pathology services are scarce. A study from Mali revealed that a low quality of health care services and a lack of social support were the factors affecting diagnostic intervals (Grosse Frie et al. 2018). We found that the risk of an advanced-stage diagnosis was increased in patients with longer intervals from symptom recognition to the final diagnosis (Tesfaw and Getachew et al. 2021). An organized effort is needed towards early diagnosis of the disease in the region and implementation of the approved harmonized guidelines of the NCCN for SSA. According to the guidelines, it is crucial to reduce wait times for treatment by expediting investigations and referrals (NCCN 2019).

3.2. Barriers to early diagnosis

According to our review of BC care in Africa, women with BC had low levels of early health-seeking practices (Kantelhardt et al. 2015). Lack of awareness of early detection; poor perception of BC; and socio-cultural factors such as belief, traditions, and fear were factors in poor health-seeking behavior among African women with BC (Akuoko et al. 2017). Early diagnosis of BC is challenging in SSA. Patient-related factors, health care providers, and the healthcare capacity to provide care are the most cited factors requiring attention to improve therapy outcomes and survival (Unger-Saldaña 2014, Kohler et al. 2017, Scheel et al. 2018). Our study in peripheral settings documented patient- and health-system-related barriers to early diagnosis of BC. Barriers on the patient side were lack of knowledge and awareness of BC, belief in traditional medicine and religious practices for treatment, and lack of social and financial support to seek care at a medical facility, whereas health-system barriers include misdiagnosis of BC, a long distance to referral facilities, the high cost of diagnostic services, long waiting times for diagnostic tests, and lack of screening and diagnostic tests in local facilities (Getachew et al. 2020). Likewise, another study from Brazil found that health care provider factors that contributed to delayed diagnosis included incomplete patient examination, inappropriate use of diagnostic tests, misinterpretation of test results, and misdiagnosis (Gonçalves et al. 2014).

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A systemic review conducted in developing and developed countries reported less comprehensive health insurance coverage, older/younger age, and false-negative diagnostic test results as the most common system-related factors, whereas non-attribution of symptoms to cancer, fear of the disease and treatment, and a low educational level were the most frequent causes of patient delays (Freitas and Weller 2015). Interestingly, a qualitative study from Kenya reported that the key barriers to early detection and treatment also included cost, inadequate knowledge, distance to health facilities, communication with health providers, medicine stock-outs, long waiting periods, limited or no counseling at diagnosis, patient vulnerability, and limited access to rehabilitation options (Gakunga et al. 2019). The same has been reported from Mali, where beliefs in traditional medicine, religious beliefs, economic hardship, poor provider knowledge, and misdiagnosis were major reasons for a delay in diagnosis (Kohler et al. 2017). From Côte d'Ivoire, we noticed that a lack of financial means, cultural habits with first intent traditional treatment, misdiagnosis, and a lack of therapeutic care were factors in late-stage diagnosis of the disease but had no effect on the delay (Toure et al. 2013). However, our study in a peripheral setting reported that patients waiting to seek care, delays within the health care system, patients who had experienced a painless breast lump at presentation, rural residence, female sex, and a history of comorbidity were associated with late-stage diagnosis of the disease (Tesfaw and Getachew et al. 2021).

The multinational African Breast Cancer-Disparities in Outcomes (ABC-DO) cohort study in SSA (Foerster et al. 2021) also found that on average, women visited their health care providers one to four times, but the intervals between visits were long. In most settings, the long journey to diagnosis was not the result of late initial presentation but of prolonged delays after initial presentation. Thus, in SSA, including Ethiopia, feasible and appropriate interventions are required to shorten the interval between presentation and BC diagnosis. In line with this work, the recent WHO GBCI initiative (Anderson et al. 2021) has released three pillars of action, and improving the availability of rapid diagnosis for BC is the second pillar, as part of an effort towards early detection and diagnosis of BC globally. Thus, as part of the down-staging effort for better outcomes, the SSA region, including Ethiopia, could benefit greatly from adherence to guidelines and incorporation of the recommendations of the ABC-DO study (Foerster et al. 2021) on promoting BC awareness and implementing accelerated referral pathways for women with suspicious symptoms.

3.3. Delay and barriers to treatment initiation

Since many patients present with advanced stages of BC in low-resource settings, treatment is highly limited and challenging (Francies et al. 2020). Most African oncology centers do not have radiation facilities, so mastectomy is often the only option, and primary systemic therapy is available for patients with locally advanced disease (Kantelhardt et al. 2015). The major difference in survival rates reported between LMIC and HIC are attributed to extended intervals until treatment initiation on top of advanced-stage presentation (Joko-Fru et al. 2020a). The ABC-DO

study found that the low BC survival rates were mainly due to advanced-stage presentation, young-age, co-morbidity, poorly differentiated tumors, among those without treatment, along with a variation in survival among those receiving treatment (McCormack et al. 2020). In Africa, however, treatment delays are poorly studied or rarely reported (Espina et al. 2017). Few studies from Africa have studied the continuum of patient pathways to care from symptom recognition to treatment. A study from Mali found that the mean time to treatment after diagnosis was 2.5 months, and the median was 1.3 months (Grosse Frie et al. 2018b). Our study in the largest cancer center in Ethiopia found a median time of 1.1 months from diagnosis to initiation of systemic treatment. Only about half (53.1%) of the patients initiated timely systemic therapy per the recommended interval (less than 90 days) (Teshome et al. 2021). A study from Aira hospital on the rural side showed that 58% of patients experienced long delays to tamoxifen initiation (median 5.7 months; IQR 0.1–10.8) after surgery (Reibold et al. 2021).

We found earlier initiation of adjuvant or neo-adjuvant systemic therapy in patients diagnosed at advanced stages and in older age groups (Teshome et al. 2021). This might be because the majority of patients presenting at a late stage worry about their health condition, and more patients found at an early stage and within the younger group may deny their cancer diagnosis and refuse surgery or may seek alternative treatment. Remarkably, our study reported that nearly one third (34%) of the patients tried alternative therapy between diagnosis and initiation of systemic therapy (Teshome et al. 2021), probably influencing the timely initiation of therapy. The study revealed that not being able to pay for the service (66%), lack of transport (54%), long waiting times (48%), and fear of treatment side effects (38%) were perceived barriers that delayed timely initiation of systemic therapy (Teshome et al. 2021). A qualitative study in peripheral settings also revealed that the absence of diagnostic tests and treatment options for BC patients contributed greatly to diagnostic and treatment delays (Getachew et al. 2020). A study from Mali reported that high costs and a lack of specialized services (Grosse Frie et al. 2018a) were the main factors affecting the pre-treatment interval after diagnosis. The BHGI recommended a three-step phased-implementation approach for establishing cancer treatment programs and decentralizing the diagnosis and treatment network to improve access (Duggan et al. 2020).

However, BC management is suboptimal in most African settings (Vanderpuye et al. 2016). Based on ABC-DO's prospective cohort study of non-metastatic BC patients in some SSA countries, only 66% of patients requiring chemotherapy initiated neoadjuvant chemotherapy or surgery within three months of their baseline diagnosis, and 35% completed the treatment adequately. Among patients in whom endocrine therapy was indicated, 67% initiated the therapy, and therapy lasted at least three years in 40% of the women (Foerster et al. 2022). The study noted that, for all types of therapies, there were substantial differences in treatment between country-specific groups. In our study, in peripheral settings of Ethiopia, only 44.1% of BC patients received chemotherapy, and 13.3% received hormonal therapy (Tesfaw et al. 2020), and even these may not be accessible at most health facilities. The study reported that the majority had favorable access to surgery,

though most had a mastectomy procedure, given that radiotherapy access is very limited in the country, and only 1% of patients in our study reported having received radiotherapy treatment (Tesfaw et al. 2021). A study in Mali even showed that at least 16% of all patients did not start any treatment, and this proportion may be even higher if those lost to follow-up were also not treated (Grosse Frie et al. 2018b).

Thus, to overcome the challenges mainly due to delays in timely initiation of systemic therapy in Ethiopia and other SSA countries at large, it would be beneficial to implement the current NCCN harmonized guidelines for SSA countries (NCCN 2019). It is advisable to also work collaboratively with the new global breast cancer initiative (GBCI), which aims for comprehensive BC management and timely access to cancer treatment for women with BC (Anderson et al. 2021).

3.4. Breast nurse intervention to improve adherence to endocrine therapy

Tamoxifen therapy is an affordable and effective endocrine therapy option with very few side-effects in BC patients (Anderson et al. 2008, Mohamed and Elamin 2020). Many randomized trials of adjuvant tamoxifen among women with early BC were conducted, and the findings showed that the absolute improvement in recurrence was greater during the first 5 years, whereas the improvement in survival grew steadily throughout the first 10 years. In the trials of about 5 years of adjuvant tamoxifen, the absolute improvements in 10-year survival were 10.9% (SD 2·5) for node-positive and 5.6% (SD 1·3) for node-negative (EBCTCG 1998) cancers. Patient-level meta-analysis of randomized trials also reported that among estrogen receptor (ER)-positive disease, five years of tamoxifen treatment substantially reduced recurrence rates throughout the first 10 years. The mortality was also reduced by about a third throughout the first 15 years (EBCTCG 2011) regardless of progesterone receptor status, age, nodal status, or use of chemotherapy.

However, tamoxifen is one of the underutilized therapy options in African settings (Kantelhardt et al. 2015). In Ethiopia, despite evidence that the majority of BC patients have hormone-receptor-positive disease (Kantelhardt et al. 2014b) utilization of therapy is still low (Tesfaw et al. 2021), (Deressa et al. 2019). This might be related to the availability of a pathology service offering hormone receptor status testing. This state-of-the-art service is often highly limited to one center or at all absent in most SSA countries, including Ethiopia (Ziegenhorn et al. 2020, Vanderpuye et al. 2016).

Adherence to adjuvant therapy was found to be a challenge for patients (Chlebowski and Geller 2006). Studies from Nigeria found that 25% of patients were non-adherent to tamoxifen therapy during one-year follow-up (Oguntola et al. 2011). Our study in southwestern Ethiopia found that only 34% of patients were adherent, with a median of 16 months of follow-up, and the adherence to therapy at 12 months was found to be 52% (Reibold et al. 2021). Interestingly, 34% of patients who initiated therapy discontinued it, and the reasons were terminal illness, difficult circumstances, lack of money, and side effects of the medication (Reibold et al. 2021). In addition to this, poor patient navigation and awareness of the disease were major reasons for non-adherence.

In line with this study, others also reported on patient characteristics, illness and therapy, health care, and social and economic factors associated with non-adherence to therapy (Sedjo and Devine 2011, Du Plessis and Apffelstaedt 2015). Moreover, it was discovered that non-adherence to endocrine therapy is a multifactorial problem highly associated with poor survival (Du Plessis and Apffelstaedt 2015, Sawesi et al. 2014) and was the core challenge to implementing innovative and feasible interventions.

Thus, our intervention used a trained breast nurse approach to improve adherence to therapy in peripheral settings of Ethiopia (Getachew et al. 2022). This interventional study was based on our pervious findings in southwestern Ethiopia (Reibold et al. 2021) and an additional formative study conducted to understand the context and challenges relating to implementation of a trained breast nurse to improve adherence. This is in line with other studies conducted elsewhere (Miaskowski et al. 2008, Doggrell 2011). The training course for the nurses emphasized the basics of BC, the patient's emphatic communications and counselling, benefits and side effects of therapy, and how to monitor the drug refill during follow-up given that a limited trained capacity for cancer care exists (Woldeamanuel et al. 2013). The proposed protocol was presented at the six breast health global initiatives meeting (Getachew et al. 2018) in Seattle, USA and was closely aligned with the recommendation to decentralize cancer diagnosis and treatment in order to improve access while maintaining quality service (Duggan et al. 2020).

Our breast nurse intervention revealed improvement in the subjective level of adherence in the intervention group (70%) compared to the control group (44.8%) (p = 0.036) in a 12-month period (Getachew et al. 2022). Interestingly, the level of adherence based on the medication position ratio (MPR) during the 12-months period was high in both the intervention (90%) and the control group (79.3%), with only small differences observed (p = 0.302). Our findings are consistent with previous studies, which revealed that nurse-lead interventions improved the level of adherence to prescribed cancer medication (Campbell 2014, Verloo et al. 2017). The intervention group also showed higher levels of adherence to therapy (91.2%) than the control group (77.8%) over a one-year period (p = 0.010) (Getachew et al. 2022). In our study, the level of persistence improved by more than in a previous study in southwestern Ethiopia (Reibold et al. 2021), and interestingly, the rate of discontinuation of therapy was low, compared to other reports so far in the region.

There is evidence that having a trained breast nurse helps patients adhere to their treatment and persist during follow-up (Getachew et al. 2022). Moreover, patients had the opportunity to contact the nurses freely and receive support as needed, the perception of which would also be an interesting topic of further studies. Another interesting area of future study is the possible use of MHealth modalities for patient care follow-up. Through our holistic intervention, patients benefited from close communication with nurses, support on knowledge gaps, and advice at every follow-up visit. We believe that the study found a promising intervention, which might be implemented in wider health systems and improve the patient level of adherence, persistence to therapy, and overall retention in follow-up care. In the absence of strong follow-up support,

patients are highly vulnerable to early discontinuation of therapy, which threatens treatment efficacy due to increased recurrence and mortality, as well as high medical costs (Walker et al. 2016, Wen et al. 2017, Galukande et al. 2015). Studies have found that in most African settings, including Ethiopia, access to trained professionals in the cancer field is highly limited (Adesina et al. 2013, Woldeamanuel et al. 2013, Vanderpuye et al. 2016). The recent GBCI from the WHO have a strong initiative to train health professionals, especially those working in primary health care settings (Anderson et al. 2021).

As our study shows, a breast nurse intervention is an effective strategy for improving patient adherence to endocrine therapy. Hence, to the entire health system, this is a very promising opportunity to see a trained nurse in a supporting role as part of a task-sharing approach (Stulac et al. 2015) to adherence and long-term cancer care support. As we have strong centralized, comprehensive cancer centers, we recommend a hub-and-spoke model (Elrod and Fortenberry 2017) to reach out to peripheral sites staffed by these trained nurses, given that there are limited professionals in cancer diagnosis and care (Woldeamanuel et al. 2013) in most African settings, including Ethiopia.

3.5. Strengths and limitations

The main strength of the intervention trial was the implementation of an innovative and feasible intervention in peripheral settings using cluster randomized trials. Nurses were trained at the cancer center and performed tamoxifen follow-ups. Multidisciplinary professionals delivered the training according to the intervention package content. A nurse-led intervention was used as part of a task-sharing role with cancer patients in the study, which was unique and innovative in its approach. Our study played a substantial role in expanding tamoxifen support to the respective hospitals and had an opportunity to follow the tamoxifen stock balance in each facility. In advance, we performed a pilot study to identify patients' and professionals' concerns, most of which were included in the design of the subsequent intervention. Additionally, the study matched the level of hospital setups based on the findings of the pilot study. Our initial study on newly implemented tamoxifen therapy in west Wellega examined the feasibility of tamoxifen treatment for BC patients in peripheral Ethiopia and measured the level of adherence and persistence to endocrine therapy as a first experience in the country.

Our multi-center, retrospective study about late-stage diagnosis and associated factors in southern and southwestern Ethiopia was based on data from the last five years and identified room for improvement within the health care system to decrease delays in diagnosis, particularly in peripheral settings. This study showed that with more delays in diagnosis from the patients' side, a late-stage diagnosis is inevitable. Moreover, it quantified the miss-diagnosis rate of BC among patients at their presentations and the extent of patient referrals within the health system for diagnosis or treatment as a baseline finding.

Our study on early diagnosis and timely initiation was unique in its exploration of barriers to early diagnosis, which indicated that almost half of patients did not initiate systemic therapy on time. The qualitative study captured barriers to early diagnosis from both the patient and the professional side and was the first study to examine this issue in depth. Most importantly, the barrier to timely initiation of therapy study also identified the possible barriers likely had relation on timely initiation of systemic therapy which could be a best case scenario to further address access challenges as a serious concern in most low-income countries.

Although our studies had many strengths, they also had certain limitations, which were stated in the respective studies. Our breast nurse interventional trial had low patient participation during adherence measurement at one-year follow-up and a small sample size despite two years' follow-up. However, a substantial comparison was still made between the two groups. The second limitation was the inclusion of patients with a prior history of endocrine therapy who were not in treatment at the time of the study. This might allow patients to be aware of therapy and thereby increase their adherence to it. However, we conducted a sensitivity analysis and found that the breast nurse intervention still had an effect even when patients who had previously taken the therapy were excluded. Thirdly, patients had been experiencing longer wait times for diagnosis and surgery due to low recruitment and limited pathological capacity in most hospitals. This had a direct effect on patient recruitment and follow-up to obtain the required sample in the cohort. The newly implemented tamoxifen therapy study also faced a limited sample size due to deaths, referrals, or losses to follow-up. For those patients who were not able to make it to the hospital at the time of the study, we attempted to interview them at home. There might, however, have been a selection bias because the poorer group, more likely to live in rural areas, might not have equal access to hospitals as compared to the wealthier group, which could access hospitals and initiate therapy. Our multi-center study on late-stage diagnosis had limited access to sociodemographic data and some clinical variables, such as educational status, behavioral factors, tumor grading, and receptor status, due to the use of secondary data. This affected our ability to better characterize the late stage and perform the factor assessment needed to control confounders. The disorganized and incomplete documentation of the date of presentation, confirmed diagnosis, and surgical treatment was a challenge we faced in some hospitals. However, we had the opportunity to collect the data by triangulating from the patients chart, follow-up, and operating room chart in some difficult cases.

Our studies on barriers to early diagnosis and timely initiation of BC therapy had certain limitations. The use of in-depth interviews alone might be not sufficient to explore barriers, and it would also be important to validate the suggested barriers by designing structured interview-based questions to improve generalizability. With respect to the timely initiation of systemic therapy, we excluded almost one third of all patients from the analysis due to missing data, particularly on the time to initiation of systemic treatment. This study had a limited ability to identify the reasons for delays in treatment due to difficulty differentiating between patient- and health-system-related

delays such as wait times. Based on the data, we were limited in generalizability and instead focused on the perceived barriers.

3.6. Conclusion

Breast cancer management and survivorship care is a challenge in most SSA settings, including Ethiopia. Our trained breast nurse intervention is an innovative and feasible approach to improving the self-reported level of adherence and persistence to tamoxifen therapy during follow-up. Patients had a remarkable surge in medication refills among the breast nurse intervention group, although the difference lacked significance compared to the usual care group. Our breast nurse intervention showed promising findings by resolving certain challenges relating to patient navigation of the health care system. The positive patient response in utilizing comprehensive interventions to improve system-wide issues in health institutions could further encourage patient engagement. Thus, our breast nurse intervention underpins the need for a task-sharing role to engage such trained breast nurses in the health system with a hub-and-spoke model to reach out the peripheral sites linked to a centralized comprehensive cancer treatments at national or regional level. . This could have a substantial impact by improving patient adherence to therapy and long-term survivorship care. This would be an area to strengthen in the health care system via a coordinated and resilient care follow-up mechanism for patient support and better outcomes, mainly in peripheral settings.

Delays in diagnosis and treatment are the main obstacles to better treatment outcomes in late-stage diseases. In our studies, more than two thirds of patients presented at an advanced stage, and the patient- and health-system-related delays were long. Importantly, those living in rural settings, having comorbidities, and experiencing breast lumps as the first symptom were more likely to be diagnosed at a late stage, probably reflecting the lack of knowledge about painless lumps. Moreover, our in-depth study determined that lack of knowledge and awareness, symptom misinterpretation, preference for traditional and spiritual means of treatment, lack of social and family support, lack of money for medical care costs and transportation, misdiagnosis of cases, long distances to referral centers, and long wait times for diagnostic tests were the major barriers to early diagnosis of BC in our study from the perspectives of patients and healthcare providers.

BC down-staging at diagnosis is a crucial area of future focus with a strong emphasis on early detection and screening. Implementation studies of clinical breast examination could be prioritized essentially with the MHealth component. Creating opportunities to educate healthcare providers, decreasing misdiagnosis, and improving the referral system require attention. It would be beneficial to align these efforts with the recent WHO GBCI initiative for BC in developing settings to create better implementation strategies.

In SSA settings, including Ethiopia, there is a huge gap in access and affordability to BC therapy. In most settings, there is access to surgery, but the majority of patients are treated with mastectomy, given that radiotherapies are limited. We found that less than one fourth of patients had access to endocrine therapy, and less than half of patients received chemotherapy. Another concern that BC

patients face is timely access to systemic therapy. Our study revealed that many patients did not initiate systemic therapy on time, and young patients and those with early-stage tumors were associated with delayed systemic therapy – further investigation is needed on this. Affordability and access to systemic cancer treatment were perceived as major barriers to timely treatment initiation despite not being associated with actual delays.

Given that systemic cancer therapy, particularly chemotherapy, is expensive, there should be more effort on the part of the government to strengthen subsidization. BC patients need to be well integrated into the community health insurance, since these middle-aged women additionally care for the rest of their families. Easy therapy interventions can be beneficial and might improve early care, systemic treatment and follow-up practices. It would be beneficial to also work with the WHO suggestion to join forces to reduce the financial burden on patients. Further attention needs to be given to BC within the universal health coverage agenda.

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5. Hypotheses

1. More than two thirds (72.5%) of BC patients were diagnosed with late-stage disease, and the majority (73%) were from rural communities. Of the patients who had a referral history, 81.5% were diagnosed with late-stage disease.

2. The median patient delay was four months, and 76% had a longer patient delay. The median health system delay was almost one month. At the initial visit to the hospital, BC was not suspected in 28.4% of patients, and no diagnosis was made at the initial visit in 12.4%. The majority (90%) presented with breast lumps or masses.

3. Early diagnosis of BC is affected by a multitude of barriers in peripheral settings of Ethiopia. Patient and health-system barriers are key to large delays in diagnosis at presentation. Patients with comorbidities, those living in rural areas, and those who had longer patient- or health-system-related delays were less likely to be diagnosed at an early stage.

4. Different beliefs contributed to delays in seeking medical care for BC. Losing a breast (mastectomy) was described as taboo. Most women hid their problem and sought medical care as a final option only after trying all traditional or cultural treatment approaches.

5. Surgery was the main type of treatment (98.3%) in peripheral settings, only 44.1% received chemotherapy, and a lower proportion (13.3%) received hormonal therapy and radiotherapy (1.2%). Overall, 35.7% of patients had a history of comorbidities.

6. Nearly half of BC patients (53%) received timely systemic treatment within 90 days of their pathological diagnosis. The median treatment initiation interval was nearly three months, and a large proportion (58%) of patients experienced a longer delay to tamoxifen initiation (median 5.7 months after surgery).

7. Age (older women) and diagnosis at a late stage were positively associated with timely initiation of systemic therapy. Not being able to pay for the service (66%), lack of transport (54%), long wait times (48%), and fear of treatment side effects (38%) were perceived as barriers to timely initiation of systemic therapy.

8. The persistent to endocrine therapy was found to be 52% during a one-year interval. Almost one third (34%) of BC patients discontinued tamoxifen therapy during one-year follow-up. Patient education and navigation was identified as a major challenge to follow-up care.

9. A breast nurse intervention had a significant effect on the self-reported level of adherence in one-year follow-up as compared to the usual care (70% vs 44.8%). The discontinuation rate of tamoxifen therapy was 6.9% (95% CI: 2.9–14.5) in the intervention group and 20% (95%CI: 12.4–30.5) in the usual care group.

10. The persistence to tamoxifen therapy was significantly improved among the breast nurse intervention group compared to the usual care group (91.2% vs 77.8%), and key lesson to use nurses in a task-sharing role in BC management and care follow up in the wider health system was learned.

6. Publications

Paper 1: Breast Nurse Intervention to Improve Adherence of Endocrine Therapy among Breast Cancer Patients in South Ethiopia

Paper 2: Perceived Barriers to Early Diagnosis of Breast Cancer in South and Southwestern Ethiopia: a qualitative study

Paper 3: Late-Stage Diagnosis and Associated Factors among Breast Cancer Patients in South and Southwest Ethiopia: A Multicenter Study

Paper 4: Perceived barriers to timely treatment initiation and Social Support Status among Women with Breast Cancer in Ethiopia

Paper 5: Adherence to Newly Implemented Tamoxifen Therapy for Breast Cancer Patients in Rural Western Ethiopia

OXFORD

Breast Nurse Intervention to Improve Adherence to Endocrine Therapy Among Breast Cancer Patients in South Ethiopia

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Abstract

Introduction: Many women in rural Ethiopia do not receive adjuvant therapy following breast cancer surgery despite the majority being diagnosed with estrogen-receptor-positive breast cancer and tamoxifen being available in the country. We aimed to compare a breast nurse intervention to improve adherence to tamoxifen therapy for breast cancer patients.

Methods and Materials: The 8 hospitals were randomized to intervention and control sites. Between February 2018 and December 2019, patients with breast cancer were recruited after their initial surgery. The primary outcome of the study was adherence to tamoxifen therapy by evaluating 12-month medication-refill data with medication possession ratio (MPR) and using a simplified medication adherence scale (SMAQ) in a subjective assessment.

Results: A total of 162 patients were recruited (87 intervention and 75 control). Trained nurses delivered education and provided literacy material, gave additional empathetic counselling, phone call reminders, and monitoring of medication refill at the intervention hospitals. Adherence according to MPR at 12 months was high in both the intervention (90%) and control sites (79.3%) ($P = .302$). The SMAQ revealed that adherence at intervention sites was 70% compared with 44.8% in the control sites ($P = .036$) at 12 months. Persistence to therapy was found to be 91.2% in the intervention and 77.8% in the control sites during the one-year period ($P = .010$).

Conclusion: Breast nurses can improve cost-effective endocrine therapy adherence at peripheral hospitals in low-resource settings. We recommend such task sharing to overcome the shortage of oncologists and distances to central cancer centers.

Key words: breast cancer; adherence; tamoxifen; breast nurse; peripheral hospitals; Ethiopia.

Implications for Practice

Patients with breast cancer in rural Ethiopia have few options to access systemic therapy. For endocrine sensitive disease, tamoxifen is highly effective, inexpensive, and has few side effects. Uptake and adherence can be a challenge especially in low-resource settings where it is highly underutilized. The results of this study show that trained breast nurses can increase the subjective level of adherence and the persistence to adjuvant endocrine therapy among patients in rural Ethiopia. Such an approach of task-sharing and de-centralizing cancer care can contribute to reducing abandonment to treatment for improved survival in line with the recent WHO Global Breast Cancer Initiative.

Introduction

Breast cancer is the most common cancer globally, but there are large disparities in outcome in different settings.[1-3] In Sub-Saharan Africa (SSA), the 5-year relative survival was shown to be only 59%,[4] while GLOBOCAN 2021 recently revealed that breast cancer is the second most commonly diagnosed cancer in East Africa and the second highest cause of cancer death in women.[1] In Ethiopia, it is the leading cancer[5,6] and recent findings have estimated that it accounts for 20.9% (16 133) of all new cancer cases (reaching up to 30.9% in

females) and accounted for 17.5% (9061) of all cancer deaths in 2020.[1] The 5-year metastatic free survival was 72% for early stage and 33% for late stage cases at the National Cancer Center.[7] In rural western Ethiopia, the 2-year overall survival rate following surgical treatment only was found to be 53%.[8]

Significant challenges exist to the development of breast cancer control programs in low- and middle-income countries (LMICs).[9] Treatment for breast cancer in low-resource settings is still limited and many of the patients present to services in at late stages, making this a challenge for health services.[3] A study from SSA countries revealed that an estimated 28%-37% of breast cancer deaths could be prevented through the earlier diagnosis of symptomatic disease and adequate treatment, with a fairly equal contribution of each.[10] Recently, the World Health Organisation (WHO) established the Global Breast Health Initiative (GBHI) to improve the outcome especially in LMICs.[11] One of the three goals aims for the completion of treatment in 90% of patients.

Endocrine (eg, Tamoxifen) therapy is one of the most cost effective and affordable therapeutic options for patients with breast cancer,[12] requiring few specialized professionals and being best utilized if hormone receptor status is available. The benefit of the therapy is well documented, with an up to 10% absolute increase in 10-year survival probability after 5 years of treatment.[12,13] It is a standard option in high-income countries but underutilized in many LMICs, including Ethiopia. The therapy has been shown to decrease the annual odds of recurrence and death by a relative 39% and 31%, respectively.[14] However, adherence to therapy in the adjuvant setting is of particular concern.[15]

Despite substantial implications for survival, the level of adherence to endocrine therapy is not always optimal. Tamoxifen non-adherence ranges from 25% to 59%, with a significant decline during follow-up.[16-19] In Africa, studies in Nigeria and South Africa reported 25% and 36% non-adherence rates for Tamoxifen, respectively.[20,21] The early discontinuation of endocrine therapy was also reported in almost one-third of the patients[22] and those who did not complete treatment ranged from 18% to 73%[23-26] Patient characteristics, illness and therapy, healthcare, and social and economic factors were the most frequently cited reasons for non-adherence to therapy in most settings[14,21,27,28]).

An intervention which is innovative and tailored to improve the adherence to therapy to address a multifactorial challenge is essential.[23,29,30] The use of an advanced nurse approach[31] or a trained nurse-based support[19,32-34] was suggested to improve adherence to endocrine treatment for women with breast cancer. To our knowledge, such an approach has not yet been tested in randomised clinical trials to date. Similarly, involving nurses to facilitate cancer care in remote areas as a task-shifting model was suggested in SSA,[35,36] due to scarcity of professionals trained in cancer diagnosis and care in the region.[37]

In Ethiopia, more than two-thirds[8,38] of patients are estrogen-receptor (ER) positive and could possibly benefit from an endocrine therapy such as tamoxifen. However, the drug is underutilised in the country. A study in west Ethiopia documented the adherence of tamoxifen therapy to be 52% in a 1-year follow-up[39] and poor patient navigation and lack of awareness about the disease were the major reasons for non-adherence to therapy. In our formative assessment prior to this intervention, we also identified the follow-up

of therapy after surgery as a challenge. There is apparently limited professional capacity in cancer care[40] in the country, although mainly in peripheral areas. The use of a trained nurse approach might have considerable effects in improving adherence to therapy, taking the recommendations from our previous study,[39] the formative assessment and experience from other settings.[32,34,41] However, there is a need to test the intervention which is tailored to the context to enhance the adherence to therapy, particularly in disparate populations outside of clinical trials and particularly in LMICs, including Ethiopia.[32]

Thus, we implemented a trained breast nurse intervention to deliver a package of services to patients in peripheral hospitals in the country with the aim of improving adherence to tamoxifen therapy during follow-up and compare adherence with control hospitals.

Materials and Methods

Study Design

A cluster randomized study design was conducted in 8 hospitals providing breast cancer care in southern Ethiopia. In this study, the clusters are units of randomization defined as a single hospital. A random allocation of 4 hospitals to the intervention and 4 hospitals to the control (usual care) group was performed using a computer running the randomization procedure. Matching was done to the level of hospitals during the random procedure for assessing the independent effect of breast nurse intervention on the level of adherence to endocrine therapy (tamoxifen) among patients with breast cancer over 1-year period.

The Study Setting

The interventional hospitals were Aira General Hospital, Attat Our lady of Lourdes Catholic Primary Hospital, Butajira General Hospital and Nigsit Eleni Mohamed Referral Hospitals, while the control hospitals were Saint (St.) Lukas Catholic Hospital, Dubo St. Mary Catholic Hospital, Durame General Hospital and Woliyta Sodo Teaching and Referral Hospitals. These hospitals were selected based on a formative assessment on existing breast cancer surgery and pathology services mainly serving rural populations. There were also options for referral for additional diagnostic services as well as limited therapy options through referral to higher level hospitals.

Study Participants, Recruitment Period and Follow-Up

All newly diagnosed patients with breast cancer who had initial surgery for breast cancer between February 1, 2018 and December 31, 2019 were recruited in all hospitals as an open cohort design. Patients were followed until a minimum of 12 months or until the end of the study on December 31, 2019. We measured adherence to tamoxifen (main outcome) among patients who attended their 6 and 12-month medication-refill appointments. Discontinuation of therapy was assessed as part of the secondary outcome.

Patient Inclusion and Exclusion Criteria

Newly diagnosed patients with a pathologically confirmed and surgically treated breast cancer with positive or unknown hormone-receptor status during the study period or during the 12 preceding months were included. The treatment

recommendation was given by the local surgeon responsible for the overall care. Patients with breast cancer and known negative hormone receptor status, pregnant women, women with any contraindication for tamoxifen (known thrombosis, stroke) and males were excluded.

Procedure

All patients received monthly tamoxifen during the first 6 months and then every 3 months during the follow-up. They were interviewed at baseline, and 6 and 12 months after surgery using standardised questionnaires including the medication refill report.

Intervention Group

All nurses (n=21) expected to participate in the study were trained on how to recruit patients, monitor the side effects of tamoxifen and any contraindications, on appropriate registration and the follow-up of patients, the completion of study documentation, and how to administer questionnaires to patients. Among these, interventional "Breast Nurses"[10] received additional detailed training and had an attachment at the central Radiotherapy Center at the National Referral Hospital in Addis Ababa. Topics included breast cancer presentation, the pathophysiology of breast cancer, empathetic communication skills, how to give medication-reminder phone calls and how to deliver support, advice and patient education. Hence, breast nurses with this additional training delivered a comprehensive package of services to improve the adherence to tamoxifen therapy for the intervention group. The intervention was developed based on review of the recommendations of different studies conducted on adherence support[19,31,34,39] and the formative study findings conducted in respective hospitals to look at the overall experience and challenges with follow-up care and support. Intervention included education on breast cancer and provision of literacy material, reminder with phone call, additional empathetic counselling and monitoring of medication refill.

Routine Care (Control Group)

The non-intervention group received the standard care provided by the respective hospitals. Patients received oral information about the disease and their recommended therapy. We involved 11 nurses from this group to recruit patients, monitor refills and compliance and conduct the study interviews during the baseline and follow-up visits.

Data Collection

All tools were translated from English to Amharic and then back. Sociodemographic and clinical information, awareness of the disease and willingness to take tamoxifen were collected at baseline. Adherence, persistence, discontinuation, referral and death-related information was collected during the follow-up. The collected data were checked for completeness and consistencies by supervisors and the principal investigator through close follow-up. A pre-tested standard questionnaire and drug refill registration forms were used. The pre-test of the tools was conducted at Tikur Anbesa Specialised Hospital with 10% of the sample size; minor corrections were considered.

Outcome Measurements

The primary outcome was adherence to tamoxifen at a 12-month duration. The secondary outcomes were persistence to therapy and discontinuation to therapy during the follow-up period. Sociodemographic information was assessed at baseline. Adherence was measured using both medication possession rate (MPR), and a simplified medication adherence questionnaire (SMAQ) scale. For the MPR, from the first day of medication received, we considered the number of tablets which the patient had prospectively received at their immediate previous visit, divided by the days since their immediate previous visit. Patients who refilled their drug ≥80% of the time were considered adherent for that time-period[39,42] and those who refilled it less than 80% of the time were considered non-adherent from the time point of the immediate previous visit for 12-month duration. In this study, we have also included the 6 months duration adherence report as the discontinuation report to our data is only in the first 6-month interval.

The SMAQ scale has been validated for endocrine treatment of patients with breast cancer with 6 questions,[43] 4 with 'yes'/'no' answers, and 2 with scales. Patients were asked at month 6 and month 12 about the last 4-12 weeks; those with ≥80% score were considered SMAQ-adherent,[42] otherwise they were considered SMAQ-non-adherent.

Persistence was described as the duration of time between the initiation of therapy and the last dose before discontinuation. Discontinuation was defined when a patient did not have a refill in a 90-day interval in the first 6 months or for 180 days onwards.

Sample Size

Sample size was calculated based on the 2-sided continuity corrected Chi-square-test ($\alpha = 0.05$) to compare the adherence of 2 independent groups with equal sample sizes. Adherence to tamoxifen in Ethiopia was reported to be 52% during 1 year.[39] We aimed to increase this adherence to 85%. To detect this difference in adherence, we used a power of 80% with significance level of 0.05 and a 5% non-inclusion rate, including the design effect of cluster randomization with intracluster correlation coefficient = 0.063 in process variables[44] and with a cluster number of 8. The sample size for each group was 77, making a total of 154 patients (nQuery Advisor 4.0 and Win Pepi Version 11.65). We added an additional 5%, so a total of 162 patients, to account for early patient deaths.

Data Analysis

Descriptive statistical methods, a 2-sided Chi-square test or Fisher's exact test were used for description and the comparison of variables and primary outcomes. The Kaplan-Meier test was used to estimate the probability of persistence and overall survival, while the log-rank test was used to compare groups. We used multivariable logistic regression to adjust for variables which had baseline differences between groups and an effect on the outcome to see the effect of the intervention on adherence. In addition to this, a sensitivity analysis was conducted to see the effect of the intervention when those patients who had prior history of tamoxifen therapy were excluded. Epi info version 7 and SPSS version 21 were used for the analysis.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board at the College of Health Science Addis Ababa University (064/17/SPH), National Ethics committee, Ethiopia and the Martin-Luther-University Halle-Wittenberg, Germany (Reg

No: 2017-142). Informed written consent was obtained from each participant at baseline. The patient data were kept confidential, so analysis was performed using de-identified data.

Results

Sociodemographic Profiles

In total, 162 breast cancer patients eligible to take tamoxifen therapy were included. The mean age of the intervention group was 41.8 (SD 11.1), which was similar to the control group 38.5 years (SD 11.1).

A CONSORT diagram (Fig. 1) shows that of the patients recruited at baseline, 65.5% (57) of the intervention group had a 6-month refill and 46% (40) had a 12-month refill of tamoxifen therapy during the follow-up; a similar pattern was reported in the control group as 58.7% (44) had a 6-month refill and 38.7% (29) had a 12-month refill and were included in the adherence analysis. During the follow-up, 33.3% (29) of patients from the intervention and 45.3% (34) from the control group were right-censored due to death, referral or discontinuation during the first year. Similarly, 20.7% (18) patients from the intervention group and 16% (12) of the

control group were left-censored due to their respective refill time period being below 12 months at time of adherence measurement in the 1 year follow-up.

Table 1 describes the sociodemographic profiles of the patients at baseline in the 2 groups. The groups were similar, apart from religion (the proportion of Muslim and Protestant religions varied between groups) and household average annual income, but the latter is a highly subjective response. We found that the majority of patients in both groups (72.4% (63) and 61.3% (46)) were living in a rural setting in the respective areas. Distance to hospitals showed that more than two thirds of patients had ≤30 km to travel from their home to the hospital.

Treatment and Clinical Characteristics

The clinical profiles of the patients in Table 2 show that most of the clinical variables were similar between the groups; only patients being advised to go to another place for diagnosis or treatment at time of their visit (44.8% of the intervention and 86.7% of the control group), stage at presentation (46.0% were diagnosed late in the intervention group and 70.6% in the control group), FNAC conducted (67.8% in the intervention
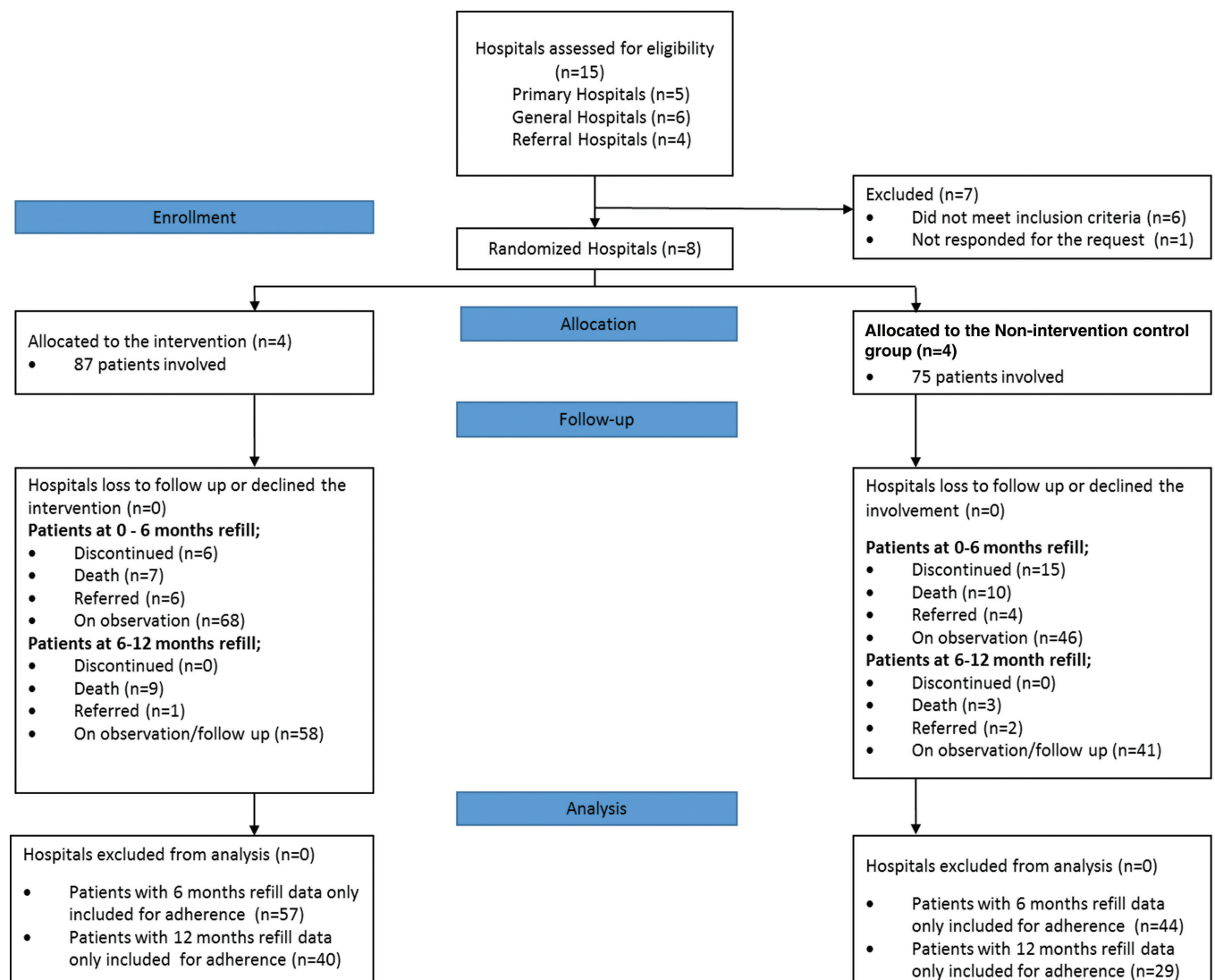

Figure 1. CONSORT flow diagram of progress through the phases of the breast nurse interventional study.

Table 1. Sociodemographic profiles of the patients at baseline among groups during breast nurse intervention.

Characteristics	Intervention group (*n* = 87) Frequency (%)	Control group (*n* = 75) Frequency (%)
Age, years		
≤30	18 (20.7)	25 (33.3)
31-40	30 (34.5)	25 (33.3)
41-50	22 (25.3)	18 (24.0)
≥51	17 (19.5)	7 (9.3)
Mean (+SD)	41.8 (11.1)	38. 5 (11.1)
Educational status		
Illiterate	55 (63.2)	40 (53.3)
Read and write	8 (9.2)	5 (6.7)
Primary school	10 (11.5)	15 (20.0)
Secondary school	8 (9.2)	11 (14.7)
College level	3 (3.4)	2 (2.7)
University level	3 (3.4)	2 (2.7)
Marital status		
Single	10 (11.5)	5 (6.7)
Married	62 (71.3)	60 (80.0)
Widowed	5 (5.7)	4 (5.3)
Divorced	9 (10.3)	6 (8.0)
Separated	1 (1.1)	0 (0.0)
Occupational status		
Housewife	59 (67.8)	55 (73.3)
Merchant	6 (6.9)	4(5.3)
Government employee	4 (4.6)	7 (9.3)
Self-employed	7 (8.0)	4 (5.3)
Others[a]	11(12.6)	5 (6.7)
Religion		
Orthodox	23 (26.4)	23 (30.7)
Protestant	35 (40.2)	39 (52.0)
Catholic	2 (2.3)	6 (8.0)
Muslim	26 (29.9)	6 (8.0)
No religion	1 (1.1)	1 (1.3)
Husband education		
Illiterate	37 (50.0)	23 (34.3)
Read and write	7 (9.5)	7 (10.4)
Primary school	17 (23.0)	25 (37.3)
Secondary school	4 (5.4)	9 (13.4)
College/university level	9 (12.2)	3 (4.5)
Husband occupation		
Merchant	7 (9.6)	10 (14.9)
Farmer	44 (60.3)	37 (55.2)
Government employee	8 (11.0)	7 (10.4)
Self-employee	5 (6.8)	3 (4.5)
Daily labourer	1 (1.4)	5 (7.5)
Others	8 (11.0)	5 (7.5)
Household average income	Annual (ETB)	
≤2500	34 (39.1)	34 (45.3)
2501-5000	9 (10.3)	16 (21.3)
5001-7500	6 (6.9)	0 (0.0)
7501-10 000	3 (3.4)	2 (2.7)
>10 000	35 (40.2)	23 (30.7)
Median (IQR)	3000 (1600, 14 000)	5400 (1500, 18 000)
Place of living		
In town	24 (27.6)	29 (38.7)

Table 1. Continued

Characteristics	Intervention group (*n* = 87) Frequency (%)	Control group (*n* = 75) Frequency (%)
Out of town	63 (72.4)	46 (61.3)
Distance of hospitals	From home in km	
≤15	26 (29.9)	35 (46.7%)
16-30	33 (37.9)	22 (29.3)
31-45	11 (12.6)	7 (9.3)
46-55	3 (3.4)	3 (4.0)
≥56	14 (16.1)	8 (10.7)
Median (IQR)	20 (10, 36)	17 (10, 30)

[a]Others = student, daily laborer, and private job.
ETB, Ethiopian Birr.

and 94.7% in the control group), and prior history of using endocrine (tamoxifen) therapy (18.4% in the intervention and 5.3% in the control group) were shown to have a difference.

Willingness to Initiate the Therapy and Awareness of the Disease

The willingness to initiate tamoxifen treatment was assessed among patients; overall, 97.75% from the intervention group and 97.3% from the control group expressed their agreement. For awareness of the disease, we found that 89.7% of patients from the intervention group and 94.7% from the control group had information about their disease, and 88.5% from the intervention group and 89.3% from the control group knew that they had breast cancer. Overall, 4.6% of the intervention group and 5.3% of the control group revealed that they had a family history of breast cancer. Our assessment found no major difference between the groups, except for responses to breast cancer being a transmissible disease (6.9% of the intervention and 16.0% of the control group) and breast cancer being detected early (54% of the intervention and 26.7% of the control group; Table 3).

Primary Outcome: Adherence to Tamoxifen at One Year

Adherence to tamoxifen therapy was measured as a primary outcome at the 12-month follow-up visit using medication refill data. The measurement was done at 12-month medication refill time for the primary outcome. In our trial, the adherence at 12 months was found to be 90% (36/40) in the intervention group and 79.3% (23/29) in the control group (scored ≥80% on MPR; *P* = .302). Similarly, the level of adherence (scored ≥80% on MPR) at 6 months was 89.5% (51/57) and 79.5% (35/44) in the intervention and control group, respectively (*P* = .164; Table 4).

A SMAQ was used as a secondary outcome to assess the self-reported adherence to observe the subjective behaviour of the patients on adherence level. It has been stated that medication adherence measurement requires more than one approach to describe the patient's adherence status.[43] Hence, in our study, where patients were assessed after 12 months of therapy, the level of adherence measured using SMAQ was 70% (28) in the intervention group and 44.8% (13) in the

Table 2. Clinical and treatment baseline characteristics of the patients in both groups during breast nurse intervention.

Characteristics	Intervention group	Control group
	Frequency (%)	Frequency (%)
Total visits to hospital till diagnosis		
1-2	40 (46.0)	31 (41.9)
3-5	38 (43.7)	38 (51.4)
≥6	9 (10.3)	5 (6.8)
Mean (SD)	3.02 (1.64)	3.08 (1.82)
Advised to go to other places (for diagnosis or treatment)		
Yes	39 (44.8)	65 (86.7)
No	48 (55.2)	10 (13.3)
Stage at presentation		
I	6 (6.9)	5 (6.7)
II	41 (47.1)	17 (22.7)
III	36 (41.4)	49 (65.3)
IV	4 (4.6)	4 (5.3)
FNAC conducted		
Yes	59 (67.8)	71 (94.7)
No	28 (32.2)	4 (5.3)
Histology result		
Ductal carcinoma	84 (96.6)	68 (90.7)
Lobular carcinoma	3 (3.4)	7 (9.3)
Days interval from diagnosis to surgery in days		
<30	51 (58.6)	41 (54.7)
31-60	11 (12.6)	3 (4.0)
61-90	4 (4.6)	5 (6.7)
≥91	21 (24.1)	26 (34.7)
Median (IQR)	18 (3, 80)	22 (5, 115)
History of using chemotherapy before		
Yes	18 (20.7)	13 (17.3)
No	69 (79.3)	62 (82.7)
History of using radiotherapy		
Yes	6 (6.9)	6 (8.0)
No	81 (93.1)	69 (92.0)
History of using tamoxifen		
Yes	16 (18.4)	4 (5.3)
No		
ER/PR status	71 (81.6)	71 (94.7)
Positive	10 (11.5)	16 (21.3)
Unknown	77 (88.5)	59 (78.7)
HER2 status		
HER2+	4 (4.6)	3 (4.0)
HER2−	6 (6.9)	13 (17.3)
Unknown	77 (88.5)	59 (78.7)
Had comorbidity illness		
Yes	14 (16.1)	8 (10.7)
No	73 (83.9)	67 (89.3)
Type of comorbid illness		
Stroke	3 (21.4)	2 (25.0)
Hypertension	8 (57.1)	3 (37.5)
Heart disease	1 (7.1)	2 (25.5)

Table 2. Continued

Characteristics	Intervention group	Control group
	Frequency (%)	Frequency (%)
Others	2 (14.3)	1 (12.5)

FNAC, fine needle aspiration cytology; ET, endocrine therapy; ER/PR, estrogen progesterone receptor; HER2, human epidermal receptor 2.

Table 3. The willingness to initiate tamoxifen therapy and patient awareness of their disease at the baseline of breast nurse intervention.

Characteristics	Intervention group	Control group
	Frequency (%)	Frequency (%)
Willing to initiate tamoxifen therapy		
Yes	85 (97.7)	73 (97.3)
No	2 (2.3)	2 (2.7)
How much willing to initiate the therapy		
Somewhat willing	3 (3.5)	7 (9.6)
Very much willing	82 (96.5)	66 (90.4)
Do you know about your disease?		
Yes	78 (89.7)	71 (94.7)
No		
How do you name disease you encountered?	9 (10.3)	4 (5.3)
Breast cancer	77 (88.5)	67 (89.3)
Breast infection	5 (5.7)	7 (9.3)
Cervical cancer	3 (3.4)	1 (1.3)
Do not know	2 (2.3)	0 (0.0)
Breast cancer is a transmissible disease?		
Yes	6 (6.9)	12 (16.0)
No	81 (93.1)	63 (84.0)
Perceive breast cancer can be detected early?		
Yes	47 (54.0)	20 (26.7)
No	18 (20.7)	26 (34.7)
I don't know	51 (31.5)	29 (38.7)
Any one in family had breast problem		
Yes	6 (6.9)	7 (9.3)
No	81 (93.1)	68 (90.7)
Anyone in the family had breast cancer		
Yes	4 (4.6)	4 (5.3)
No	83 (95.4)	71 (94.7)

control group (*P* = .036), indicating that the intervention had an effect on the self-reported level of adherence at 12 month duration. Similarly, we had a measurement at 6 months which revealed that 63.2% (36) of the intervention group and 52.3% (23) of the control group showed adherence to tamoxifen therapy (*P* = .271; Table 4).

For further analysis of the self-reported adherence difference at 12 months through the SMAQ, we adjusted for variables which had relevant differences at baseline (Table 5). Variables like stage at presentation, FNAC conducted or not, patients being advised to go another place, history of using endocrine (tamoxifen) therapy and patient's response to breast cancer being detected early or not were included in the model. The multivariable logistic model revealed that patients in the intervention group were 4 times more likely to have self-reported adherence than in the control group (AOR = 4.05; 95%CI (1.17-14.03)) and the remaining variables showed no strong influence (Table 5). Furthermore, we looked at sensitivity analysis including only patients who did not have a prior history of endocrine therapy (tamoxifen) use and still found a significant difference (P = .005) for self-reported level of adherence at 12 months between the groups. The multivariable model analysis also retained a significant effect of the intervention (AOR = 4.90; 95%CI (1.27-18.97)) on the self-reported level of adherence at 12 months, when including patients with no prior history of endocrine therapy use in the model.

Secondary Outcomes: Discontinuation, Persistence

In our secondary analysis, overall we found that 6.9% (95% CI: 2.9-14.5) of the intervention group and 20% (95%CI: 12.4-30.5) of the control group discontinued tamoxifen therapy during a 1-year period. The level of persistence with the therapy during 12 month was found to be 91.2% in the intervention and 77.8% in the control group. The mean ± SE duration of persistence, as measured by mean time to tamoxifen discontinuation (in months) and by Kaplan-Meier analysis, was 11.3 ± 0.36 months (95% CI, 10.8-11.8) in the intervention group and 9.8 ± 0.5 months (95% CI, 8.9-10.8) in the control group during the 12-month follow-up (P = .010; Fig. 2).

Table 4. Effect of breast nurse intervention on adherence expressed as a proportion of adherent patients using the medication possession ratio and simplified medication adherence questionnaire.

Adherence measures during refill time	Intervention group	Control group	P-value
	Frequency (%)	Frequency (%)	
MPR at 12 months			
Adhered	36 (90.0)	23 (79.3)	.302
Not adhered	4 (10.0)	6 (20.7)	
SMAQ at 12 months			
Adhered	28 (70.0)	13 (44.8)	.036
Not adhered	12 (30.0)	16 (55.2)	
MPR at 6 months			
Adhered	51 (89.5)	35 (79.5)	.164
Not adhered	6 (10.5)	9 (20.5)	
SMAQ at 6 months			
Adhered	36 (63.2)	23 (52.3)	.271
Not adhered	21 (36.8)	21 (47.7)	

MPR, medication possession ratio; SMAQ, simplified medication adherence questionnaire.

Table 5. Multivariable logistic model to assess the effect of breast nurse intervention on adherence of endocrine therapy (tamoxifen) during a 12-month refill period.

Variables	Self-reported Adherence status at 12 months		AOR (95% CI)	P-value
	Adhered frequency (%)	Not-adhered frequency (%)		
Intervention status				
Intervention group	28 (68.3)	12 (42.9)	4.05(1.17, 14.03)	.028[a]
Control group	13 (31.7)	16 (57.1)	1	
Stage at diagnosis				
I	4 (9.8)	5 (17.9)	1	
II	19 (46.3)	9 (32.1)	1.93 (0.34, 10.94)	.47
III	16 (39.0)	13 (46.4)	0.94 (0.17, 5. 18)	.94
IV	2 (4.9)	1 (3.6)	2.51 (0.14, 45.2)	.53
FNAC conducted				
Yes	32 (78.0)	20 (71.4)	1.55 (0.38, 6.29)	.54
No	9 (22.0)	8 (28.6)	1	
History of using ET				
Yes	5 (12.2)	6 (21.4)	0.37 (0.84, 1.65)	.19
No	36 (87.8)	22 (78.6)	1	
Advised to go to another place				
Yes	26 (63.4)	16 (57.1)	1	.46
No	15 (36.6)	12 (42.9)	0.62 (0.17, 2.25)	
Breast cancer can be detected early				
Yes	20 (48.8)	12 (42.9)	1.73 (0.41, 7.23)	.45
No	13 (31.7)	6 (21.4)	2.59 (0.53, 12.73)	.24
Do not know	8 (19.5)	10 (35.7)	1	

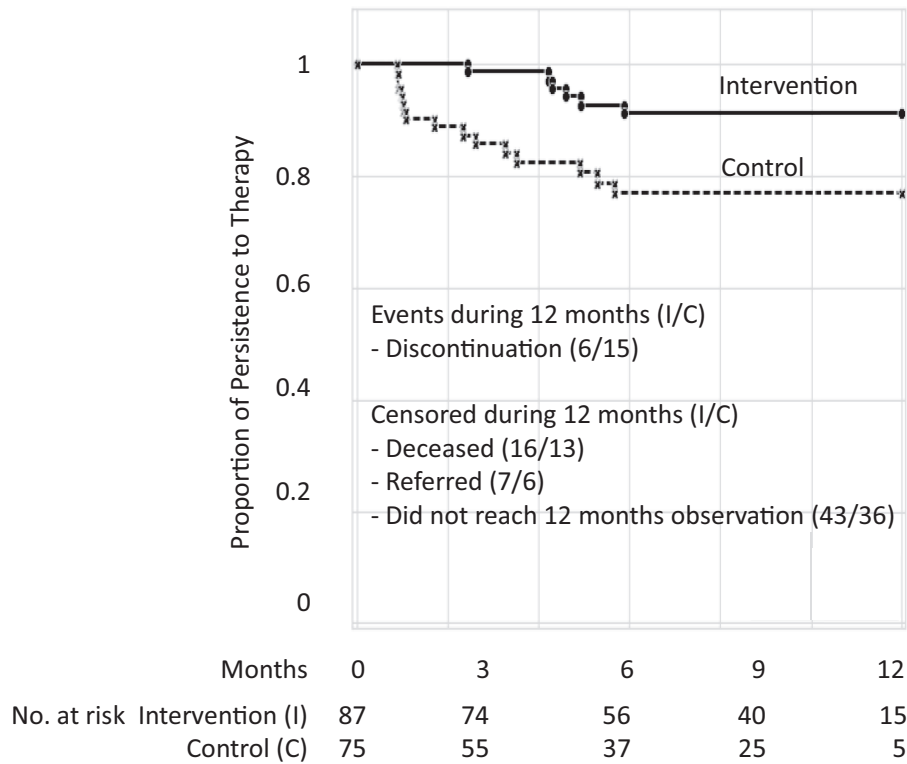ET, endocrine therapy; AOR, adjusted odds ratio.

Figure 2. Kaplan-Meier survival curves with time to discontinuation of refilling (months) tamoxifen therapy among groups in a 12-month period.

Discussion

This study evaluated a breast nurse intervention which delivered a package of services with the aim of improving level of adherence to tamoxifen therapy among patients with breast cancer. We measured adherence by combining the refill data with a self-reported questionnaire to provide a broad understanding of the adherence behaviour of patients[43,45] The 12 months MPR revealed higher adherence (90%) in the intervention group compared with the control group (79.3%), although no statistical difference was observed (*P* = .302). However, we observed a higher level of medication refill in both groups compared to our previous finding of 52% (39). The results of the SMAQ assessment revealed higher levels of patient adherence to tamoxifen therapy (70%) in the intervention group compared to the control or usual care group (44.8%) during the 1-year period. The adjusted finding revealed that patients from intervention group were 4 times more likely to have self-reported levels of adherence than the control group. However, despite a significant increase in the objectively measured levels of adherence in both groups, there was no difference observed. This might be because the training of data collection nurses on the basics of breast cancer motivated the non-intervention group and helped them to build good communication with patients during their follow-up.

Our findings show that a trained breast nurse intervention had promising effects on improving adherence to adjuvant endocrine (tamoxifen) therapy and was consistent with other studies.[31,33,34] A previous study reported that nurses are in a good position to assess, monitor and promote adherence to the endocrine therapy, give adequate time to patients and improve communication with them.[31]

A study from Canada also suggested that nurse-led interventions improved patient adherence to oral cancer therapy and follow-up.[46] One systemic review similarly showed an effect of nurse-led intervention on adherence to prescribed medications.[47] These findings underscored our hypothesis on the effect of trained nurses on sidestepping levels of non-adherence of the therapy due to multifactorial issues[21,34,39] and a pragmatic setup. This could contribute to reducing adherence challenges to both the health system and professionals[15] as part of a task-sharing approach as stated to further support long-term cancer care across the entire health system.[35]

The persistence of therapy after initiation was also statistically significantly higher in the intervention group than in the control group (*P* = .010). The findings also revealed a high level of persistence compared with our previous single-center study (52%) at the 1 year time point.[39] Importantly, there was a low proportion of discontinuation of therapy among the intervention group compared with the non-intervention group. In other studies, we found higher levels of discontinuation after initiating the therapy,[22,23] and noted that the early discontinuation of therapy is highly associated with increased recurrence and breast cancer-specific mortality rates, as well higher medical costs.[23,24,48-50] Similarly, the loss to follow-up is a major issue that threatens the efficacy of treatment protocols, even when treatment is available in most scenarios.[51] An improved level of persistence with therapy in our intervention group is also a very promising finding for breast nurse interventions with a comprehensive package of services (education on breast cancer, reminder services, empathetic communication and counselling, and further monitoring of drug refills). Other studies have also reported independently improved levels of adherence and persistence[52-54] in certain regions of the US and France.

The majority of patients in our study were from rural regions and their awareness of the disease was relatively

better when initiating therapy since they received information during the diagnostic pathways and surgical care; this is in line with other findings stating that patients who understand their disease are more likely to show compliance with therapy.[55]

In our study, 97.7% of the intervention group and 97.3% of the control group showed willingness to initiate adjuvant tamoxifen therapy. Our study demonstrated that more patients were willing to initiate therapy compared to only 51% in a previous study.[39] The high willingness and eventual initiation of therapy in our study might be because most patients came from rural areas and a significant number had little education, meaning that they were likely to agree with the suggestions of medical professionals. Another study similarly stated that less educated women were more likely to take tamoxifen, and that their willingness to initiate therapy was not determined by knowledge of risk/benefit or risk perception.[56] Moreover, patients may have agreed as the drug was available free of charge, and there were few other treatment options, similar to that seen in other African settings.[57,58]

In general, the finding showed that trained breast nurses have shown some promising effects on improving self-reported levels of adherence and persistence with tamoxifen therapy during their 1-year follow-up. The higher level of adherence which was also observed in both groups as per the medication refill report compared with a previous study, although it lacked a significant difference between groups. Hence, to the entire health system this is a very promising opportunity to see a trained nurse support as part of a task-sharing role[35] for adherence and long-term cancer care support, given that there are limited professionals in cancer diagnosis and care in most African settings, including Ethiopia.[37,40,59]

Our study has certain limitations. First, the low participation of patients during adherence measurement at one year in both groups: 52% of the intervention group and 37.7% of the control group. This may be due to patients exiting the follow-up due to death, referral or discontinuation of therapy during follow-up and also because some were not willing to accept surgery or the adherence support for adjuvant therapy. However, in general we tried to advertise the availability of tamoxifen services in both groups and encouraged women who had a confirmed diagnosis to take the therapy after surgery, followed by recruitment to our respective adherence support group during follow-up.

The second limitation is the inclusion of patients with a prior history of endocrine intake, which might increase an awareness of adherence to therapy. However, we conducted sensitivity analysis by excluding patients with prior experience of taking the therapy before the initiation of the intervention and observed that the effect of the breast nurse intervention was maintained. The third limitation is a lack of greater pathology capacity in the respective settings and patients being referred to other centers during the diagnostic process, as this caused delays to patient recruitment after surgery in some sites during the study period.

Nevertheless, we had strength in implementing a very innovative and feasible intervention tailored to the context. We involved multidisciplinary professionals who had knowledge and skills in breast cancer and adherence support and improved communication to patients. There was also the close supervision in respective hospitals, including the tamoxifen availability in timely manner to the patients during follow up. In addition to these, the formative study was conducted to understand the hospital setups, experiences and challenges in follow-up care in order to shape the intervention which is tailored to the context.

Conclusion

Our trained breast nurse intervention in Ethiopia improved the self-reported level of adherence and the persistence with tamoxifen therapy among women after breast cancer surgery. Substantial levels of adherence were observed in both groups, as per medication refill data. This indicates that by documenting the patient's medication refills and having a structured follow-up, including exposure to certain disease- and treatment-related questions, might have brought positive effects on medication adherence to the usual care group.

Our study underpins the positive effect to have a task-sharing role by engaging trained breast nurses improving the follow-up care, including adherence to therapy and timely referral for those in need of further attention. During the study period, we were also able to assure tamoxifen availability in the respective hospitals; from the early inception with formative assessment throughout the process of intervention and supervision. Our findings generally encourage giving more responsibilities to nurses around all other issues related to improve the care of patients. Basic cancer care within the context of emerging non-communicable diseases can become part of the regular nursing curriculum. EHealth solutions can link nurses with higher level professionals to assure supervision and referral if needed. While acknowledging the need for centralized comprehensive cancer centers, we support the idea of a hub-and-spoke model to reach out back and forth to peripheral sites staffed by trained nurses. This will bring basic cancer care within the vicinity of rural patients who are otherwise unable to reach highly specialized centers.[60] This might have an impact of strengthening the primary healthcare system with strong survivorship care and adherence support to improve patient adherence to treatment as recommended by the BHGI WHO initiative.

Conflict of Interest

Author Contributions

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

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Perceived barriers to early diagnosis of breast Cancer in south and southwestern Ethiopia: a qualitative study

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Abstract

Background: Early diagnosis is a key determinant of breast cancer prognosis and survival. More than half of breast cancer cases are diagnosed at an advanced stage in Ethiopia, and the barriers to early diagnosis in this country are not well understood. We aimed to identify the perceived barriers to early diagnosis of breast cancer from the perspective of patients and health care providers in south and southwestern Ethiopia.

Methods: A qualitative study was conducted from March to April 2018 using in-depth interviews of breast cancer patients and breast cancer health care providers from six public hospitals located in urban and rural areas of south and southwestern Ethiopia. All participants provided verbal consent before participating. A thematic analysis was performed using Open Code 4.02.

Results: Twelve breast cancer patients and thirteen health care providers were included in the study. Patient and health-system related barriers to early diagnosis of breast cancer were identified. Patient-related barriers were lack of knowledge and awareness of breast cancer, belief in traditional medicine and religious practices for treatment, and lack of social and financial support to seek care at a medical facility. Health-system related barriers were misdiagnosis of breast cancer, long distance to referral facilities, high cost of diagnostic services, long waiting time for diagnostic tests, and lack of screening and diagnostic tests in local facilities.

Conclusions: Early diagnosis of breast cancer is affected by multiple barriers in south and southwestern Ethiopia. Awareness campaigns and education about the disease, prevention, and early detection are needed to increase early diagnosis of breast cancer. Opportunities exist to improve early diagnosis and timely treatment in rural areas.

Keywords: Breast cancer, Early diagnosis, Barriers, Ethiopia

Background

Breast cancer is the most prevalent cancer in African women, responsible for one in four diagnosed cancers and one in five cancer deaths [1]. In Ethiopia, in the year 2015, it was estimated that the prevalence of breast cancer case is 13,987 with a crude incidence rate of 28.2 per 100,000 and it accounts for 33% of all cancer cases among women [2]. The global cancer data (GLOBO-CAN) also estimated in 2018 for Ethiopia the age

standardized incidence and mortality rate per 100, 000 among all ages to be 41.2 and 22.9 [1]. If breast cancer is identified at an early stage (I-II), it has a high chance of cure and is more likely to respond to treatment than if diagnosed at a later stage (III-IV) [3]. Delays in diagnosis lead to advanced stage presentation and poor clinical outcomes [4, 5]. Most breast cancer patients in low-income countries such as Ethiopia experience very long delays, are diagnosed at advanced stages, and have low survival rates [6, 7].

Previous studies have identified several patient and health system -related barriers to early diagnosis of breast cancer in Africa but the barriers vary from region to region [6–9]. African women delay presenting to

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health facilities mostly due to lack of information or knowledge about initial signs and symptoms, poor quality of health facilities, belief in traditional medicine in favour of seeking medical care, lack of trust, and a lack of access to health care [10, 11]. Belief in traditional medicine, religious beliefs, economic hardship, poor provider knowledge, and misdiagnosis were major reasons for a delay in diagnosis in Malawi [12].While a low education level was also associated with a patient delay in Rwanda [13]. Health care provider factors that contribute to delayed diagnosis in Africa include incomplete patient examination, inappropriate use of diagnostic tests, misinterpretation of test results, and misdiagnosis [14]. Less comprehensive health insurance coverage and false negative diagnostic tests are also common health-system related factors [15].

Breast cancer awareness and knowledge about the benefits of early detection and diagnosis are poor in most sub-Saharan African countries including in Ethiopia, and consequently, advanced stage presentation is a common problem in the region [16–19]; and women living in rural areas present at a later stage of breast cancer than women living in urban areas [20, 21].

In Ethiopia the national cancer control plan was launched in 2016 [22] and as result health care providers' capacity and training are expanding. Screening for breast cancer is recommended for women over the age of 18 years. However, organized screening modalities are still not in place at the facility and community levels. Despite lack of specific breast cancer screening and care guideline in the country, clinical breast examination services are provided in some facilities.

Thus, given the clinical significance associated with delayed diagnosis and the paucity of understanding related to the reasons for delayed breast cancer diagnosis in Ethiopia, we examined the perceived barriers to early diagnosis of breast cancer in Ethiopia from the perspective of patients and health-care providers.

Methods

Study approach and setting

A qualitative in-depth interview method was used to explore perceptions of barriers related to early diagnosis of breast cancer among breast cancer patients and health-care providers. The study was conducted from March to April 2018 and included six public hospitals in south and southwestern Ethiopia (Durame General Hospital, Attat Hospital, Dubo St. Mary Hospital, Wolliso St. Lukas Hospital, Butajira General Hospital, and Hawassa Comprehensive Referral Hospital).

Participants and recruitment

The participants in this study were newly diagnosed female breast cancer patients (age > 18 years old) and

health-care providers (surgeons, oncologist, and nurses) who were involved in the diagnosis and management of breast cancer for ≥ 1 year. Breast cancer patients receive follow up are in surgery departments only as there are no oncology clinics available at those sites. Therefore, health care providers were invited from those surgery departments. The patients were recruited through discussions with surgeons and nurses from surgical department and oncology units on the basis of their lived experiences and understanding of the study.

The hospitals were selected because they serve mostly rural populations and have experience with treatment services for breast cancer patients. Hospitals were approached and the hospital leadership linked the research team to the providers and patients. The research team gave all the hospitals, health-care providers, and patients a description of the study. The research team gave all the hospitals, health-care providers, and patients a description of the study including the objectives, the benefit expected from the study findings and the fact that participation in interviews was voluntary.

Ethical considerations

Ethical clearance was approved from the Research and Ethical Committee (REC) of School of Public Health, and the Institutional Review Board (IRB) of College of Health Science Addis Ababa University. Verbal consent was obtained from each of the patients in the study and written consent is taken from health care providers. Verbal consent was taken from the patients based as the rapid ethnographic assessment (REA) conducted to inform the informed consent process revealed that majority are not able to read and write in addition to major cultural concerns on signature. This procedure was approved by the Institutional Review Board of Addis Ababa University mentioned above. In addition, permissions were obtained from the selected hospitals prior to data collection. The objectives and importance of the study were explained to the participants before the interview. Participants were notified that their participation was voluntary and that they could withdraw at any time during the interview process. All information provided by the participants was de-identified to maintain participant privacy.

Data collection

In-depth interviews were conducted for each participant using a semi-structured interview guide to balance openness and focus during the interviews. The guide was developed by the research team following a thorough literature review and initial key informant interviews. It was first developed in English and then translated to the local language (*Amharic*) to facilitate communication with participants. Interview themes/questions focused

on healthcare provider experiences with breast cancer early detection methods and potential reasons for late diagnosis of breast cancer or perceived lack of early diagnosis, and on patient experiences with what was felt when a breast change was first noticed and reasons for visiting a health facility after the disease had advanced (for the complete interview guide see Supplementary File 1). All interviews were conducted within the hospital setting during the day; and lasted 40–60 min. All interviews were tape-recorded and transcribed verbatim and translated into English. All information was de-identified under transcription. Transcripts and translations were cross-checked for accuracy and consistency. Appropriate written notes were also taken in the event the audio recorder could not capture content during the interviews. The interview process was continued until the data reached saturation, defined as that point when answers were no longer providing new/additional information to the research question and recurrent patterns became evident in the patients' narratives.

Data analysis

Translated notes were read and re-read by two independent coders who had qualitative research experience. The data were then organized by coding or dividing the text into meaningful elements using Open Code version 4.02 software. The coding process continued until all the data were exhausted. The coders identified themes and sub-themes from the data and thematic analysis was used to identify themes and sub-themes by grouping related codes.

The analysis was mainly performed by the author and all co-authors reviewed and approved the different scripts and developed themes and sub themes.

Results

Socio-demographic characteristics

Twenty five patients and health care providers participated; 12 breast cancer patients and 13 healthcare providers. Patient age ranged from 26 to 65 years (Table 1).

Health care providers included an oncologist, gynaecologist and obstetrician, general surgeons, public health officers, and nurses who were involved in diagnosis, treatment and management of breast cancer patients (Table 2).

Themes and sub-themes (categories) identified

Two main themes emerged from the narrations of the participants regarding the barriers to early diagnosis of breast cancer - patient- and health system-related barriers. Five sub-themes were identified. Within the theme of patient-related barriers, three sub-themes were identified - lack of awareness and knowledge about breast cancer, beliefs in traditional and religious treatments, and

Table 1 Socio demographic profile of breast cancer patients involved in the interviews

Characteristics	Frequency	Percentage
Age		
≤ 30	1	8.3
31–40	8	66.8
41–50	1	8.3
51–60	1	8.3
≥ 61	1	8.3
Residence		
Urban	4	33.3
Rural	8	66.7
Marital status		
Married	9	75.0
Widowed	3	25.0
Educational status		
Illiterate	5	41.7
Primary school	3	25.0
Secondary school	1	8.3
Diploma and above	3	25.0
Occupational status		
House wife	2	16.7
Farmer	6	50.0
Merchant	1	8.3
Government employ	3	25.0

Table 2 Socio-demographic profile of Health care professionals involved in the interviews

Characteristics	Frequency	Percentage
Age		
20–30	5	38.5
31–40	5	38.5
41–50	2	15.3
> 51	1	7.7
Educational status		
Diploma level	3	23.0
Degree level	5	38.5
Specialization level	5	38.5
Profession		
Nurse	6	46.3
Public health officer	2	15.3
General Surgeon	3	23.0
Gynecologist	1	7.7
Clinical Oncologist	1	7.7

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lack of financial and social support. Within the theme of health system-related barriers, two sub-themes were identified - services rendered by healthcare providers and the functioning of the health care facilities.

Patient related-barriers

Lack of knowledge and awareness about breast cancer.

Almost all patients described a general lack of awareness and knowledge about risk factors, signs and symptoms of breast cancer as well as a general lack of community activity and attention given to early detection of breast cancer. Most patient participants were unaware of breast cancer before diagnosis and had limited knowledge about the disease, and this had great impact on when they sought medical attention. Most sought medical intervention once the disease was advanced. Most patient participants explained that they detected abnormalities on their breasts accidentally when they were in bathroom or when undressing before bed. None had a history of breast self-examination or clinical check-ups.

"I never heard about breast cancer before. I saw the swelling four years back but I did not inform to anyone in the family since it was painless but later becomes large and produce discharge." (Patient, Age range 41–50 yrs old).

"I did not check my breast before. I saw the swelling accidentally. I did not go to health facility for check-up of my breast." (Patient, Age range 21–30 yrs old).

Patients' perceptions that their initial symptoms were harmless delayed them seeking medical care. Many failed to seek early medical care unless the symptoms interfered with their day-to-day activities. Some did not give attention to early symptoms.

"I saw the swelling on my breast 4 years ago. But I was not going to any health facility since I was healthy for a long time and it was painless."(Patient, Age range 31–40 yrs old).

Patients also explained that the painless nature of a swelling or mass led them to perceive the breast change as a common and self-limiting problem, and this resulted in delays seeking medical care. Many patients explained they did not initially think their symptoms could be cancer and all patients sought medical care at least 12 months after they first noticed symptoms. Patients from rural areas described delays in seeking healthcare due to distance, transportation challenges, cost of care, but mostly due to lack of information related to the disease.

Beliefs in traditional medicine and religious practice for treatments.

All patients interviewed delayed seeking medical care in favour of using traditional and spiritual treatments (holy water) because there is a preference to go traditional healers as the first choice of treatment rather than to heath care facilities; many also believed that swelling could be healed or treated by applying herbal medications. Patients stated that limited knowledge led them to perceive their illness with the same traditional beliefs pervasive in many villages.

"I was using traditional treatment like onion, Tena Adam and other leaves. I thought it was the disease given from God." (Patient, Age range 51–60 yrs old).

"I went to traditional healer and I took herbal medication for a long time since I thought it as 'Bigunji' (local name to swelling with pus) and continued to use the traditional treatment. Finally I came to hospital when the disease becomes sever and sever." (Patient, Age range 41–50 yrs old).

The patient interviews further revealed different beliefs that contributed to delays in seeking medical care for breast cancer. Losing a breast (mastectomy) was described as taboo. The fear expressed was that if a woman loses her breast due to surgery, she might die, could not give birth, or she would be divorced by her husband. As a result, most women hid their problem and sought medical care as a final option only after trying all traditional or cultural treatment approaches. Again, patients shared that most of people are not aware of the disease or its treatment, and therefore don't advise women to go health facilities. Swelling in the breast is not perceived as a treatable medical problem, but rather as "God's punishment". This ailment commonly called "Meksefit" in the community is locally believed as a disease related to demonic/ witchcraft.

"My community does not support the medical treatment related breast cancer since they perceived that.......if it is touched by scissor or syringe it will spread and kill the patient." (Patient, Age range 21–30 yrs old).

"I was not thinking that cancer has any treatment in the hospital since my community perceived that cancer is killer and does not have any treatment in the hospital. But we believe on herbal medication and holy water." (Patient, Age range 41–50 yrs old).

Lack of financial and social support

Many patients explained they did not have financial resources to afford the treatment and transportation costs; thus contributing to delays in care and a barrier to early diagnosis. Those individuals with economic means were better positioned to get early diagnosis and treatment. Patients described borrowing money from a neighbor, friend, or family to get medical care, but explained how this was not easy in their communities where everyone had limited economic recourses. Patients also felt their family responsibilities and a general lack of social and family support prevented them from seeking early medical care; and even after seeking medical care almost all

patients face economic hardship with little money to pay for medical costs. To amass money for care patients engaged in borrowing, begging on streets, or selling their land, cattle, or other property; and during that time interval the disease is untreated and progresses.

"I have family responsibility since my husband is died. My breast problem starts before two years. But I could not come early to health facility because I did not have money for transport and treatment service requested, there is no anyone who supports me."(Patient, Age range 51–60 yrs old).

"I had no money for medication and transportation since my husband was died and all the family responsibility is on me. Even now I was not paid the money for surgery. I came to this hospital after selling my farm land and borrowing some money from my families."(Patient, Age range 31–40 yrs old).

Health system related barriers
Health care provider's perception related barriers
Similar to patient accounts, providers also described poor breast self-awareness and knowledge regarding importance of recognizing breast changes, and early signs and symptoms of breast cancer.

"Majority of the patients are coming late after the disease is advanced. This is because lack of awareness and knowledge about the disease since they did not consider the initial signs and symptoms as serious." (Gynaecologist, Age range 51–60 yrs old).

"Most of the patients came at advanced stage (Above stage III) and this is due to lack of awareness about the disease. Their awareness about breast self-examination and early clinical check-up is nil". (General Surgeon, Age range 21–30 yrs old).

Healthcare providers also stated that most women coming from rural areas present at advanced stage disease compared to urban patients. Providers described a perception that lack of access to information among rural women may have to do with lower level of education, literacy rate, working in the home.

"......since there is no information access either through magazines, newspapers or media, the awareness of the rural people is very low. Peoples from the urban areas relatively come early as they feel any changes on their breast."(General Surgeon, Age range 31–40 yrs old).

The providers added that most patients go to the hospital as a last option after the cancer is advanced and/or is metastatic. They stated most patients perceive cancer as a disease related traditional or cultural things. As a result, patients would take herbal medications or holy water remedies. Also, providers described fear of receiving care in health facilities. For example, providers described a belief that if someone were to go to a health facility and get an injection, the needle would hide the disease; it would spread inside the body, and then kill the patient.

"There are a lot of patients who went to their home without getting definitive diagnosis due to their inability to pay for transportation and diagnosis when they are referred." (Nurse, Age range 21–30 yrs old).

"I can say almost all patients are used herbal medications before coming to hospital. Some patients also spend most of the time going to holy water in orthodox religion and praying in Protestants since they consider it as a cultural disease". (Nurse, Age range 21–30 yrs old).

Many patients experienced delays in transitions of care due to poor provider knowledge and misdiagnosis. Patients are often given analgesics or other treatments for several months at primary care facilities before receiving an appropriate referral to a facility for breast cancer care. They describe delays in getting the right diagnosis and how the providers contribute to delays in care. Misdiagnosis and delays in referring patients early to the regional diagnostic hospital were the most frequently mentioned problem leading to patient's presenting with late stage disease. Almost all patients described a history of misdiagnosis during their initial visits to the health care provider and being placed on some form of prolonged treatment for an incorrect diagnosis.

"I went to private health facility first and they told me as it is other breast problem and they gave me treatment but I was not improved. Then I went to another private hospital and they said me you have breast TB and they gave me TB treatment and I took for 6 month." (Patient, Age range 31–40 yrs old).

"First I went to the private clinic and the doctor told me that do not worry for this. It is the effect of the contraceptive you used before so it would be lost by itself and he ordered me 6 injections. I was hoping him and I wait a long time but the swelling becomes increase and starts to produce bloody discharge then I came to hospital and diagnosed as cancer."(Patient, Age range 31–40 yrs old).

Health care providers also stated that misdiagnosis is a common problem in breast cancer care. This is usually a problem at primary health care facilities since they fail to detect such cases early and refer patients in a timely fashion. Clinical breast examination is not commonly practiced in the facilities unless patients are coming with complaint of breast abnormalities. Patients elaborated on appointment delays, poor attention given to them while in the facilities, inadequate examinations and poor communication between health care providers and patients. These were some of the reasons which led patients not to have additional follow up visits to the health care facilities and instead look to traditional means of treatment.

"Usually there is misdiagnosis of cases especially among the young's as a breast lump or fibro adenoma but after

sometime the patients may came again with advanced stage breast cancer. I know a woman who was diagnosed with other breast problem but after a long time she come again and diagnosed as breast cancer." (Patient, Age range 31–40 yrs old).

"The first doctor who has diagnosed me was not good. He said all part of your breast should be removed. He did not reassure me. He made me to worry and frightened then I went to traditional treatment areas but I was not improved of the problem and now the disease is spread to my body."(Patient, Age range 21–30 yrs old).

Health facility related barriers

The patients faced problems with access to health facilities due to long distances of the facilities from their home and high transportation costs. The referral experience was also very poor at health centers and private clinics even in cases when patients presented early for appropriate diagnosis and treatment. All of the patients had a referral history to other health facilities for diagnostic investigations. The most important health facility barrier mentioned by the providers and patients was diagnostic waiting time. They mentioned that the waiting time for getting pathologic lab test results takes usually more than a month, and the absence of the tests in some of the hospitals makes the problem worse. Patients explained they required several visits to health facilities to get their diagnosis. They first went to health centres where drugs were prescribed without proper assessment. When they saw that their situation was not changing as they expected, the patients then went to private clinics. It was after these attempts that the women were then finally referred to the diagnosing hospital. At a minimum, patients visited two health facilities before they got their final diagnosis. The providers similarly explained that the absence of diagnostic tests and treatment options for breast cancer in the hospitals were the main problem contributing to delays in care. Providers described situations when they felt obligated to refer patients to other hospitals for diagnosis and treatments, knowing this could be very expensive for patients and that they quite possibly patients would not be able to afford to go the referral center.

"I wait a month to get my laboratory result but I faced many difficulties when they referred me to this hospital because of distance. Since there is no transport access and the medical care costs are so expensive. I came to this hospital last week but they said me there is no bed and I returned back at that time and now I came again. I visited three health facilities one private and two government health facilities before."(Patient, Age range 31–40 yrs old).

"Our major challenge here is we have no diagnostic tests, standard treatments and a screening tool. So we refer patients to Addis Ababa for pathologic tests and treatments but sometimes they come back without getting the service due to over schedule, so we cannot do anything to them because they have non-operable cancer then they will disappeared or die in their home." (Surgeon, Age range 31–40 yrs old).

Patients explained that the absence of screening and health education programs, including skilled professionals, are some of the health system challenges to providing early detection, diagnosis and treatment of breast cancer. Once the patients have already paid for prior (incorrect) treatment, travel, and clinic visits during the referral process, they stated they cannot afford the additional costs of care when they arrive at a facility capable of diagnosing and treatment breast cancer. They mentioned that the surgery itself cost much as 2000 Ethiopian birr, and they also have to consider the cost additional transportation, the hospital bed, diagnostic tests, and medications.

"...........there is no organized way of giving health education about breast cancer in this hospital since there are no skilled professionals on the area." (Medical oncologist, Age range 21–30 yrs old).

"Cancer treatment is very, very expensive. I have no word to describe the costs. I finished all my money for laboratory, transportation, bed and other treatments. The cost is very much.... not only for the poor but also for the riches. The government should give attention to it."(Patient, Age range 31–40 yrs old).

Discussion

Early stage of diagnosis is a key determinant factor for survival of breast cancer patients, and delays in diagnosis and advanced stage of presentation are associated with poor clinical outcomes [6, 23]. The barriers to early diagnosis of breast cancer are multifaceted ranging from individual patient level to organizational or facility levels. Barriers also vary from country to country, depending on their economic growth, cultural and religious factors, as well as availability of and accessibility to health infrastructure and man power [10].

Our study identified several socio-demographic, economic, cultural, religious, health facility and health care provider related barriers to early diagnosis of breast cancer in south and southwestern Ethiopia. A major patient related barrier to seeking early medical care for breast cancer was the low access to information about breast cancer in the country. This finding is similar to studies in other Sub-Saharan African countries which have shown that lack of knowledge was a major contributing factor for late presentation [15, 22]. Lack of knowledge about the disease delays the search for early medical care, even when patients may have early signs and symptoms because the patients often ascribe different

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meaning to these breast changes, and may not recognize them as serious. Findings from our study revealed how patients let the sign and symptoms take their natural course without seeking early medical care. This behavior has underpinnings in traditional or religious practices, which are strong and common in Ethiopia [24]. Most patients often first use traditional medicines and holy water before they seek access to medical care, presenting with late stage disease. Patients' fear of losing their breast, anxiety about medical procedures, failure to disclose their problems to others also contributed to their delay to seek medical attention.

Being from a rural residence and remote areas also contributes to delays in early diagnosis, similar to other studies conducted in African countries [20, 21]. General lack of access to information through magazines, newspapers and media in rural areas was also described as a contributing factor for patients not seeking early medical attention when they noticed breast abnormalities. Patients who had a painful wound or ulcer on their breast were less likely to delay presentation than patients who had painless lump. It was explained that painless lumps were often considered not serious or self-limiting, and patients would seek medical care only when the symptoms became painful or when they interfered with day to day activities. Our finding is consistent with research from Egypt in which women without any pain were more likely to present at later stage than those having pain as the first symptom [25].

Patients' diagnostic pathways from initial symptom recognition until arrival at cancer diagnosing centers contributed to their delay in diagnosis and advanced stage of presentation. Women faced health system barriers at all points of the diagnostic pathway, especially during diagnostic investigations and the referral period in which patients endured long journeys to diagnostic centers and then long waiting times to get results. A similar situation was reported in a qualitative study in Aracaju, Brazil, even though it is a different social, economic, cultural and health care context [14].

Patients described several barriers they face to seeking early medical care, including family responsibilities, feeling shyness to check their breasts, and fear to disclose their problems to others. They shared a perception that culturally it is not acceptable for women to have one breast, or to show a breast to another person except the husband. Patients also explained the tendency to relate breast changes to symptoms associated with pregnancy, breastfeeding and contraceptive use, thereby delaying them to seek early medical care until the problem worsened.

In Ethiopia the accessibility and availability of cancer diagnostic centers is very limited. There is only one radiotherapy center in the country and majority of diagnostic centers are located at the capital city of Addis Ababa [26]. As a result majority of patients suffer a lot of difficulties including transportation costs and prolonged waiting times to get the service when they referred to diagnostic facilities. The situation has made it difficult for primary health care providers to effectively provide breast cancer diagnostic and treatment services in the rural setups which further create delays in care. Such limitations are reported elsewhere as impediments of cancer care in primary care settings [27].

Our study has strengths and limitations. This is the first study conducted in south and southwestern Ethiopia to explore health system and patient related barriers to early diagnosis of breast cancer. We consider capturing the perspectives from patients and health care providers a major strength of the study. However, we only used in-depth interviews for data collection with limited number of participants.

Conclusion
Lack of knowledge and awareness, symptom misinterpretation, preference for traditional and spiritual means of treatment, lack of social and family support, and lack of money for medical care costs and transportation, misdiagnosis of cases, long distance to referral centers and long waiting time for diagnostic tests were the major reasons for delays in diagnosis of breast cancer in our study on perspectives of patients and healthcare providers in South and Southwestern Ethiopia.. Our findings show the need for community awareness and education programs about breast cancer signs, symptoms, and treatment options. Opportunities exist to educate healthcare providers, decrease misdiagnosis, strengthen the referral system, and streamline care with the goal of improving outcomes for patients with breast cancer in Ethiopia.

Supplementary information

Additional file 1.

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questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, were appropriately investigated, resolved, and the resolution documented in the literature.

Availability of data and materials
The raw data analyzed for the current study is deposited by the authors in the data archives of the Non Communicable Diseases (NCD) Research Working Group of Addis Ababa University. Both the first author and the last author are core members of the team. The de-identified data is available upon reasonable request through the authors, please email to: adamu.addis-sie@aau.edu.et and safoget@yahoo.com .

Ethics approval and consent to participate
Ethical clearance was approved from the Research and Ethical Committee (REC) of School of Public Health, and Institutional Review Board of College of Health Science (IRB) of Addis Ababa University. Verbal consent was obtained from each of the patients in the study and the written consent is taken from provider side and all signed in the prepared consent form. Verbal consent was obtained from each of the patients in the study and written consent is taken from health care providers. Verbal consent was taken from the patients based on the rapid ethnographic assessment (REA) conducted to inform the informed consent process revealed that majority are not able to read and write in addition to major cultural concerns on signature. This procedure was approved by the Institutional Review Board of Addis Ababa University mentioned above. We took verbal consent from patient side based on the discussion as all want to take the verbal one. We took written consent from the provider side. Permission was obtained from the selected hospitals prior to data collection. The objectives and importance of the study were explained to the participants before the interview. Participants were notified that their participation was voluntary and that they could withdraw at any time during the interview process. All information provided by the participants was de-identified to maintain participant privacy.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Original Study

Late-Stage Diagnosis and Associated Factors Among Breast Cancer Patients in South and Southwest Ethiopia: A Multicenter Study

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Abstract

We examined data of patients with advanced stages of breast cancer in large regions of south and southwest Ethiopia to determine the occurrence of late-stage disease. We found the main factors that contributed to late-stage diagnosis included patient delaying in seeking care, having comorbid illnesses, and a rural residence. **Background:** Breast cancer is a leading cause of cancer death in women in low- and middle-income countries, largely because of late-stage diagnosis. Yet studies are very limited in the Ethiopian context. Therefore, we determined the occurrence of late-stage disease and associated factors in selected public hospitals in south and southwest Ethiopia. **Patients and Methods:** A 5-year retrospective cross-sectional study was conducted on breast cancer patient medical records from January 2013 to December 2017 in 6 hospitals. Multivariable logistic regression was performed to identify factors associated with late-stage disease (stage III and IV). Adjusted odds ratios (AOR) with 95% confidence intervals were used. $P < .05$ was considered statistically significant. **Results:** Overall, 426 breast cancer patients were identified, and 72.5% were diagnosed with late-stage disease. The mean ± standard deviation patient age was 42.8 ± 13.4 years. Factors associated with late diagnosis were patient delay in seeking care (AOR = 2.50; 95% confidence interval [CI], 1.51-4.16); health system delays (AOR = 1.62; 95% CI, 1.02-2.59); female sex (AOR = 3.46; 95% CI, 1.50-7.98); rural residence (AOR = 2.37; 95% CI, 1.45-3.86); chief complaint of breast lump (AOR = 3.01; 95% CI, 1.49-6.07); and history of comorbidities (AOR = 1.72; 95% CI, 1.02-2.91). **Conclusion:** The majority of patients were diagnosed with late-stage diagnosis of breast cancer. Patient delays in seeking care, health system delays, being female, rural residence, and patient comorbidities were associated factors. These findings provide evidence that efforts to increase public and health provider awareness to promote early breast cancer diagnosis, particularly in rural areas, are needed in south and southwest Ethiopia.

Introduction

Breast cancer is one of the most common diagnosed malignant tumors among women worldwide, representing 24% of all cancer cases and 15% of all cancer deaths among women.[1] Almost half of breast cancer cases and over half (58%) of deaths occur in low- and middle-income countries.[2] Studies have shown that 46% to 76% of patients in Africa (including in 17 sub-Saharan countries, Libya, Zimbabwe, Rwanda, and Morocco) present with late-stage (III and IV)[3] breast cancer[4-8] compared to 8% to 22% of breast cancer patients from high-income countries (Australia, Canada, Denmark,

Norway, Sweden, and the United Kingdom).[9] Early stage diagnosis is a key factor for improved survival of breast cancer patients, and delay in diagnosis and treatment predicts poor clinical outcomes.[10] Understanding the diagnostic patterns and associated factors in breast cancer patients from Africa is therefore important to improve patient outcomes.

Several studies have identified determinants of late-stage diagnosis of breast cancer in some African countries.[11-19] The major contributing factor is diagnostic delay related to patient factors (lack of awareness, belief in traditional medicine, economic hardship, linking initial symptoms with pregnancy or breastfeeding, or not seeking help unless in pain); diagnostic delay related to health care providers (poor knowledge about breast cancer diagnosis and treatment); and diagnostic delay related to health care capacity to care for breast cancer patients (for example, a patient visits multiple health care providers and hospitals to receive appropriate assessment and referral, then endures long wait times to receive treatment). Patient and health care system delays are significantly associated with late-stage disease,[7] and long total delay to treatment increases the risk of late-stage disease by approximately 6-fold.[8]

In Ethiopia, breast cancer is the most prevalent and frequently diagnosed cancer, accounting for 33% of cancer cases in women and 23% of all cancer cases.[20] Patients diagnosed at early stages of disease (I and II) have better 5-year survival than patients diagnosed at late stage (III) (72% vs. 33%, respectively).[21] However, efforts to build capacity for cancer care throughout the country, particularly in rural communities, have been incremental. In 2016, Ethiopia launched a National Cancer Control Plan.[22] As a result, health care provider capacity and training are expanding across the country. Understanding the factors that contribute to late-stage diagnosis of breast cancer in Ethiopia is therefore vital to inform policy and program development and to improve patient care and outcomes.

To address this, in the current study, we sought to understand the magnitude of late-stage diagnosis and the factors associated with late-stage diagnosis of breast cancer patients in south and southwest Ethiopia.

Patients and Methods
Study Design, Geographic Area, and Patient Population

We conducted a retrospective cross-sectional study of breast cancer patient medical records between January 1, 2013, to December 31, 2017, in 6 hospitals in south and southwestern Ethiopia. These hospitals provide breast cancer care to the urban and rural communities: Hawassa Comprehensive Referral Hospital, Attat Our Lady of Lourdes Hospital, Dubo St Mary Primary Hospital, Wolliso St Lukas Primary Hospital, Durame General Hospital, and Butajira General Hospital.

Hawassa Comprehensive Referral Hospital is located 273 km south of Addis Ababa (the capital of Ethiopia) and provides complete diagnostic, surgical, hormone, and chemotherapy treatment services for breast cancer patients. As a tertiary-care referral hospital and academic medical center, it serves 15 million patients from the south of the country. Patients are then referred to Addis Ababa to receive radiotherapy at the only facility in the country with a cobalt radiation machine. Attat Our Lady of Lourdes Hospital is located 175 km southwest of Addis Ababa and provides diagnostic (fine needle aspiration cytology), surgery, and hormone treatment for

breast cancer patients. The other 4 hospitals provide diagnostic (fine needle aspiration cytology) and surgical services for breast cancer patients. Butajira General Hospital is located 130 km south of the capital and serves approximately 1.3 million people in its catchment area. Wolliso St Luke Hospital is in Wolliso town, 116 km southwest of Addis Ababa. Durame General Hospital is in the southern region of Ethiopia, 240 km south of Addis Ababa. Dubo St Mary Hospital is located 300 km southwest of Addis Ababa.

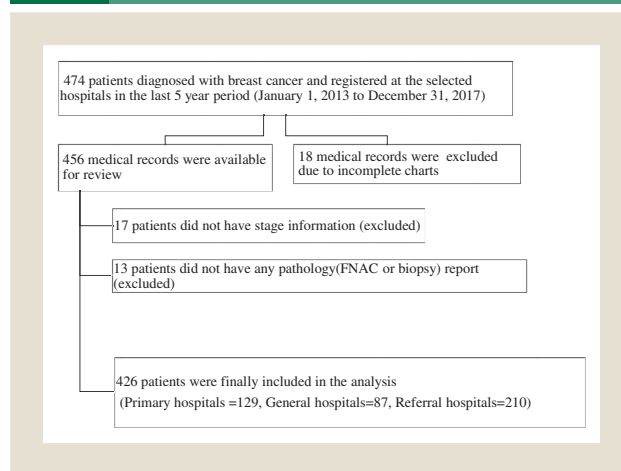### Sample Size, Sampling Technique, and Data Collection Procedures

Data from patient medical records were reviewed to identify breast cancer patients diagnosed from January 1, 2013, to December 31, 2017, at the hospitals described above. Patients who had confirmed breast cancer on pathology review and who had clear stage information documented in their medical record were included in the study; patients with incomplete and unavailable medical records were excluded from the study (Figure 1).

Data were collected on sociodemographic, clinical, and behavioral variables. Patient delay was defined as the time from a patient first becoming aware of symptoms until the first medical consultation. A delay of < 3 months was considered a short delay and of ≥ 3 months was considered a long delay.[6,7,16] Health system delay was defined as the time between a patient's first visit to a health facility and the date of the first pathology report confirming breast cancer. Short health system delay was defined as the median delay or less. Long health system delay was defined longer than the median delay.[7] Total diagnostic delay was defined as the time between the patient first recognizing symptoms and the final pathologic diagnosis of breast cancer; ≥ 6 months was defined as a long delay and a < 6 months was defined as a short delay.[7]

Information on tumor size (T) and node status (N) was used to derive disease stage by the American Joint Committee on Cancer staging system (7th edition).[3] Data were abstracted from patient records. Stage III and IV disease was defined as late stage, and stage I and II disease was defined as early stage.[7,23]

A rural area is defined as localities comprising mostly small, single-family, self-sustaining farms; traditional areas are characterized by low population densities, predominantly agricultural

Figure 1 Flow Diagram of Breast Cancer Patients

474 patients diagnosed with breast cancer and registered at the selected hospitals in the last 5 year period (January 1, 2013 to December 31, 2017)

456 medical records were available for review

18 medical records were excluded due to incomplete charts

17 patients did not have stage information (excluded)

13 patients did not have any pathology(FNAC or biopsy) report (excluded)

426 patients were finally included in the analysis (Primary hospitals =129, General hospitals=87, Referral hospitals=210)

Table 1 Sociodemographic and Clinical Characteristics of Breast Cancer Patients in South and Southwestern Ethiopia	
Characteristic	**Frequency (%)**
Hospital name	
Hawassa referral hospital	210 (49.3)
Durame general hospital	53 (12.4)
Dubo S. Mary primary hospital	37 (8.7)
Attat primary hospital	45 (10.6)
Butajira general hospital	34 (8.0)
Wolliso St Lukas hospital	47 (11.0)
Age group	
<30 y	61 (14.3)
30-39 y	127 (29.8)
40-49 y	111 (26.1)
50-59 y	64 (15.0)
60+ y	63 (14.8)
Mean ± standard deviation (years)	42.78 ± 13.4
Sex	
Male	28 (6.6)
Female	398 (93.4)
Home residence	
Rural	292 (68.5)
Urban	134 (31.5)
Menopause status (n = 339)	
Premenopausal	192 (56.6)
Perimenopausal	61 (18.0)
Postmenopausal	86 (25.4)
HIV status (n = 372)	
Negative	362 (97.3)
Positive	10 (2.7)
Pregnancy status (n = 340)	
Not pregnant	321 (94.4)
Pregnant	19 (5.6)
Family history of breast cancer (n = 356)	
Yes	51 (14.3)
No	305 (85.7)
History of any comorbidities	
Yes	152 (35.7)
No	274 (64.3)
Use of traditional treatment (n = 320)	
Yes	188 (58.8)
No	132 (41.3)
History of smoking (n = 297)	
Yes	5 (1.7)
No	292 (98.3)
History of alcohol (n = 298)	
Yes	14 (4.7)
No	284 (95.3)
Presenting chief complaint[a]	
Breast lump or mass	383 (89.9)

Table 1 Continued	
Characteristic	**Frequency (%)**
Swelling or lump in armpit	40 (9.4)
Pain/wound	180 (42.3)
Other[b]	13 (3.1)
Diagnosis at initial visit	
Breast cancer was not suspected	121 (28.4)
Diagnosed as breast cancer clinically	252 (59.2)
No diagnosis was made at initial visit	53 (12.4)

Data are presented as n (%) unless otherwise indicated.
[a]Multiple answers possible.
[b]Nipple retraction, nipple discharge, skin color change.

economic activity, and a low level of infrastructure. Urban areas are generally defined as localities with 2000 or more inhabitants primarily engaged in nonagricultural activities and with good infrastructure.

To assure the quality of the data, data extraction checklists were prepared in a simple and easily understandable language. One-day training was provided for data collectors and supervisors before data collection. Strict supervision and monitoring were performed during data collection.

Data Analysis

Descriptive analysis was conducted using frequency and other summary measures. Bivariate and multivariable logistic regression analyses were used to identify factors associated with late-stage diagnosis of breast cancer. All factors potentially known to influence presentation to late stage were considered in the univariate analysis. Variables found to be significant with $P < .05$ in bivariate logistic regression were exported to the multivariable logistic regression model. However, variables like education status, religion, and ethnicity were not included in the model because this information was not documented in the medical record. The crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) at statistically significant level of $P < .05$ were used to report the results.

Ethical Considerations

Ethical approval was obtained from the research ethics committee of School of Public Health, Addis Ababa University. Written permission and consent were obtained from the hospitals before the study after a brief explanation of the purpose of the study. Patient information was kept confidential in compliance with health information and privacy practices in Ethiopia.

Results
Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristic of the patient population. Of 474 patients identified with breast cancer, 426 eligible patients were included in the study (Figure 1). Most patients were female (398/426, 93.4%), and over half were from rural communities (292/426, 68.5%) with no history of comorbidities (274/426, 64.3%). The mean ± standard deviation age at

diagnosis was 42.78 ± 13.4 years. Over half the patients were premenopausal (192/339, 56.6%), less than a quarter had family history of breast cancer (51/356, 14.3%), and most were HIV negative (362/372, 97.3%). Most patients presented with a breast lump (383/426, 89.9%), and many (180/426, 42.3%) complained of painful breast wounds. At their initial visit, 121 (28.4%) of 426 patients were misdiagnosed with benign disease.

Tumor and Treatment Characteristics

Table 2 shows the tumor and treatment characteristics of the patient population. Most patients presented with clinical lymph-adenopathy (368/426, 86.4%), and 260 (61%) of 426 had a breast tumor size > 5 cm. Most patients were diagnosed with invasive ductal carcinoma (396/426, 93%); lobular carcinoma was diagnosed in 22 (5.2%) of 426 patients. On pathology review, 84 (43.3%) of 194 patients had poorly differentiated invasive carcinoma (grade III). Nearly all patients were treated with surgery (409/426, 98.3%),

Table 2	Tumor and Treatment Characteristics of Breast Cancer Patients in South and Southwestern Ethiopia
Characteristic	**Frequency (%)**
Axillary lymph node status	
Positive	368 (86.4)
Negative	58 (13.6)
Tumor metastasis to other body parts	
Yes	65 (15.3)
No	361 (84.7)
Type of tumor	
Ductal	396 (93.0)
Lobular	22 (5.2)
Other[a]	8 (1.9)
Tumor size	
≤5 cm	166 (39.0)
>5 cm	260 (61.0)
Median & IQR	6 (4-8)
Tumor grade	
I	31 (16.0)
II	79 (40.7)
III	84 (43.3)
Patient had received any treatment	
Yes	415 (97.4)
No	11 (2.6)
Type of treatment received	
Surgery	408 (98.3)
Chemotherapy	183 (44.1)
Hormone therapy	55 (13.3)
Radiotherapy	5 (1.2)
Patient current status[b] (n = 185)	
Alive	182 (98.4)
Dead	3 (1.6)

Data are presented as n (%) unless otherwise indicated.
Abbreviation: IQR = interquartile range.
[a]Mixed tumors and inflammatory carcinomas.
[b]Based on records indicating presence of follow-up activity.

and almost half received chemotherapy (183/426, 44.1). Fifty-five (13.3%) of 426 received hormone therapy, and 5 (1.2%) of 426 received radiotherapy. Of the total 426 cases reviewed, 185 (43.4%) had information on the survival status of patients, and of those, 3 deaths (1.6%) were reported.

Late-Stage Diagnosis Among Breast Cancer Patients

The stage at breast cancer diagnosis is shown in Figure 2. Of the 426 records reviewed, almost three quarters of the patients had late-stage disease at diagnosis (309/426, 72.5%; 95% CI, 68.3-76.5); 244 patients (57.3%) were diagnosed with stage III disease and 65 (15.2%) with metastatic disease (stage IV). Subgroup analysis showed that of the 309 patients diagnosed with late-stage disease, 224 patients (73%) were from rural communities compared to 85 (28%) who were from urban areas. Nearly three quarters of the female patients were diagnosed with late-stage disease (74.4%) whereas 46.4% of male patients had late-stage disease at diagnosis. Over the study period, the number of breast cancer cases diagnosed increased (Figure 3).

Medical Care Pathways and Diagnostic Delay Periods

Table 3 shows the diagnostic journey and delay periods among breast cancer patients. Of 426 breast cancer patients, 146 (34.3%) had a referral history from another health facility; 48 (32.9%) were referred for breast cancer care from a public health center, and 81 (55.5%) were referred from private health facilities. A total of 119 (81.5%) of 146 were diagnosed with late-stage disease. Of those patients who did not have a referral history (280), 190 (67.9%) were diagnosed with late-stage disease ($P = .003$). The median patient delay was 120 days; 311 (76%) of 426 patients had a long patient delay, and within that subset 240 patients (77.2%) were diagnosed with late-stage disease. By comparison, 115 (26.9%) of 426 patients had short patient delay, and 60 patients (60%) in that subgroup were diagnosed with late-stage disease.

The median health system delay was 32 days. The median total delay was 184 days. Significantly higher proportions of patients who had long total delay were diagnosed with late-stage disease compared to patients who had a short total delay (77.4% vs. 67.3%, respectively, $P < .05$) (Table 3).

Factors Associated With Late-Stage Disease Diagnosis

Table 4 shows the factors associated with late-stage breast cancer diagnosis. Breast cancer patients who had long patient delay were 2.5 times more likely to be diagnosed with late-stage breast cancer than those with short patient delay (adjusted odds ratio [AOR] = 2.50; 95% CI, 1.51-4.16). Similarly, patients experiencing long health system delay were 2 times likely to be diagnosed with late-stage disease than those with short health system delay (AOR = 1.62; 95% CI, 1.02-2.59). Patients with a history of comorbidities were approximately 2 times more likely to be diagnosed with late-stage disease than those with none (AOR = 1.72; 95% CI, 1.02-2.91). Patients from rural communities were approximately 2.4 times more likely to be diagnosed with late-stage disease than urban residence (AOR = 2.37; 95% CI, 1.45-3.86). Female subjects were approximately 3.5 times more likely to be diagnosed with late-stage disease than male subjects (AOR = 3.46; 95% CI, 1.50-7.98). Patients who reported breast lump or mass as the chief complaint at
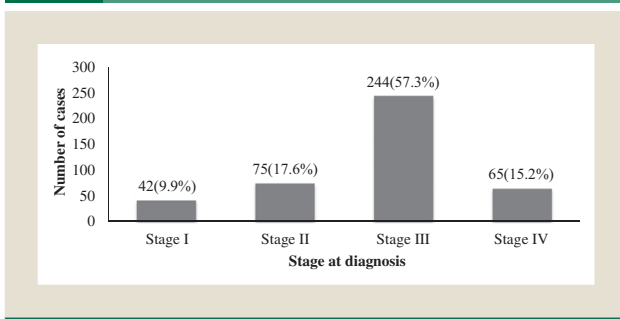
presentation were 3 times more likely to be diagnosed with late-stage disease than those who did not (21 women complained about pain/wound, 2 complained of an axillary mass, and 20 did not specify a chief complaint) (AOR = 3.01; 95% CI, 1.49-6.07).

Discussion

Late-stage disease diagnosis is associated with poor prognosis in patients with breast cancer.[11,24] Although many contributing factors for late-stage disease diagnosis have been identified in developing countries, these vary across regions and depend on local awareness, health care capacity, and resources.[19,25] We determined the occurrence of late-stage disease diagnosis and associated factors in south and southwestern Ethiopia.

We found that almost three quarters of patients (72.5%) were diagnosed with late-stage disease. This is similar to findings in other sub-Saharan African countries. A systematic review and meta-analysis in 17 sub-Saharan African countries found the median percentage of late-stage disease was 74·7%.[4] A study in Libya found late stage of breast cancer in 65.5% of patients.[5] In Zimbabwe, 72.6% of breast cancer patients presented at late stage.[6] Similarly in Rwanda 52% of the women had stage III disease and 24% had stage IV disease at diagnosis.[7] In Morocco, 46% of the patients were diagnosed at an advanced stage.[8]

Most of the breast cancer patients in our study were 30 to 39 years of age. This is similar to studies conducted at Tikur Anbesa Specialized Hospital in Addis Ababa, Ethiopia,[21] in Zimbabwe,[6] and in other hospitals in sub-Saharan Africa.[4] We identified a median total diagnostic delay of 6 months, patient delay of 4 months, and health system delay of 32 days. Notably, across all

categories, the delays we identified are lower than a study in Rwanda, which found median delays of 15 months (total delay) and 5 months each (patient and health system delays).[7] The variations could be due to a difference in the characteristics of the sample, and other sociocultural and infrastructure difference.

In our patient population, delayed diagnosis, both due to patient delay and health system delay, were significantly associated with late-stage diagnosis of breast cancer; these factors likely contributed to late-stage diagnosis. Several other studies of breast cancer patients in Africa also report a significant association between delayed diagnosis and late-stage disease.[4,7,26,27]

We found that patient delay of > 3 months was associated with increased odds of late-stage disease diagnosis. Women were 3.5 times more likely to present with late-stage disease than men, and women from rural areas were more 2.4 times more likely to have late-stage disease than from women from urban areas. Additionally, patients who had breast lump at presentation were more likely to be diagnosed with late-stage disease. Findings from a study in Egypt showed that "no pain" was a reason for delay of diagnosis.[16] This might be because a painless breast lump (in contrast to a smaller lesion that caused pain) may not initially be considered as serious and therefore a delay in seeking medical care.

Our study revealed an increase in the trend of breast cancer cases over the 5-year period from 2013 to 2017. This is consistent with a study conducted at Tikur Anbesa Specialized Hospital in Addis Ababa, Ethiopia.[28] The Ethiopian National Cancer Control Plan of 2016 advocates for clinical breast examination for patients over age 18 receiving medical care in a health facility. We observed a trend of more absolute numbers of breast cancer patients seeking care at the hospitals over the 5 years, which indicates increases in demand for breast care services. Countries like Uganda and Zimbabwe have shown up to 3.5% annual increase in population-based incidence rates over the last 20 years.[29,30] These data underscore the need to strengthen the health care system's capacity to manage breast cancer cases.

Interestingly, in our study, a history of comorbidities increased the likelihood of being diagnosed at late stage by approximately 2-fold, even though these patients likely had contact with the health care system to manage their other medical problems. Therefore, the association may be a coincidental finding or caused by an unknown underlying factor.

Our study identifies opportunities for improvement within the health care system to decrease delays in diagnosis. We have shown the extent to which delays within the health care system increases risk of late-stage diagnosis. We have quantified the need to improve the misdiagnosis rate of breast cancer among health care providers, as 121 (28.4%) of 426 patients were initially misdiagnosed. We also described the extent to which patients are referred within the health care system in the south and southwestern region (146/426, 34.2%), a baseline metric from which future improvements to streamline and coordinate care of breast cancer patients can be compared.

Our study has certain limitations and strengths. This is the first multicenter study of breast cancer conducted at public hospitals in the south and southwestern Ethiopia, which serves the majority of the population in those regions of Ethiopia. We have captured data on breast cancer cases treated over the 5 years (from 2013 to 2017)
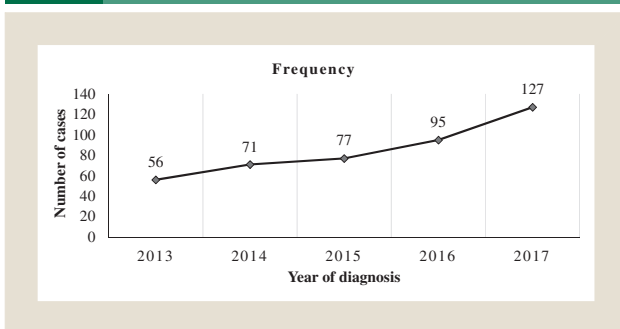
Table 3 Diagnostic Journey and Delay Periods Among Breast Cancer Patients at Selected Hospitals of South and Southwestern Ethiopia

Characteristic	All Patients	Late-Stage Disease at Diagnosis		P
		Yes	No	
Had referral history (n = 426)				
Yes	146 (34.3)	119 (81.5)	27 (18.5)	.003
No	280 (65.7)	190 (67.9)	90 (32.1)	
Immediate referring facility (n = 146)				
Health center	48 (32.9)	34 (70.8)	14 (29.2)	.040
Hospital	17 (11.6)	12 (70.6)	5 (29.4)	
Private health facility	81 (55.5)	71 (87.7)	10 (12.3)	
Diagnosing hospital type (n = 426)				
Primary hospital	129 (30.3)	82 (63.6)	47 (36.4)	<.001
General hospital	87 (20.4)	53 (60.9)	34 (39.1)	
Referral hospital	210 (49.2)	174 (82.9)	36 (17.1)	
Patient delay (n = 426)				
Short delay	115 (27)	69 (60.0)	46 (40.0)	<.001
Long delay	311 (73)	240 (77.2)	71 (22.8)	
Median & IQR	120 (60, 365)			
Health system delay (n = 426)				
Short delay	197 (46.2)	132 (67.0)	65 (33.0)	.018
Long delay	229 (53.8)	177 (77.3)	52 (22.7)	
Median & IQR	32 (23, 46)			
Total diagnostic delay (n = 426)				
Short delay	205 (48.1)	138 (67.3)	67 (32.7)	.020
Long delay	221 (51.9)	171 (77.4)	50 (22.6)	
Median & IQR	184 (109, 386)			

Data are presented as n (%) unless otherwise indicated.
Abbreviation: IQR = interquartile range.

in a variety of hospitals serving this population (local to tertiary referral level). The limitations of the study include incompleteness of the medical record and that absence of variables like educational status, marital status, behavioral factors, family history of cancer, income, religion, and distance to health facility, as well as factors about the disease itself, including tumor grade, and data on tumor receptor status. Importantly, we also noted disorganized documentation of the date of presentation, confirmed diagnosis, and surgical treatment.

Conclusion

More than two thirds of patients were diagnosed at a late stage of breast cancer in our study. Long patient and health system delay, female sex, rural residence, breast lump at presentation, and having a history of comorbidities (HIV, hypertension, tuberculosis, diabetes, and asthma) were found to be factors significantly associated with late-stage disease diagnosis. The increase in the number of breast cancer cases highlights the need to expand services and strengthen referral links. Efforts to decrease delays in diagnosis could include increasing breast self-awareness in the rural population, especially among young women aged 30 to 39 years. More importantly, there should be an in-depth exploration of reasons for late-stage diagnosis among urban and rural populations, as different health education approaches and interventions may be needed. Opportunities exist to decrease misdiagnosis and increase screening in regional health care facilities treating conditions like hypertension, asthma, tuberculosis, and diabetes.

Clinical Practice Points

- Patient delaying seeking care, having a comorbid illnesses, and having a rural residence were found to be the main factors contributing to late-stage diagnosis.
- These findings underscore the need for increasing public and health provider awareness to promote early breast cancer diagnosis, especially in rural areas.

Table 4 Multivariable Analysis of Factors Associated With Late-Stage Diagnosis of Breast Cancer in South and Southwestern Ethiopia

Characteristic	Late-Stage Disease at Diagnosis		COR (95% CI)	P	AOR (95% CI)	P
	Yes	No				
Age group						
<30 y	39 (63.9)	22 (36.1)	1	.315	1	.795
30-39 y	93 (73.2)	34 (26.8)	1.54 (0.80, 2.97)	.194	1.12 (0.55, 2.29)	.764
40-49 y	87 (78.4)	24 (21.6)	2.05 (1.03, 4.08)	.042	1.42 (0.66, 3.03)	.370
50-59 y	47 (73.4)	17 (26.6)	1.56 (0.73, 3.32)	.253	0.93 (0.39, 2.18)	.862
60+ y	43 (68.3)	20 (31.7)	1.21 (0.58, 2.55)	.612	0.95 (0.39, 2.25)	.903
Health system delay						
Short (≤32 days)	132 (67.0)	65 (33.0)	1		1	
Long (>32 days)	177 (77.3)	52 (22.7)	1.68 (1.09, 2.57)	.018	1.62 (1.02, 2.59)	.043
Patient delay						
Short (<3 months)	69 (60.0)	46 (40.0)	1		1	
Long (≥3 months)	240 (77.2)	71 (22.8)	2.25 (1.43, 3.56)	<.001	2.50 (1.51, 4.16)	<.001
Comorbidities[a]						
Yes	119 (78.3)	33 (21.7)	1.59 (1.00, 2.53)	.048	1.72 (1.02, 2.91)	.043
No	190 (69.3)	84 (30.7)	1		1	
Chief complaint at presentation lump/mass						
Yes	287 (74.9)	96 (25.1)	2.85 (1.50, 5.42)	.001	3.01 (1.49, 6.07)	.002
No	22 (51.2)	21 (48.8)	1		1	
Misdiagnosed at initial visit						
Yes	97 (80.2)	24 (19.8)	1.77 (1.07, 2.95)	.027	1.76 (0.99, 3.12)	.52
No	212 (69.5)	93 (30.5)	1		1	
Had referral history						
Yes	119 (81.5)	27 (18.5)	2.09 (1.28, 3.39)	.003	1.72 (0.99, 2.97)	.054
No	190 (67.9)	90 (32.1)	1		1	
Sex						
Male	13 (46.4)	15 (53.6)	1		1	
Female	296 (74.4)	102 (25.6)	3.35 (1.54, 7.28)	.002	3.46 (1.50, 7.98)	.004
Residence						.001
Rural	224 (76.7)	68 (23.3)	1.89 (1.22, 2.96)	.005	2.37 (1.45, 3.86)	
Urban	85 (63.4)	49 (36.6)	1		1	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: AOR = adjusted odd ratio; CI = confidence interval; COR = crude odd ratio.
[a]Hypertension, diabetes mellitus, tuberculosis, asthma, cardiovascular disease.

- Further research to understand barriers to care in distant facilities mainly in rural areas is needed to design effective interventions.

Disclosure

The authors have stated that they have no conflict of interest.

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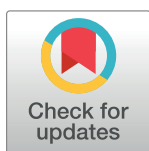
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Perceived barriers to timely treatment initiation and social support status among women with breast cancer in Ethiopia

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Abstract

Timely care is essential to increase breast cancer survival. However, patients in Ethiopia still face multilevel barriers on their pathway to timely treatment initiation. This cross-sectional study at Tikur Anbessa Specialized Hospital Oncology Unit in Addis Ababa assessed systemic treatment initiation intervals of breast cancer patients and quantified the impact of socio-demographic and clinical factors, perceived barriers, and the patients´ perceived social support status on timely systemic treatment initiation (chemotherapy or hormonal therapy). A structured questionnaire was designed based on Pechansky´s "Concept of Access". Applying simple and multivariate logistic regression we analysed the influence of patients´ characteristics as well as their perceived barriers on timely treatment initiation. We measured social support with the Multidimensional Score of Perceived Social Support (MSPSS) and used the Wilcoxon Rank-Sum Test to assess its relationship with timely treatment initiation. Of 196 patients included into the study, 53% received systemic treatment within 90 days of their pathological diagnosis–the median treatment initiation interval was 85 days (IQR 123.5). Older women and patients diagnosed at late stages had higher odds of timely treatment initiation. Not being able to pay for services and lack of transport were most often perceived as barriers towards timely care. However, none of the perceived barriers showed a substantial influence on timely treatment initiation in the multivariate regression model. The patients´ perceived social support was found to be high, with an average MSPSS score of 73 out of 84 (SD 13,63). No impact of the perceived social support status on timely treatment initiation was found. The percentage of breast cancer patients waiting longer than 90 days from pathological diagnosis to systemic treatment initiation in Ethiopia remains unacceptably high. While women generally feel well supported by their social environment, costs and accessibility of treatment are perceived to be major barriers towards timely treatment initiation.

Introduction

Breast cancer is the most frequent cancer in women in Sub-Saharan Africa (SSA) [1] and is becoming a major health burden, as life expectancy, reproductive patterns and lifestyles are changing [2]. In Ethiopia, breast cancer is currently estimated to make up for 33% of all new cancer cases in women and 17% of all cancer deaths [1].

Survival rates differ significantly between low- or middle-income and high-income countries [3]. This has been largely attributed to late stages at diagnosis and extended intervals until treatment initiation in countries with high cancer mortality [3].

Social support is one factor which has been particularly emphasised to influence the women´s pathways throughout the disease. In the US, studies found a two-fold increased risk of mortality from breast cancer for women with low levels of social integration and lower odds of treatment initiation for socially isolated women [4, 5].

Research on cancer patient pathways in low- and middle-income countries has been focusing on the intervals between first symptom appraisal and diagnosis [6]. Even though time between diagnosis and treatment initiation has been equally established to influence the outcome of breast cancer therapy [7], there is a paucity of studies reporting on reasons for delay in treatment initiation in low- and middle income countries [6, 8]. Additionally, the patients´ own perception of barriers as well as the role of social support within the cancer care continuum have been mainly addressed on an exploratory level [9–11].

In this study we determined systemic treatment initiation intervals of breast cancer patients at a tertiary referral hospital in Ethiopia and assessed the impact of socio-demographic and clinical factors, as well as patients´ perceived barriers and their perceived social support status on timely treatment initiation.

Methods

Study design and setting

This cross-sectional study was conducted between March and May 2018 at the Oncology Unit of Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia. The hospital serves as a third-level governmental referral hospital and is the only hospital in the country offering fully comprehensive cancer treatment. Applying the "Model of Pathways to Treatment", we defined the treatment initiation interval as the period between pathological diagnosis and the begin of systemic treatment (chemotherapy or hormonal therapy) [12].

The primary outcome of the study was timely systemic treatment initiation, which we defined as ≤ 90 days between pathological diagnosis and systemic treatment initiation. In the absence of official guidelines, this cut-off value was chosen based on similar studies in comparable settings [13, 14]. Patients receiving radiotherapy were not included into the study, as, with only one radiotherapy machine in the country, the number of breast cancer patients being treated with radiation within the study period was judged to be too small to receive reliable results.

Population, sample, and data collection

The study constituted pathologically diagnosed breast cancer patients who were on systemic treatment or follow-up care and 18 years or older at time of data collection. Patients who were critically sick and unable to communicate were excluded. To compensate for large outliers, we also excluded patients whose treatment initiation intervals could not be determined or whose treatment initiation interval was longer than two years.

Simple random sampling was used to identify study participants; in advance of each day of data collection 70% of all patients appointed for treatment or follow-up were randomly

selected to participate in the study. Women were interviewed face-to-face by trained oncology nurses before their appointments at the oncology unit. A structured questionnaire was prepared in cooperation with a senior oncologist in easily understandable local language (Amharic), pretested by the principal investigator on 10% of the original sample size (n = 32) and adapted accordingly to assure understandability (S1 Questionnaire). Questions addressing perceived barriers to timely treatment initiation were designed according to the "Concept of Access" by Pechansky and Thomas. [15]. In this model access is defined to summarize five specific "dimensions of fit" between patients and the health system: Availability, accessibility, accommodation, affordability, and acceptability. The first four dimensions can be summarised by Walter´s *healthcare providers and system factors*, whereas *acceptability* mainly describes *patient factors*, such as social environment, culture, and previous experiences. Clinical data generated through interviews were triangulated with data from patient charts where possible.

The 12-item Multidimensional Scale of Perceived Social Support (MSPSS) was used to measure the perceived social support of patients. The tool was designed and validated to evaluate the adequacy of social support received from family, friends and significant other persons [16]. Four questions each cover one of the three items and are later summed up to build the score. A seven-point Likert scale enables patients to choose between 1 (= very strongly disagree) and 7 (= very strongly agree).

Data analysis

Data was entered into EpiData and transferred to R Version 4.0.3 for analysis. Descriptive analysis was applied to calculate treatment initiation intervals, the patients´ perception of barriers to timely treatment as well as social support. Because of large outliers, median and interquartile range (IQR) were used to describe intervals. For patients, whose method and date of diagnosis were unknown, we assumed date of surgery to be date of pathological diagnosis.

Socio-demographic and medical factors influencing timely treatment initiation were modelled using simple and multivariate logistic regression. A separate model was applied to assess the influence of perceived barriers, which was adjusted for age and stage. Crude odds ratios (COR) and adjusted odds ratios (AOR) are presented with 95% confidence intervals.

The Wilcoxon rank-sum test was performed to analyse the relationship between the treatment initiation interval and social support. This non-parametric test was chosen, as the assumption of normality was not fulfilled.

Ethical considerations

Ethical clearance was obtained from the Ethical Review Committee at the School of Public Health of Addis Ababa University. Written informed consent was obtained from all participants in advance of the interview.

Results

From 302 patients, 106 patients were excluded from analysis due to missing dates of diagnosis or treatment. Of the 196 women included into the study, most were diagnosed at stage II or III (Table 1).

Use of alternative medicine (traditional or spiritual healers) between diagnosis and systemic treatment initiation was reported by 34% of all patients.

The median treatment initiation interval in the study cohort was 85 days (IQR 123.5) (Table 2).

Based on the cut-off value of 90 days, 53% of the patients received systemic treatment in time, while 47% received treatment later than 90 days after their diagnosis.

Table 1. Socio-demographic and clinical characteristics of study cohort.

Variable	Frequency	Percentage (%)
Number of patients	196	100
Age[a] (in years)		
≤ 45	114	58.2
> 45	58	29.6
Unknown	24	12.2
Residence		
In town	106	54.1
Out of town	84	42.9
Unknown	6	3.1
Marital status		
Married	113	57.7
Not married	83	42.3
Education		
Primary school or lower	58	29.6
Secondary school or higher	88	44.9
Unknown	50	25.5
Stage		
I	29	14.8
II	64	32.7
III	67	34.2
IV	28	14.3
Unknown	8	4.1
Use of alternative treatment[b]		
Yes	66	33.7
No	129	65.8
Unknown	1	0.5

[a] 45 years cut-off was chosen as this is commonly judged the median age of menopause in this population.

[b] Alternative treatment includes visits at traditional or spiritual healers.

In the regression models, women older than 45 years had higher odds of timely treatment initiation (COR 1.47 and AOR 3.18) than younger patients (Table 3).

Stage was also associated with timely treatment initiation–in the multivariate model women diagnosed with stages II, III or IV had 3.5 to 4.5 times the odds to initiate treatment in time compared with patients diagnosed at stage I.

Patients´ perceived barriers towards timely treatment initiation were grouped into four items based on the *Concept of Access to Care* (Table 4).

Affordability and *accessibility* were perceived as most important barriers: 66% of all patients considered not being able to pay for the service had been a barrier towards timely care, and 54% perceived lack of transport as a barrier. Concerning *accommodation and acceptability*, long waiting times were perceived by 48% of all women as an important barrier, while 38% reported to have been hindered by their fear of the treatment´s side effects.

In the multivariate regression, patients who had not perceived lack of transport and long waiting times as barriers had higher odds of timely treatment initiation (AOR 2.08 and 1.31)– however those findings were not significant on a 5% significance level (p-values 0.09 and 0.54).

The patients´ scores in the Multidimensional Score of Perceived Social Support were found to be high, with an average total score of 73 out of 84 (SD 13,63) (Table 5).

Table 2. Systemic treatment initiation interval by treatment and type of administration.

	n (%)	Median (IQR)	Range
All patients	196 (100)	85 (123.5)	1–726
Timely	104 (53.1)	32.5 (43.2)	1–90
Not timely	92 (46.9)	158.5 (170)	91–726
Type of treatment			
Chemotherapy	169 (86.2)	85 (112)	1–697
Hormonal therapy	21 (10.7)	85 (310)	1–726
Unknown [a]	6 (3.1)	65.5 (73.2)	12–110
Type of treatment administration			
Adjuvant	145 (74)	85 (108)	1–697
Neoadjuvant	35 (17.9)	80 (159.5)	1–726
Without surgery[b]	9 (4.6)	32 (112)	8–184
Unknown	7 (3.6)	160 (420.5)	8–539

IQR interquartile range

[a] Unknown due to contradicting information between patients´ charts and questionnaire data.

[b] Palliative intent.

https://doi.org/10.1371/journal.pone.0257163.t002

Table 3. Simple and multivariate logistic regression for factors associated with timely systemic treatment initiation ($\leq$ 90 days since pathological diagnosis) of breast cancer patients.

Characteristic	All	Timely (%)	COR (CI)	p[a]	AOR (CI)	p[b]
Age (years)						
$\leq$45	114	58 (50.9)	Reference			
>45	58	35 (60.3)	1.47 (0.77–2.79)	0.24	3.18 (1.2–8.38)	0.02
Stage						
I	29	8 (27.6)	Reference			
II	64	37 (57.8)	3.6 (1.39–9.33)	0.01	4.5 (1.29–15.72)	0.02
III	67	39 (58.2)	3.66 (1.42–9.44)	0.01	3.62 (1.03–12.77)	0.05
IV	28	16 (57.1)	3.5 (1.16–10.58)	0.03	3.52 (0.79–15.68)	0.1
Residence						
Out of town	84	41 (48.8)	Reference			
In town	106	60 (56.6)	1.37 (0.77–2.43)	0.29	1.07 (0.48–2.43)	0.86
Marital status						
Not married	83	40 (48.2)	Reference			
Married	113	64 (56.6)	1.4 (0.79–2.48)	0.24	1.08 (0.49–2.4)	0.85
Education level						
Secondary or higher	88	47 (53.4)	Reference			
Primary or lower	58	35 (60.3)	1.33 (0.68–2.6)	0.41	1.1 (0.48–2.49)	0.82
Use of alternative treatment[c]						
Yes	129	65 (50.4)	Reference			
No	66	38 (57.6)	1.34 (0.73–2.43)	0.34	1.59 (0.7–3.59)	0.26

COR crude odds ratio, *CI* confidence interval, *AOR* adjusted odds ratio, *p* p-value

[a] P-value for simple regression models.

[b] P-value for multivariate regression model.

[c] Alternative treatment includes visits at traditional or spiritual healers.

https://doi.org/10.1371/journal.pone.0257163.t003

Table 4. Simple and multivariate regression modell of the influence of patients´ perceived barriers on timely systemic treatment initiation for breast cancer patients.

	Total (%[a])	Timely (%[b])	COR (CI)	p[c]	AOR[d] (CI)	p[e]
AFFORDABILITY						
Lack of money						
Important	130 (66.3)	63 (48.5)	Reference			
Not important	64 (32.6)	39 (60.9)	1.66 (0.9–3.05)	0.1	1.12 (0.47–2.67)	0.79
ACCESSIBILITY						
Lack of transport						
Important	106 (54.1)	51 (48.1)	Reference			
Not important	86 (43.9)	52 (60.5)	1.65 (0.93–2.93)	0.09	2.08 (0.88–4.91)	0.09
ACCOMMODATION						
Long waiting times						
Important	94 (48.0)	43 (45.7)	Reference			
Not important	99 (50.5)	60 (60.6)	1.82 (1.03–3.23)	0.04	1.31 (0.56–3.05)	0.54
Nobody to look after children						
Important	50 (25.5)	26 (52)	Reference			
Not important	141 (71.9)	75 (53.2)	1.05 (0.55–2)	0.88	0.81 (0.29–2.24)	0.68
Lack of time						
Important	38 (19.4)	22 (57.9)	Reference		Reference	
Not important	155 (79.1)	81 (52.3)	0.8 (0.39–1.63)	0.53	0.38 (0.11–1.24)	0.11
ACCEPTABILITY						
Fear of side effects						
Important	74 (37.8)	36 (48.6)	Reference			
Not important	120 (61.2)	67 (55.8)	1.33 (0.75–2.39)	0.33	1.02 (0.44–2.39)	0.96
Wanted to handle it by oneself						
Important	59 (30.1)	34 (57.6)	Reference			
Not important	132 (67.3)	66 (50)	0.74 (0.4–1.37)	0.33	0.9 (0.36–2.24)	0.82
Embarrassment						
Important	57 (29.1)	25 (43.9)	Reference			
Not important	138 (70.4)	78 (56.5)	1.66 (0.89–3.1)	0.11	2.04 (0.84–4.98)	0.12
Hope for disease to disappear by itself						
Important	56 (28.6)	28 (50)	Reference			
Not important	135 (68.9)	71 (52.6)	1.11 (0.59–2.07)	0.74	1.07 (0.41–2.79)	0.9
Bad experiences with past treatment						
Important	38 (19.4)	20 (52.6)	Reference			
Not important	155 (79.1)	82 (52.9)	1.01 (0.5–2.06)	0.98	0.85 (0.29–2.55)	0.77

COR crude odds ratio, *CI* confidence interval, *AOR* adjusted odds ratio, *p* p-value

[a] Percentages in relation to total number of patients (n = 196). Missing answers excluded.

[b] Row wise percentages.

[c] P-value for simple regression models.

[d] Additionally adjusted for age and stage.

[e] P-value for multivariate regression model.

https://doi.org/10.1371/journal.pone.0257163.t004

Average scoring for support by the family and a significant other person was 25 of 28, and social support by friends slightly lower with a mean score of 22. There was no substantial difference in average scores between patients with timely treatment initiation and those with a treatment initiation interval longer than 90 days.

Table 5. Multidimensional Score of Perceived Social Support (MSPSS) of breast cancer patients.

	Family	Friends	Significant other	Total
MSPSS max. score	28	28	28	84
Mean (SD)	25 (4.42)	22 (6.37)	25 (5.59)	73 (13.63)
Median (IQR)	27 (4)	25 (9)	27 (4)	76 (13)
p-value[a]	0.35	0.64	0.35	0.51

[a] Wilcoxon rank-sum test

https://doi.org/10.1371/journal.pone.0257163.t005

Discussion

In this retrospective Ethiopian breast cancer cohort, we found almost half of all patients to receive systemic treatment later than 90 days after their pathological diagnosis and quantified the importance of affordability and accessibility of systemic treatment in the perception of patients. Women with breast cancer at Tikur Anbessa Specialized Hospital Oncology Unit felt highly supported by their social environment, however we could not find an association between social support and timely treatment initiation. As common in countries in SSA, patients were predominantly diagnosed at young age and late cancer stages [3]. However, with 47.5% of the patients being diagnosed at stage I and II, a shift towards earlier stages at diagnosis was visible in comparison with a study from the same hospital in 2011 [17]. As there is still no regular screening for breast cancer available in Ethiopia, this dynamic might point towards higher awareness of breast cancer and improved access to diagnosis and care today compared with 2011. Rates of patients receiving surgery as well as the systemic treatment patterns observed in this study were in coherence with previous data from Addis Ababa [17].

In its "Guide to Cancer Early Diagnosis" the World Health Organization calls for a maximum of 90 days between symptom onset and treatment initiation [18]. The median of 85 days between diagnosis and systemic treatment initiation in our study (which does not include time from symptom onset until pathological diagnosis) shows that the WHO´s standard does not mirror reality for most breast cancer patients in Ethiopia. This observation has been reported by multiple studies from SSA [19]. A study based on the Addis Ababa Cancer Registry analysed treatment initiation intervals for all cancer entities and found a median time to therapy of 2.1 months [20]. However, this interval was measured from date of therapy planning until treatment initiation, which does not include time between diagnosis and planning of systemic therapy. In a comparable referral hospital in Botswana a median treatment initiation interval of 91 days was found [14].

The influence of age on treatment initiation has been discussed controversially in literature [8, 14]. A multi-centre prospective study on treatment initiation of breast cancer patients in Namibia, Nigeria and Uganda found women below 40 years having the lowest odds of initiating treatment within one year of diagnosis [21]. This observation supports the results from our study and might be explained by a less stable financial situation of younger women as well as larger responsibilities at home, with children and at work. However, our study did not collect adequate data to support or contradict this explanation.

Our observation that diagnosis at higher stages might be positively associated with timely treatment initiation is in line with findings from a cross-sectional study on pathways of breast cancer patients in South-Africa [11]. Patients with small tumours might be less aware of the seriousness of the disease; however, as breast cancer patients treated at early stages have considerably better outcomes than when treated in later stages [3], this finding is disconcerting. The inverse correlation of early stage with timely treatment initiation needs to be further

investigated and awareness must be raised among medical personnel to assure timeliness for these patients. Currently, there is no triage system in place for cancer patients.

Most patients perceived affordability and accessibility of care as most important barriers. While we could not find a correlation between perceived barriers and timely treatment initiation, the findings show the strong influence of the socio-economic status on timely treatment initiation in countries where treatment-costs are being paid out-of-pocket [21]. Even though patients without financial resources can get free treatment in government hospitals in Ethiopia, the bureaucratic hurdles to receive the so-called "poor papers" (proofing eligibility for free treatment), as well as the indirect costs linked to cancer treatment, still seem to hinder patients when aiming to receive treatment.

The steep increase in patient volumes at Tikur Anbessa Specialized Hospital over the last years [22] might be another reason why we found nearly half of all patients receiving systemic treatment more than three months after diagnosis. Long waiting times were considered a barrier towards timely treatment initiation by 48% of all patients, a finding which reinforces the government´s efforts to increase workforce and technical capacities by establishing multiple peripheral cancer centres within its Health Sector Transformation Plan.

Interestingly, factors concerning *acceptability* were generally perceived as less of a barrier. Although, every third women reported having tried alternative treatment in the course of her disease, patients' sentiments towards conventional medicine seemed generally positive.

The high level of social support patients reported in this study is consistent with another study from Ethiopia [23]. Women with breast cancer in Ethiopia have been found to have good social networks [24], which are possibly cushioning the negative impact of the disease and its treatment. This consistent high support might be an explanation, why our study could not find any correlation between the patient's social support status and their treatment initiation intervals. Notably, studies observing a quantifiable link between social support and delayed treatment initiation are exclusively from high-income-countries, such as the United States [4, 5], where health-system mediated barriers towards timely treatment are comparably smaller and social networks possibly weaker.

Strengths and limitations

The question how to improve access to cancer treatment in resource-limited countries is complex and much debated in public health sciences. We consider it a strength of this study to have captured different aspects of this challenge within one breast cancer study cohort.

However, we had to exclude almost one-third of all patients from analysis due to missing data. This means the sample may not fully reflect the variety of patients´ situations. As the study is hospital-based and retrospective, it also allows for some bias of selection as well as recollection.

In addition, our data does not allow us to distinguish between a "patient interval" (delay in treatment due to the patient not making an appointment) and a "health care provider interval" (delay in treatment due to waiting times). This limits the study´s ability to draw conclusions on reasons for the delay in treatment initiation.

Conclusion

In the last decade, policy makers, non-governmental organisations, and health researchers in Ethiopia have increased their attention on cancer, amounting in the publication of the first National Cancer Control Plan in 2015. The urgency to expand cancer care capacities is underlined by our finding that nearly half of all breast cancer patients received systemic treatment later than three months after diagnosis. Reasons why young patients and early stage tumors

are associated with delayed systemic treatment initiation clearly need further assessment to support these important patient groups.

Affordability and access to systemic cancer treatment were perceived as major barriers towards timely treatment initiation despite not being associated with actual delay. This reveals a dilemma faced by many healthcare systems in low- and middle-income countries that have to distribute financial resources between competing priorities. Since systemic cancer therapy is costly, international initiatives such as the World Health Organisation suggest joining forces to reduce the financial burden for these countries. The high-perceived level of social support underlines a great strength of the Ethiopian society which cannot be highlighted enough and sets an example for others.

Supporting information

S1 Dataset.
(XLSX)

S1 Questionnaire.
(PDF)

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Adherence to Newly Implemented Tamoxifen Therapy for Breast Cancer Patients in Rural Western Ethiopia

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Abstract

Introduction: Endocrine therapy for breast cancer (BC) patients is highly underutilized in rural Ethiopia and other African countries. ***Objective:*** This study aims to assess the feasibility of and adherence to tamoxifen therapy in rural Ethiopia. ***Methods:*** We ascertained the hormone receptor (HR) status in 101 women diagnosed with BC from January 2010 to December 2015 and who had surgery in Aira Hospital, in rural Ethiopia. From 2013, tamoxifen was offered to patients with HR-positive (HR+) tumors. Prescription refill records and a structured questionnaire were used to assess receipt of and adherence to tamoxifen. ***Results:*** Of the 101 BC patients tested for HR status during the study period, 66 (65%) patients were HR+ and were eligible for tamoxifen treatment. However, 15 of the HR+ patients died before tamoxifen became available in 2013. Of the remaining 51 HR+ patients, 26 (51%) initiated tamoxifen but only 9 of them (35%) adhered to therapy (medication possession rate ≥80%, me-

dian observation 16.2 months). After 1 year, 52% of the patients were still adherent, and 9 patients had discontinued therapy. The reasons for non-initiation of tamoxifen included patient factors ($n = 5$), including financial hardship or lack of transportation, and health care provider factors ($n = 12$). ***Conclusions:*** Endocrine therapy for BC patients seems feasible in rural Western Ethiopia, although non-adherence due to financial hardship and a less developed health care infrastructure remains a major challenge. We postulate that the implementation of breast nurses could reduce patient and health system barriers and improve initiation of and adherence to endocrine treatment.

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Published by S. Karger AG, Basel

Introduction

Breast cancer (BC) is the most common cancer and leading cause of cancer death in sub-Saharan Africa [1, 2], including in Ethiopia, where the estimated incidence in 2018 was 15,244 [3, 4]. The estimated 2-year survival rate in a rural hospital in Western Ethiopia was only 53% [5] compared to 5-year survival rates of >81% in Europe [6].

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Fig. 1. Patients eligible for analysis from those enrolled in our study over the period January 26, 2010 to December 31, 2015. Tamoxifen treatment was initiated on March 18, 2013 and the adherence assessment period was March 18, 2013 to December 31, 2015. HR, hormone receptor; TAM, tamoxifen.
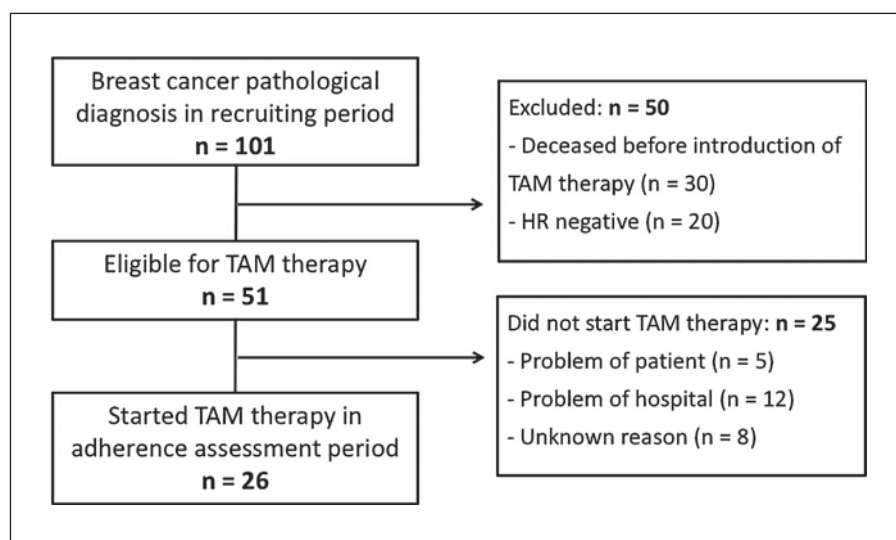
Reasons for these disparities in outcome include differences in stage at first presentation [7], availability of therapy [8], and underlying levels of investment in health care [9]. Like in many sub-Saharan African countries, only basic surgical treatment services are available at regional hospitals in Ethiopia [10]. Hospitals offering adjuvant systemic therapy and the only radiotherapy center are located in urban Addis Ababa. The majority of patients with BC face serious challenges in accessing these facilities [11] since 80% of the Ethiopian population reside in rural areas [12].

Tamoxifen is an effective treatment option for patients with hormone receptor-positive (HR+) and unknown receptor status BC [13, 14]. It is easy to administer (oral), inexpensive, and has few serious side effects [15, 16]. In women with HR+ non-metastatic BC, the absolute reduction in the risk of recurrence after 15 years with 20 mg of tamoxifen daily over 5 years is 13.2%, and the reduction in the mortality rate is 9.2% [17]. Although the majority (65%) of BC patients in Ethiopia are HR+ [18] and tamoxifen is on the essential drug list of Ethiopia [19], it is not widely used in rural Western Ethiopia.

The Breast Cancer Initiative 2.5 developed resource-stratified guidelines for BC control in sub-Saharan Africa [20]. In line with these guidelines the National Cancer Control Plan (NCCP) of Ethiopia aims to "strengthen cancer control capacities," including de-centralization of oncology care [21].

In this pilot project, funded by the German Gynecologic Oncology Working Group (AGO), Aira Hospital in rural Western Ethiopia offered pathology workup including immunohistochemistry for the detection of HR expression and provision of tamoxifen treatment. Extreme poverty in addition to a high rate of illiteracy are thought to pose significant challenges for women to adhere to long-term tamoxifen treatment.

Materials and Methods

Study Design

This is an explorative, prospective, hospital-based cohort study to assess the feasibility of administering tamoxifen to patients with BC in rural Western Ethiopia. Feasibility was investigated by focusing on the adherence to therapy, defined as "the extent to which a person's behavior – taking medication [...] corresponds with agreed recommendations from a health care provider" [22].

Setting

Ethiopia has a three-tier health care system, with 1st regional Primary Health Care Units, 2nd General Regional Hospitals in zones, and 3rd Specialized Referral Hospitals. Aira Hospital in Oromia State, Western Wollega District, officially provides primary health care to 68,000 people, but unofficially serves 500,000 inhabitants due to the presence of a specialist surgeon.

The international collaboration between Aira Hospital and the Department of Gynecology, Martin Luther University (MLU) Halle-Wittenberg, Germany began in 2010. In March 2013, free endocrine treatment with tamoxifen (20 mg/day) was provided for BC patients. Patients received tamoxifen in packages containing 30 tablets each, usually three packages (range 1–4).

Participants

All BC patients operated at Aira Hospital between January 2010 and December 2015 were included (n = 101), 66 (65%) were HR+ or receptor status unknown. Of these, 15 had passed away before the initiation of treatment and 51 were eligible for tamoxifen therapy (Fig. 1). C.F.R. and a local nurse visited all HR+ BC patients in their homes in February 2016.

Data Sources/Measurement

A questionnaire obtained clinical, social, and reproductive factors. A structured interview including open questions assessed: (i) difficulties in the provision of the medication, (ii) patients' perception about the beneficial effects, and (iii) reasons for adherence or non-adherence. The questionnaire was developed by a panel of experts (W.T., C.T., E.J.K., S.U., C.F.R.) based on the MARS (Medication Adherence Rating Scale) questionnaire and considering the sociocultural context, comments from local health workers, and previous experiences [5].

The questionnaire was translated from English into local Oromifa then proofread and revised. A local nurse with experience in qualitative research read the questions to the patients and they answered in their local language. Patient perception was only assessed for a total of 22 patients alive. Computer-based prescription refill records were also used to assess implementation, initiation, and treatment persistence (adherence). Clinical and pathological information was obtained from the patient files.

Definitions

Adherence is defined by initiation, implementation, and discontinuation [23]. Initiation is the date of the first handover of tamoxifen. Implementation equates to the medication possession ratio (MPR), which describes the patient's medication intake compared to the prescribed drug dosing regimen [24]. An MPR of ≥80% was defined as an acceptable adherence [25]. Discontinuation occurred when the patient stopped taking tamoxifen and did not present for a refill. In this study, discontinuation was defined as a refill gap of more than 6 months [26]. Adherence was defined as the length of time between initiation and last dose before discontinuation. Descriptive statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Of the study population of 101 patients, due to predefined criteria, a total of 51 patients were eligible for tamoxifen therapy. Table 1 shows characteristics of eligible women. The mean age at diagnosis was 45 years (IQR 35–51). Almost 80% were residents outside Aira. Most women were illiterate (77%). The mean walking time to the next health center (nurse available) was about 1.1 h (range 0.1–3) and travel to Aira hospital (physicians available) required 6.1 h (range 0.1–24). At the time of diagnosis, the vast majority of the patients had stage 2 or 3 disease ($n = 30/33$; 91%). One third ($n = 15/44$; 34%) underwent modified radical mastectomy; due to lack of consent, lumpectomy ($n = 7$; 16%) and quadrantectomy ($n = 6$; 14%) were also performed. Of 51 patients eligible for tamoxifen therapy, 25 (49%) did not initiate endocrine treatment. The reasons for non-initiation included problems on the health care provider side (12; 48%) where patients had not been given an appointment ($n = 9$), the physician was absent ($n = 2$), and other ($n = 1$). Reasons on the patient side (13; 52%) included lack of money ($n = 2$), too weak to travel ($n = 1$), fear of treatment ($n = 1$), and private reasons ($n = 1$). No information was available for 8 patients. One patient explained: "I went to the hospital, and the surgeon was not at the hospital, or maybe didn't know about my presence."

During the observed March 2013 to December 2015 treatment adherence assessment period, of the 26 patients who initiated tamoxifen therapy (Fig. 1), 9 discontinued treatment (Table 2). One patient recounted, "I took two tablets a day and then waited for the appointment," although she had already finished her medication. Another

Table 1. Patient characteristics ($n = 51$)

Age at diagnosis, years	45 [35–51]
Number of children	4 (0–11)
Walking time to health center, h	1.1 (0.1–3)
Travel time to hospital, h	6.1 (0.1–24)
Age group	
<35 years	11 (22)
35–50 years	25 (49)
>50 years	15 (29)
Premenopausal	24 (47)
Postmenopausal	27 (53)
Place of residence ($n = 48$)	
Rural	38 (79)
Urban	10 (21)
Religion ($n = 48$)	
Christian	38 (79)
Muslim	9 (19)
Other	1 (2)
Literate ($n = 38$)	
No	31 (77)
Yes	9 (23)
Profession ($n = 49$)	
Housewife	28 (57)
Farmer	17 (35)
Student	1 (2)
Other	3 (6)
Marital status ($n = 41$)	
Married	38 (93)
Not married	3 (7)
Survival status	
Deceased	21 (46)
Alive	21 (35)
Unknown	9 (18)
AJCC stage ($n = 33$)	
1	2 (6)
2	10 (30)
3	20 (61)
4	1 (3)
Clinical tumor size ($n = 38$)	
T1	3 (6)
T2	22 (46)
T3	18 (38)
T4	5 (10)
Pathological diagnosis	
NST	47 (92)
Other	4 (8)
Grading	
Grade 1	3 (6)
Grade 2	14 (27)
Grade 3	34 (67)
HR status	
ER+PgR+	28 (55)
ER+PgR–	9 (18)
ER–PgR+	12 (23)
Unknown	2 (4)
HER2	
Negative (0 to 2+)	39 (76)
Positive (3+)	10 (20)
Unknown	2 (4)
Ki-67	
Negative (<14%)	16 (31)
Positive	33 (65)
Unknown	2 (4)
Surgical treatment ($n = 44$)	
Modified radical mastectomy	15 (34)
Simple mastectomy	4 (9)
Radical mastectomy	1 (2)
Lumpectomy[1]	7 (16)
Quadrantectomy[1]	6 (14)
Mastectomy (not specified)	11 (25)

Data are presented as the mean [IQR], mean (range), or n (%). AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PgR, progesterone receptor; NST, non-specific type of BC.
[1] No irradiation in breast-conserving therapy.

Table 2. Patient perception of tamoxifen

Symptom duration, months	22.4 (6–24)
Time to treatment of those patients operated in the adherence assessment period, months	5.7 (0.1–10.8)

Questionnaire	
What is the most important medical problem for women in this area? (n = 22)	
"No idea"	14 (64)
Back pain	3 (14)
Cervical cancer	3 (14)
Mastitis	1 (4)
Gastritis	1 (4)
What is cancer? (n = 22)	
"No idea"	11 (50)
Disease	5 (23)
Deadly disease	6 (27)
Do you have cancer? (n = 20)	
No	10 (50)
Yes	10 (50)
Is tamoxifen necessary? (n = 19)	
No	0 (0)
Yes	19 (100)
Would you pay for tamoxifen? (n = 14)	
No	11 (79)
Yes	3 (21)
Wherefore do you take tamoxifen? (n = 17)	
"No idea"	6 (35)
Prevents cancer	9 (53)
Is helpful	1 (6)
Minders the power of cancer	1 (6)
Why did you stop taking tamoxifen? (n = 9)	
Terminal illness	2 (22)
Difficult circumstances	2 (22)
Lack of money	2 (22)
Side effects of therapy	2 (22)
Unknown	1 (11)
Describe complaints on your health (n = 20; more than one answer possible)	
None	14 (41)
Nausea	3 (9)
Hot flushes	3 (9)
Sweating	6 (18)
Vaginal discharge	1 (3)
Diarrhea	1 (3)
Changes in mood	2 (5)
Other	4 (12)
Describe discomforts with the taking of tamoxifen (n = 21; more than one answer possible)	
"No problems"	14 (59)
Difficult to swallow	7 (29)
Interrupts daily work	2 (8)
Reminds of the disease	1 (4)

Data are presented as the mean (IQR) or number of answering patients (%). n = 22 of 26 who initiated tamoxifen; families of 3 deceased patients were not found, and 1 husband was unable to answer the questionnaire

woman said, "I missed one appointment because my child was sick and I was afraid of presenting too late." One woman described tamoxifen as "hard medicine" causing epigastric burning and vomiting. Another shared she "had to borrow money from neighbors for traveling."

Figure 2 provides the patients' refill and possession data for tamoxifen with a resolution of 10 days for the 26 patients who initiated tamoxifen treatment. All except 2 patients had at least one refill delay of 10 days. Of the women who received surgery and initiated adjuvant tamoxifen, most (7; 58%) of the 12 patients experienced a long delay from the time of operation to the initiation of tamoxifen (median 5.7 months; IQR 0.1–10.8).

The mean MPR was 54% (IQR 28–89). During a median observation time of 16.2 months (range 1–35.7), 17 patients (65.4%) took less than 80% of the prescribed dose and were declared non-adherent, while 9 patients (34.6%) were adherent to therapy. After 1 year the Kaplan-Meier estimated proportion of persistence to therapy was 52%; 6 patients took tamoxifen for more than 1 year (Fig. 3).

Table 2 shows the results of open questions on the patient self-reported perception of health and treatment. The mean time between the first breast symptoms and the patient's presentation at the hospital was 22.4 months (IQR 6–24). Half of the patients had "no idea" what cancer is. At least a few identified cancer as a disease or as a "killer disease." Tamoxifen was considered necessary to all patients, but only 3 were willing to pay for it. Two thirds identified tamoxifen as an anti-cancer drug. For some patients, tamoxifen was difficult to swallow, interrupted daily work, or reminded them of the disease.

Discussion

About half the patients in rural Ethiopia initiated the therapy and of those, half still used the medication after 1 year. Limited data are available concerning the adherence to tamoxifen therapy in Africa. A study from Nigeria reported very high adherence rates of 75.5% after 1 year in an urban setting [27]. Data from Europe and the USA show that 90 and 74.6% of BC patients take up adjuvant endocrine therapy [28, 29]. Generally, reviews on endocrine treatment reveal a great range of adherence of between 41 and 93.4% after 1 year (including non-initiation and discontinuation) [30, 31].

Challenges on the Health Care Provider Side
According to the incidence rates of BC in Ethiopia, and a population coverage of 500,000, 488 BC patients were expected at Aira Hospital within 5 years compared to the actual cohort of 101 patients, revealing significant underutilization of the service. The non-initiation and delay of initiation of tamoxifen treatment in this study reflects common shortcomings in rural settings in sub-Saharan Africa of inadequate pathology capacity and infrastructure [32, 33] and a small number of overburdened physicians [34]. Additional staff including dedicated cancer nurses to track and navigate patients may enhance initiation and adherence and avoid ineffective discontinuation of chronic tamoxifen treatment. A step forward would be the implementation of local pathology and better referral services to increase initiation and adherence.

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Fig. 2. Summary of 3-year adherence assessments for the 26 patients who initiated tamoxifen treatment and were censored for prescription refill between March 26, 2013 and March 10, 2016. TAM, tamoxifen; Int., interrupted; OP, operation.

Fig. 3. Kaplan-Meier estimates of the duration of tamoxifen therapy. Discontinuation: no patient contact for more than 6 months, 9 events in 26 patients.

Challenges on the Patient Side

A review showed that high out-of-pocket costs are associated with poor adherence to chronic cancer treatment [30] and remain a barrier to adequate health care access [35]. A Nigerian study listed costs for the drugs, laboratory expenses, and transportation to the hospital as the most common reasons for non-adherence [36]. Although this study minimized financial efforts, they were still the main reason for discontinuation or non-initiation on the patient side. Tamoxifen has been available in Addis Ababa since 1999 in private pharmacies [37]. As most people in rural parts of Ethiopia are farmers with a low income, the average cost of living of about USD 70/month makes tamoxifen (USD 9/month) inaccessible in remote areas (personal inquiry).

Being convinced of the necessity of medication seems to be an important factor in adherence [38]. Patients who understand their disease are more likely to adhere to therapy [25, 39]. Although most patients in this study were convinced of the necessity of tamoxifen, half of the patients in this study had "no idea" what cancer is and they stopped therapy at some time. Reminders and encouragement by SMS or phone calls has improved adherence to HIV medication in South Africa [40]. Patient education and pharmacotherapeutic follow up by health professionals such as breast nurses could be helpful in improving adherence to endocrine treatment [31]. A study in Ghana suggested that women are more likely to complete treatment (71.4%) if they know a person who survived cancer [41]. Therefore, long-term survivors should be included in awareness campaigns to demonstrate the effect of continuous treatment.

Limitations

First, the sample size of our study is small. There could be selection bias since wealthy patients would be more able to access the hospital and very poor patients were probably among the estimated 80% who never arrived at the hospital. Second, the adherence (continuation after initiation) of those patients who initiated therapy and who already understood the necessity of treatment was assessed. These patients could have a better adherence than those who did not initiate any therapy. It follows that even if the adherence rate in this study was low, findings may still overestimate the adherence rate of all patients. Third, a potential bias of the qualitative data could be the suggestive character of the questionnaire and imprecise answers about adherence by relatives of deceased patients. Such an influence was minimized by performing the structured interviews in the local language with a nurse experienced in qualitative research and home visits. We have shown that most BCs in Ethiopia are HR+ [5, 42]; therefore, implementation of endocrine treatment is a promising approach in Ethiopia. The administration of endocrine ther-

apy in rural Ethiopia was implemented, but major challenges remained. Histopathological reports including diagnosis and immunohistochemical services were fully supplied from outside the system; tamoxifen was given by donation. Patient education and navigation was identified as a major shortcoming. Comprehensive interventions to improve system-wide issues in health institutions and to improve patient engagement are needed. One potential health care provider intervention is training and allocating time for breast nurses. We agree with the *Lancet* series on health, equity, and women's cancers in suggesting a persuasive opportunity for breast nurses to educate patients, administer tamoxifen, and relieve the burden of cancer patients [43]. In alignment with the NCCP, we state that treatment for cancer patients must be subsidized by government in low-income rural settings [21].

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Declaration of Independence (Selbstständigkeitserklärung):

I hereby declare that I have written this work independently and have never used any sources or tools other than those specified.

 Halle, 05/10/ 2022
Place and date   Signature

Explanation of Previous dissertation attempt (Erklärung über frühere Dissertationsversuche):

I hereby declare that this work is the first attempt of writing a dissertation. I also declare that this work is exclusively submitted as a dissertation for the Medical Faculty of the Martin Luther University Halle Wittenberg.

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Acknowledgments: