

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 patients²² 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 approach³¹ 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-up³⁹ 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 care⁴⁰ 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 Woliya 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 $\geq 80\%$ 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 $\geq 80\%$ 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 variables⁴⁴ 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

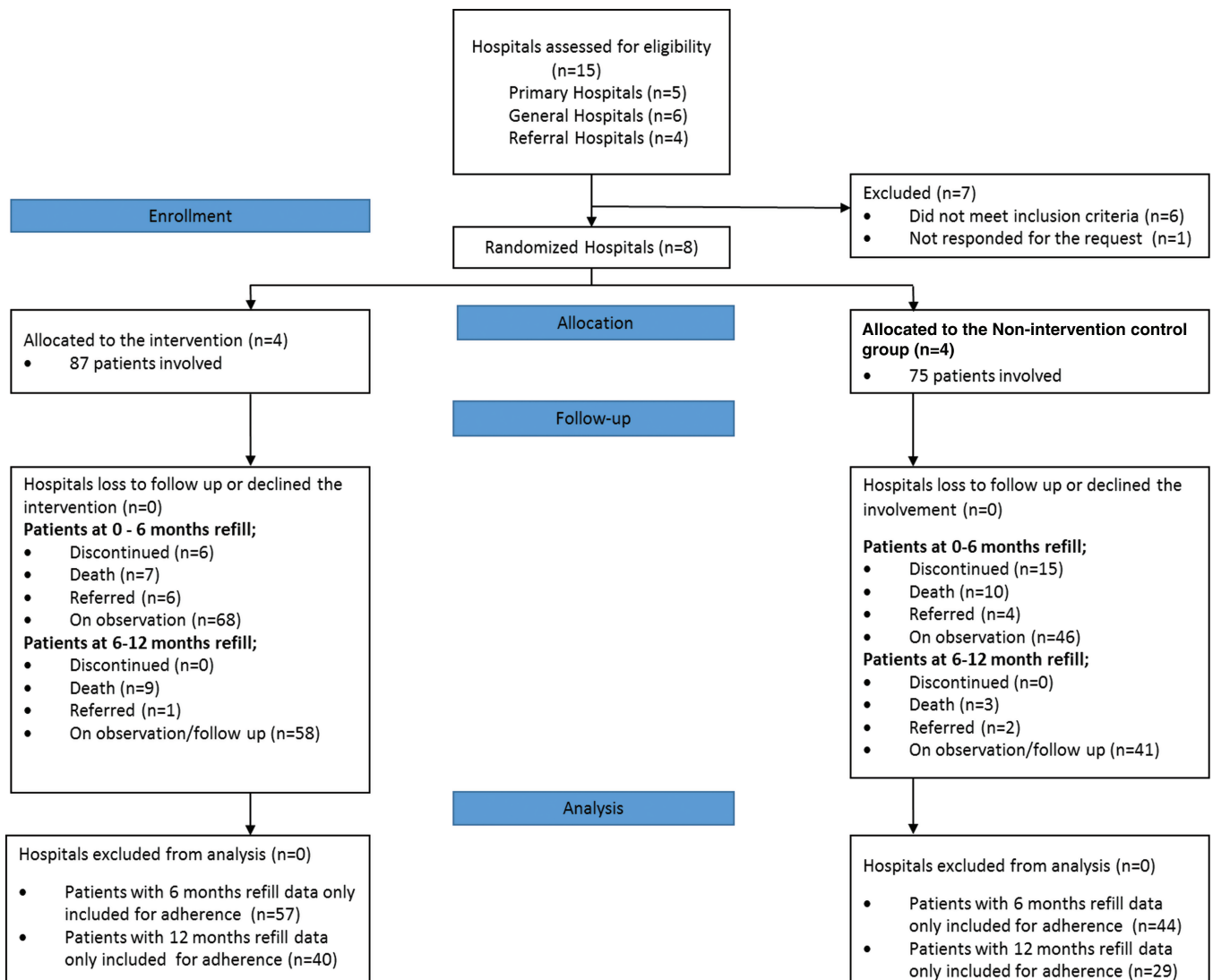


Figure 1. CONSORT flow diagram of progress through the phases of the breast nurse interventional study.

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

Characteristics	Intervention group	Control group
	(n = 87)	(n = 75)
	Frequency (%)	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	Control group
	(n = 87)	(n = 75)
	Frequency (%)	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)

^aOthers = 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		
Positive	71 (81.6)	71 (94.7)
Unknown	10 (11.5)	16 (21.3)
HER2 status		
HER2+	77 (88.5)	59 (78.7)
HER2-	4 (4.6)	3 (4.0)
Unknown	6 (6.9)	13 (17.3)
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,

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.

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 \pm 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 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	.47
II	19 (46.3)	9 (32.1)	1.93 (0.34, 10.94)	
III	16 (39.0)	13 (46.4)	0.94 (0.17, 5.18)	
IV	2 (4.9)	1 (3.6)	2.51 (0.14, 45.2)	
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)	
Do not know	8 (19.5)	10 (35.7)	1	

ET, endocrine therapy; AOR, adjusted odds ratio.

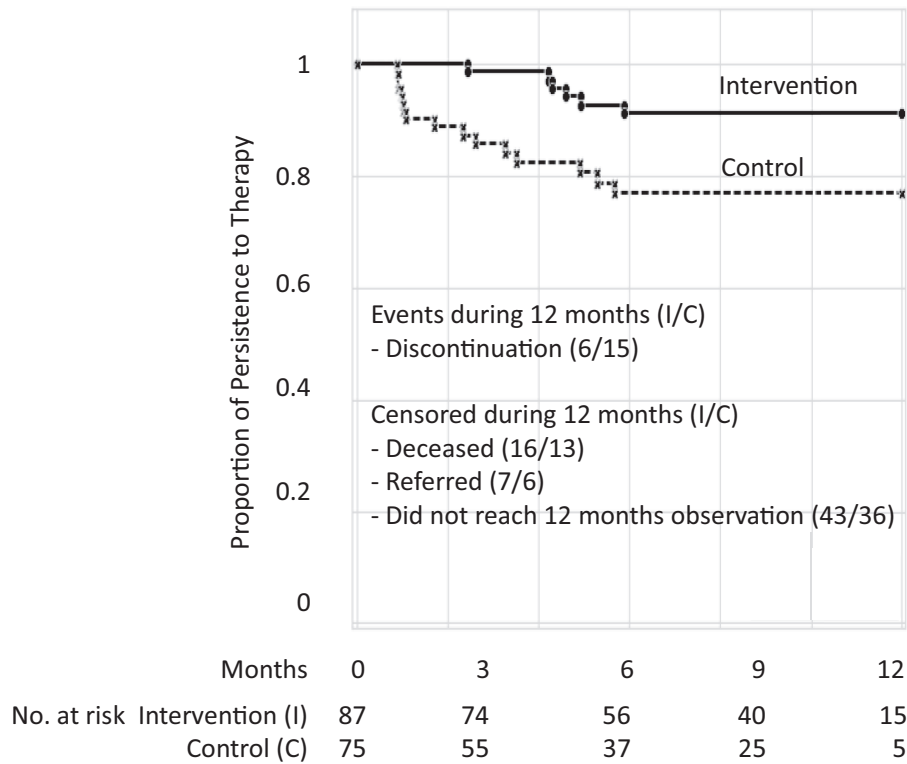


Figure 2. Kaplan-Meier survival curves with time to discontinuation of refilling (months) tamoxifen therapy among groups in a 12-month period.

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 professionals¹⁵ 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 persistence⁵²⁻⁵⁴ 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 role³⁵ 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.

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Conflict of Interest

The authors indicated no financial relationships and no conflicts of interest.

Author Contributions

Conception/design: S.G. and E.J.K. Provision of study material or patients: S.G., T.W., E.S., A.A. Collection and/or assembly of data: S.G., E.J.K., A.A. Data analysis and interpretation: S.G., E.J.K., A.A., A.W., S.U. manuscript writing: S.G., A.A., E.S., T.W., S.U., A.J., L.T., A.W., E.J.K. Final approval of manuscript: All authors.

Data Availability

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

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