ORIGINAL RESEARCH

Adherence to Adjuvant Hormonal Therapy and Associated Factors Among Women with Breast Cancer Attending the Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2019: A Cross-sectional Study

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Background: In breast cancer patients, adherence to adjuvant hormone therapy (AHT) is uncertain. Seven in every 10 patients were hormone receptor positive and adjuvant hormone therapy (AHT) is prescribed for 5–10 years for a woman with breast cancer. Therefore, the aim of this research was to examine adherence to adjuvant hormone therapy and related factors among women with breast cancer attending the Tikur Anbessa Specialized Hospital Oncology Center.

Methods: An institutional-based cross-sectional study was conducted from March to April, 2019. Systematic random sampling technique was used to select participants. A semi-structured questionnaire was used. Medication possession ratio (MPR) was used where score ≥80% was adherence. Data were entered in EpiData version 4.4.2.1 and transferred to SPSS version 25, and analyzed using binary logistic regression.

Results: Out of 216 women with breast cancer 209 participated in the study with a response rate of 97%. The overall adherence in this study was 77.5%. Getting social support (OR=3.959, 95%CI: 1.570–9.980), being on anastrozole (OR=0.139, 95%CI: 0.040–0.485), getting a thorough therapeutic communication about treatment (OR=4.590, 95%CI: 1.061–19.863), undergoing mastectomy (OR=0.215, 95%CI: 0.059–0.788), having side effects (OR=0.210, 95%CI: 0.085–0.517) were found to be significantly associated with adherence to AHT.

Conclusion: In general, the overall adherence to AHT was 77.5% for women with breast cancer. Factors such as types of adjuvant hormone therapy, lack of side effects, mastectomy, getting social support, and thorough therapeutic communication were strongly linked with adherence to them.

Keywords: adherence, adjuvant hormone therapy, breast cancer, Ethiopia

Introduction

Breast cancer has remained a significant public health concern worldwide, including in Ethiopia. It accounts for around one-fourth of all cancer cases and one-sixth of all deaths associated with cancer. Breast cancer is the principal cause of cancer mortality, according to the Addis Ababa cancer registry, which precedes cervical cancer. In Ethiopia, nevertheless, hormone receptor staining is sometimes not

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available. However, some studies showed that in every 10 women with breast cancer seven of them were hormone receptor-positive (HR+).[1–4] In countries such as Kenya, Tanzania, and Uganda, the prevalence of hormone receptor-positive (ER+/PR+) among women with breast cancer was 27%, 40%, and 51%. Tamoxifen is used to treat ER+ BC cancers, in sub-Saharan Africa it is administered without knowledge of receptor status. Besides countries without these facilities blindly administer hormonal therapies.[2,5–9]

These therapies include a selective modulator of the estrogen receptor (tamoxifen 20 mg po daily) works by blocking the effects of estrogen and aromatase inhibitors (anastrozole 1 mg po daily) that inhibit the biosynthesis of estrogen. Adjuvant tamoxifen and anastrozole reduce the risk of recurrence in women with ER+ BC by 40% and 12%, and mortality by 33% and 9%, respectively.[10,11] As patients are expected to take the drug for almost 5–10 years, the duration of adjuvant hormonal therapy is relatively extended. Thus, this lengthy oral therapy duration stressed whether or not the patient complied with the prescribed regimen. Despite its efficacy in treating breast cancer only one in two patients adhered to the medicated AHT regimen. Consequently, it then accelerates their mortality risk.[10,12–18]

Adherence is a multidimensional problem that is strongly linked with adherence to tamoxifen and AIs linked to the patient, therapy, health-care system, sociodemographic, disease, and behavioral factors.[18–20] In the Nigeria study, financial burdens and side effects were the most factors responsible for not complying with the regimen.[21] The excellence or incapability to conform to adjuvant hormone therapy was the duration, while the increase in medication duration resulted in a reduction in adherence owing to intolerable adverse effects. For example, tamoxifen and anastrozole adherence rates in the first to fifth years were around 79% to 65% and 80% to 72%, respectively.[13,22–24]

Different efforts have been made to mitigate the concern of adherence by educating patients on medication and also its adverse effects, skills on self-management of side effects, strengthening connections between patient and provider and securing health-care coverage, providing connections to social support and designing policies and practices to overcome factors that influenced adherence to AHT. Consequently, this improved breast cancer outcomes amongst survivors of breast cancer care.[11,25–30] There is, however, a paucity of reporting on the adherence status of

Ethiopian women receiving adjuvant hormonal therapy and its relevant factors in the study area. This research was therefore aimed at determining adherence status and associated factors for adjuvant hormone therapy among patients with female breast cancer attending TASH oncology center.

Methods and Materials
Study Design, Period, and Setting
An institutional based cross sectional study was conducted from March to April, 2019 at the oncology center of TASH. The hospital is found in Addis Ababa Lideta Sub City. This hospital worked as the nation's sole cancer referral center and has given radiotherapy, chemotherapy, concurrent cancer treatment services and palliative care for patients with cancer. According to the registry in the unit, more than 10,000 cancer cases were seen in this hospital per year. The most common cancer cases seen in this hospital were breast, cervical, and sarcomas.[1]

Population
All women diagnosed with breast cancer in the TASH oncology center were the source population and those are available during the data collection period were the study population. Patients who were severely ill and incompetent to interview were excluded.

Sample Size Determination and Sampling Procedure
To determine the sample size assuming number of the study subjects as n, the standardized normal distribution curve value for 95% confidence level (1.96), taking 50% of proportion because no previous similar study on adherence to adjuvant hormonal therapy and associated factors among women with breast cancer. By applying single population proportion formula for a cross-sectional survey, the sample size was 384.

$$n = \frac{(z/2)P(1-p)}{d} = \frac{(1.96)0.5(0.5)}{(0.05)}\frac{(1.96)0.5(0.5)}{(0.05)} = 384$$

where Z=1.96; P=0.5; d=0.05.

Since the flow of patients during data collection period was less than 10,000, then a correction formula was applied.

$$nf = \frac{n}{1+\frac{n}{N}} = \frac{384}{1+\frac{384}{398}} = 196$$

where n_f=desired sample size; n=the calculated sample size; N=total population (during data collection period).

After adding a 10% nonresponse rate the final sample size was 216. Then, data was collected by using a systematic sampling method. Every two patients were interviewed.

Operational Definition

Adherence: those who score medication possession ratio ≥80%.

Nonadherence: Those whose score medication possession ratio <80%.[2]

Adjuvant hormonal therapy: includetamoxifen 20 mg po/day and anastrozole 1 mg po/day in this study.

Data Collection Tools

Data was collected using a pretested and semi-structured face-to-face interview and patient health records were used. The question was translated in to Amharic by experts in both languages before, and translated back to English after data collection to ensure its consistency.

The interview-guided questionnaire was used to collect information on patients' sociodemographics, clinical and health-care system related characteristics. Patient charts review guide and prescription paper were used to identify date and days of supply and types of the AHT. Adherence was defined by the medication possession ratio (≥80%).[2,3] Medication possession ratio (MPR), defined as the days' supply of medication during the period from the first dispensing to the last dispensing in the time period of three months, divided by number of days.

Data Quality Control

Data quality assurance was applied using different techniques. Firstly, a content validity test was conducted. Then the pretest was done at Hawassa University Specialized Hospital by taking 5% of the study sample. Findings and experiences from the pretest were utilized in modifying the data collection tool. Training was given by the principal investigator for one day for data collectors and supervisors. The supervisor and principal investigator reviewed each questionnaire daily and checked for completeness and were then edited; the necessary feedback was given to the data collectors the next morning.

Data Processing and Analysis

Data were first checked, coded and entered using EpiData version 4.4.2.1 and transferred to SPSS version 25. Description of frequency, mean, median, proportion,

and SD was used. Significance was determined using odds ratios with 95% confidence intervals. To assess the association between the different predictor variables with the dependent variable, first bivariate analysis were conducted between each independent variable and outcome variable, those eligible with P-value <0.2 were then entered in multivariate analysis. Those variables with a P-value <0.05 and a 95% confidence interval were regarded as significant factors using an binary logistic regression.

Results
Sociodemographic Characteristics of the Study Participants

From 216 selected participants, 209 were involved in the study with a response rate of 97%. Of 209, 88 (42.1%) were in the age group 45–65 years, 121 (57.9%) were from urban, 103 (49.3%) were high school and above, 154 (73.7%) of the participant were married, 139 (66.5%) were Orthodox by faith, 82 (39.7%) were Amhara by ethnicity, 117 (56%) were housewives (Table 1).

Patient-related Factors

Of 209, 207 (99.1%) of the study participants had no smoking habit, 205 (98.1%) never drank alcohol before and 140 (67%) were socially supported (Table 2).

Disease-related Factors

Of 209, 190 (90.9%) had no family history, 187 (89.5%) were ductal carcinoma, 151 (72.2%) with advanced stage, 143 (68.4%) were postmenopause women, 186 (89.0%) with unknown receptor status, 205 (98.1%) were with one breast unilateral, respondents who received chemotherapy, surgery and radiotherapy were 194 (92.8%), 188 (90.0%) and 51 (28.2%), respectively, 189 (90.4%) undergoing mastectomy, 159 (76.1%) have no comorbidity, Among 50 (23.9%) those who had comorbidity; 24 (48%) were diabetic, 12 (24%) were HIV/AIDS, 8 (16%) had a heart problem and 6 (12%) had a respiratory problem (Table 3).

Medication-related Factors

Of 209, 118 (56.5%) were on tamoxifen, 62 (29.7%) initiated in the year 2019, 122 (58.4%) had not experienced side effects. Among 87 those who reported side effects; nausea and vomiting 25 (28.7%), tiredness and fatigue 23 (26.4%), joint and muscle pain 20 (23.0%),

Table 1 Sociodemographic Characteristics of Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019 (N=209)

Variable	Frequency (N)	Percentage (%)
Age of respondent		
<45	88	42.1
45–65	71	34.0
>65	50	23.9
Place of residence		
Rural	88	42.1
Urban	121	57.9
Educational status		
Unable to read and write	53	25.4
Primary education	53	25.4
High school and above	103	49.3
Marital status		
Unmarried	55	26.3
Married	154	73.7
Religion		
Orthodox	139	66.5
Muslim	38	18.2
Protestant	23	11.0
Others[a]	9	4.3
Ethnicity		
Amhara	82	39.7
Oromo	59	28.2
Gurage	32	15.3
Others[b]	36	17.2
Occupation		
Housewife	117	56.0
Private employee	21	10.0
Government employee	36	17.2
Others[c]	35	16.7

Notes: [a]Catholic, Adventist. [b]Tigre, Silte, Gamo, Gofa, Wolayta, Anyuak. [c]Student, merchant, labor worker, housemaid, retired, job seeker.

Table 2 Patient-related Variables of Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019 (N=209)

Variable	Frequency (N)	Percentage (%)
Smoking		
Yes	2	0.9
No	207	99.1
Alcohol		
Yes	4	1.9
No	205	98.1
Social support		
Yes	140	67.0
No	69	33.0

Table 3 Disease-related Variables of Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019 (N=209)

Variable	Frequency (N)	Percentage (%)
Family history		
Yes	19	9.1
No	190	90.9
Types of breast cancer		
Ductal	187	89.5
Lobular	22	10.5
Stage		
Early stage	58	27.8
Advanced stage	151	72.2
Menopausal status		
Premenopause	66	31.6
Postmenopause	143	68.4
Hormone receptor status		
Positive	23	11.0
Unknown	186	89.0
Laterality of the cancer		
Unilateral	205	98.1
Bilateral	4	1.9
Radiotherapy		
Yes	51	28.2
No	158	71.8
Chemotherapy		
Yes	194	92.8
No	15	7.2
Surgery		
Yes	188	90.0
No	21	10.0
Types of surgery		
Mastectomy	189	90.4
Lumpectomy	20	9.6
Comorbidity		
Yes	50	23.9
No	159	76.1
Comorbid illness		
Diabetes mellitus	24	48
HIV/AIDS	12	24
Heart problem	8	16
Respiratory problem	6	12

weight gain 9 (10.3%), sleep disorder 7 (8.0%), hot flash 3 (3.4%) (Figure 1, Figure 2). One hundred and twelve (53.1%) were getting their medication free of charge, 110 (52.6%) had follow-up of one year (Table 4).
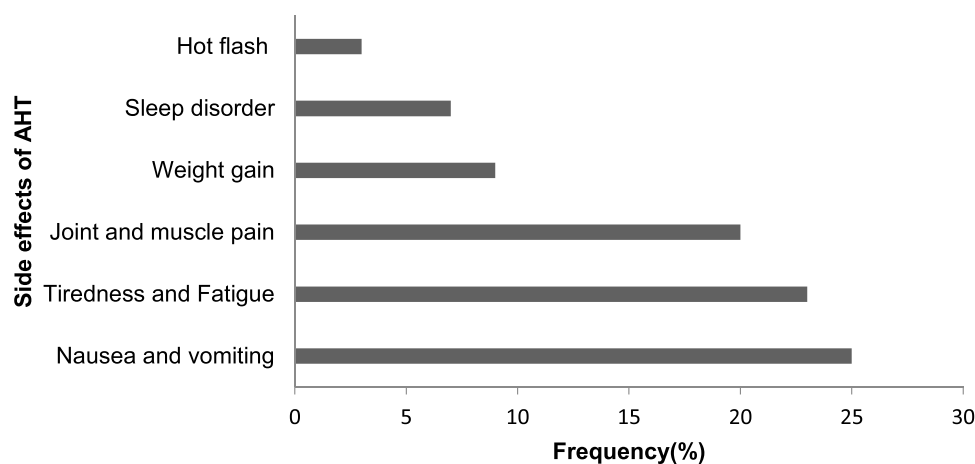
Figure 1 Side effects of adjuvant hormonal therapy's reported by the respondents among women with breast cancer attending oncology center at TASH, Addis Ababa, Ethiopia, 2019 (N=209).
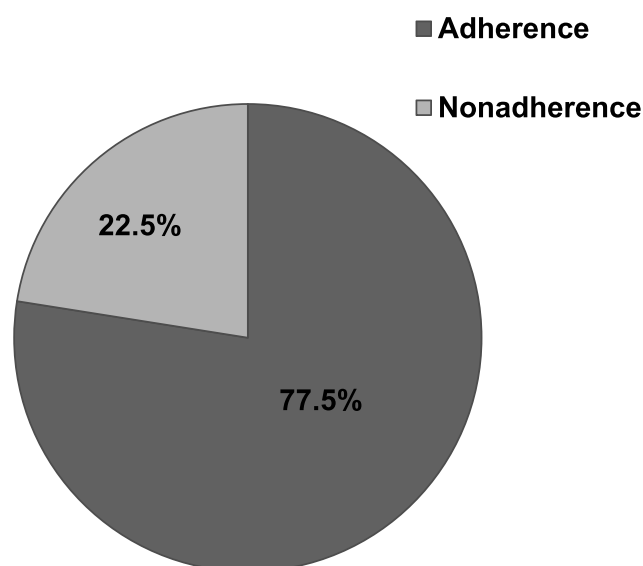

Figure 2 AHT adherence among women with breast cancer attending oncology center at TASH, Addis Ababa, Ethiopia, 2019 (N=209).

Health Care System-related Factors

Among the respondents, 136 (65.1%) reported adjuvant hormonal therapy is not available, 151 (72.2%) have had thorough therapeutic communication from a health-care provider, 102 (48.8%) took more than seven hours to reach hospital (Table 5).

Prevalence of Adherence to Adjuvant Hormonal Therapy

The overall adherence to adjuvant hormonal therapy in the current study was 77.5% (95%CI; 71.3–83.3) (Figure 1).

Factors Associated with Adherence to Adjuvant Hormonal Therapy

A binary logistic regression model was used to identify factors that affect the outcome variable. In bivariable analysis; place of residence, educational status, getting social support, family history of breast cancer, types of breast cancer, stage of breast cancer, types of hormonal therapy, side effects, types of surgery and types of payment were fitted at P-value <0.2. But in multivariable analysis, getting support, types of hormonal therapy, side effects, thorough therapeutic communication, types of surgery were significantly associated with the outcome at P-value <0.05 with 95%CI. Being socially supported (OR=3.959, 95%CI: 1.570–9.980), Being on anastrozole (OR=0.139, 95%CI: 0.040–0.485), Getting a thorough therapeutic communication (OR=4.590, 95%CI: 1.061–19.863), undergoing mastectomy (OR=0.215, 95%CI: 0.059–0.788); having side effects (OR=0.210, 95%CI: 0.085–0.517), were found to be significantly associated in multivariate analysis (Table 6).

Discussion

A central component of breast cancer patients who are undergoing hormone therapy is adherence to adjuvant hormonal therapy. However, little is known about the status of women adhering to this therapy in Africa, including Ethiopia. Therefore, the purpose of this study was to assess adherence to adjuvant hormone therapy and the associated factor of TASH breast cancer among women. This study showed that the prevalence of adherence was 77.5%. The current study is in agreement with studies

Table 4 Medication-Related Variables of Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019 (N=209)

Variable	Frequency (N)	Percentage (%)
Types of adjuvant hormonal therapy		
Tamoxifen	118	56.5
Anastrozole	91	43.5
Year of initiation		
2015	36	17.2
2016	24	11.5
2017	29	13.9
2018	58	27.7
2019	62	29.7
Do you experience side effects?		
Yes	87	41.6
No	122	58.4
Types of side effects		
Nausea	25	28.7
Fatigue	23	26.4
Arthralgia	20	23.0
Weight gain	9	10.3
Sleep disorder	7	8.0
Hot flash	3	3.4
Types of payment		
Free of charge	112	53.6
Out-off-pocket money	66	31.6
Medical insurance	31	14.8
Follow-up status		
1 year	110	52.6
2 years	38	18.2
3 years	20	9.6
4 years	24	11.5
5 years	17	8.1

Table 5 Health-care System-Related Factors of Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019 (N=209)

Variable	Frequency (N)	Percentage (%)
Availability of adjuvant hormonal therapy		
Yes	73	34.9
No	136	65.1
Did you get thorough therapeutic communication from HCP?		
Not at all	31	14.8
Somewhat	69	33.0
Very well	109	52.2
Travel time to hospital		
<3 h	31	14.8
3–6 h	76	36.4
≥7 h	102	48.8

91.4%.[41] Sample size, study design, different socioeconomic status, and study duration could differ. In multivariate analysis the following factors were associated with adherence to adjuvant hormonal therapy. In the current study, those who were getting social support, being on tamoxifen, getting thorough therapeutic communication about treatment, undergoing lumpectomy, lack of side effects were found to be significantly associated in multivariate analysis.

A significant variable that affected adherence was obtaining social support in the current study. Those getting social support from others were nearly four times more committed than those who did not. This finding is consistent with the study conducted in northern California,[42] UK,[43] and a study from Los Angeles, California, Houston, and Texas.[44] These similarities might be attributed to supportive social reinforcement, emotional support, as well as comforting them to comply with the medication and providing a better influence on adherence to the medication.

In the current study, those who had thorough therapeutic communications with the health-care provider about their treatment are 4.6 times more likely to be adherent than those who did not. This finding is supported by the studies conducted in California,[45] and the UK.[43] These similarities could be patient–provider interaction and effective communication about the use of medicines had a positive impact on AHT adherence. In this study, compared to those who had no side effects, of those who had

conducted in Brazil 76.3%,[32] Sweden 79%,[33] New York 76%,[34] North Carolina 78%,[35] another study in North Carolina 81.7%,[34] and Nigeria 75%.[21] The similarities may be attributed to the adherence measurement method, sample size, study nature, study population. Except in Nigeria, where their socioeconomic status and sample size may be almost similar. The current study finding is higher than studies conducted in Rome 60%,[36] Ireland 67.8%,[37] China 63.1%,[38] Singapore 40.8%,[25] and Texas 44%.[39] The difference could be the population of the study, different tools for measuring adherence, sample size, and design of the study. However, our results were lower than studies in Sweden 92%[40] and South Carolina

Table 6 Bivariate and Multivariate Analysis of Factors Associated with Adherence to AHT Among Women with Breast Cancer Attending Oncology Center at TASH, Addis Ababa, Ethiopia, 2019

Characteristics	Outcomes		COR (95%CI)	AOR (95%CI)	P-value
	Adherent N (%)	Nonadherent N (%)			
Residence					
Rural	64 (73)	24 (27)	0.473 (0.379–0.590)	0.859 (0.320–2.305)	0.763
Urban	98 (81)	23 (19)	I	I	I
Educational status					
High school and above	87 (84)	16 (16)	0.184 (0.108–0.313)	0.575 (0.180–1.840)	0.351
Primary education	38 (72)	15 (28)	0.395 (0.217–0.718)	0.691 (0.228–2.091)	0.513
Unable to read and write	37 (70)	16 (30)	I	I	I
Getting social support					
Yes	46 (67%	23 (33)	0.500 (0.303–0.825)	3.959 (1.57–9.98)	0.004*
No	116 (83)	24 (17)	I	I	I
Family history					
Yes	16 (84)	3 (16)	0.534 (0.452–0.632)	1.399 (0.262–7.481)	0.695
No	146(77)	44 (23)	I	I	I
Types of breast cancer					
Lobular	17 (77)	5 (23)	0.340 (0.253–0.457)	0.499 (0.115–2.166)	0.353
Ductal	145 (78)	42 (22)	I	I	I
Stage of breast cancer					
Early stage	47 (81)	11 (19)	0.234 (0.121–0.451)	1.289 (0.461–3.601)	0.628
Advanced stage	115 (76)	36 (24)	I	I	I
Types of adjuvant hormonal therapy					
Anastrozole	81 (89)	10 (11)	0.123 (0.064–0.238)	0.139 (0.040–0.485)	0.002*
Tamoxifen	81 (69)	37 (31)	I	I	I
Time of initiation					
2015	26 (72)	10 (28)	0.216 (0.112–0.414)	0.877 (0.281–2.739)	0.822
2016	20 (83)	4 (17)	0.318 (0.174–0.581)	0.399 (0.052–3.029)	0.374
2017	21 (72)	8 (28)	0.381 (0.169–0.860)	0.125 (0.006–2.494)	0.174
2018	44 (76)	14 (24)	0.200 (0.068–0.585)	0.206 (0.015–2.838)	0.238
2019	51 (82)	11 (18)	I	I	I
Experiencing side effects					
Yes	57 (66)	30 (34)	0.162 (0.097–0.270)	0.210 (0.085–0.517)	0.001*
No	105 (86)	17 (14)	I	I	I
Types of payment					
Free of charge	89 (79)	23 (21)	0.258 (0.163–0.409)	2.044 (0.494–8.453)	0.324
Out-of-pocket-money	47 (71)	19 (29)	0.404 (0.237–0.689)	1.517 (0.356–6.462)	0.573
Medical insurance	26 (84)	5 (16)	I	I	I
Getting a thorough therapeutic communication					
Very well	83 (76)	26 (24)	0.313 (0.202–0.487)	4.590 (1.061–19.863)	0.041*
Some what	54 (78)	15 (22)	0.278 (0.157–0.492)	2.945 (0.676–12.841)	0.150
Not at all	25 (81)	6 (19)	I	I	I
Types of surgery					
Mastectomy	150 (79)	39 (21)	0.260 (0.183–0.370)	0.215 (0.059–0.788)	0.045*
Lumpectomy	12 (60)	8 (40)	I	I	I

Note: *Indicates significantly associated.

encountered side effects around 79% were apt to become nonadherent. This result is consistent with the result of different studies in North America, Europe, and Australia,[17] China,[38] California,[45] Ireland,[37] New Zealand,[46] and Nigeria.[21] The similarities might be due to the unbearable side effects such as hot flash, nausea, mood swings and muscle or joint pain. In this study, those who were on anastrozole were 86% less likely to have adhered than those who were on tamoxifen. This finding is in agreement with studies conducted in Singapore,[25] North America,[47] and Canada.[48] These similarities might be because those on anastrozole appear to complain of more muscle pain and joint stiffness and/or pain and a higher risk of fracture, as they have different side effect levels. In the current study, those who have to undergo lumpectomy were about 78.5% likely to be adherent compared to those who had a mastectomy. This finding is supported by the study conducted in Texas.[49] The similarities may be attributed to the fact that they are less at risk of being disregarded because their entire breast has been removed. Those undergoing lumpectomy, however, are also afraid of residue during surgery, that is why they tend to be more adherent than those undergoing mastectomy.

Limitations

Even though this study involved a relatively small sample size, the establishment of a causal relationship could not be possible since it is a cross-sectional study. In addition, the study was conducted in one setting which could not represent the whole of the country.

Conclusion

In general, the overall adherence to AHT was good for women with breast cancer. Factors such as types of adjuvant hormone therapy, lack of side effects, types of surgery, getting social support, and thorough therapeutic communication were strongly linked with adherence to them. Much has to be achieved by resolving the above-mentioned factors and ensuring the relevance of recommended therapies to scaling up medication adherence. Side effects of the drugs, good social support and effective communication with a patient should be given great emphasis. Adherence counseling instructions on adjuvant hormone therapy for breast cancer should also be created. In addition, they can work on promoting AHT adherence, including the distribution of leaflets, as an alert, using mobile message technology. Finally, various adherence assessment tools should be used by future researchers

and different study designs should be warranted, ie longitudinal study. In addition, they need to evaluate the impact of adherence to AHT on the outcome of breast cancer.

Abbreviations

AAU, Addis Ababa University; AET, adjuvant endocrine therapy; AHT, adjuvant hormonal therapy; AIs, aromatase inhibitors; OR, odds ratio; BC, breast cancer; CI, confidence interval; COR, crude odds ratio; DC, data collector; ER+, estrogen receptor positive; ETB, Ethiopian Birr; HCP, health care provider; HR+, hormone receptor-positive; PgR+, progesterone receptor positive; SD, standard deviation; SERMs, selective estrogen receptor modulators; SPSS, Statistical Package for the Social Sciences; TAM, tamoxifen; TASH, Tikur Anbessa Specialized Hospital.

Data Sharing Statement

Data will be available upon request from the corresponding author.

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from the Institutional Review Board of the School of Nursing and Midwifery, Addis Ababa University and approved with IRB protocol number: 012/19/SNM. The letter of permission was written from the School of Nursing and Midwifery to the cancer centre of TASH. Then, the cancer centre chief administrator allowed collection of the data from breast cancer patients. Written informed consent was obtained from individual patients. In the data collection questionnaire, the names of the patients, as well as their medical record numbers, were not included for the sake of their privacy. All the processes of the research were performed and secured as per the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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