



SCHOOL OF NURSING

Time to recurrence and predictors of breast cancer among women patients treated in public hospitals of Addis Ababa, Ethiopia, 2024.

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Abbreviation and Acronyms

AHR	Adjusted Hazard Ratio
AJCC	American Joint Commission on Cancer
BCT	Breast Conservative Therapy
BMI	Body Mass Index
BSc	Bachelor of Science
CI	Confidence Interval
CHR	Crude Hazard Ratio
ETB	Ethiopian Birr
HR	Hazard Ratio
IRB	Institutional review board
LRR	Loco-regional Recurrence
LR	Log-rank
MSc	Masters of Science
PMRT	Post Mastectomy Radiotherapy
PIS	Personal Investigators
RFS	Recurrence Free Survival
SPHMMC	Saint Paul's Hospital Millennium Medical College
TASH	Tikur Anbessa Specialized Hospital

Abstract

Introduction: Breast cancer is a disease causing uncontrollable changes in breast tissue cells. Breast cancer recurrence is declared when the disease returns following surgery. Time to breast cancer recurrence and factors affecting it are not well studied in Ethiopia. Therefore, the aim of this study was to assess time to recurrence and predictors of breast cancer among women patients treated in public hospitals of Addis Ababa, Ethiopia, 2024.

Methods: Two public hospitals were selected by lottery method; a retrospective cohort study design was conducted from April 30- May 30, 2024 among randomly selected 322 of medical records. The study covered the period from September 11, 2018 to September 12, 2023. Sample size was allocated proportionally to TASH and SPHMMC, and medical records of patients were tracked from sample frame randomly. Data were collected by kobo toolbox and analyzed by Stata Version 15. To identify predictor's variables, the Cox proportional hazard model was used. The Cox-proportional hazard model assumption was checked using Schoenfeld residual/global test (0.79). Multi-collinearity was checked using variance inflation factor (3.72). Variables with P-value < 0.25 in bivariate analysis were entered into the final multivariate analysis. Variable with P-value <0.05 at 95% confidence level were considered as independent predictors of recurrence.

Result: The study response rate was 96%. The incidence rate of breast cancer recurrence was 6.8 per 100 women years (95%CI=5.34-8.13) follow-up. The 75%RFS time was 44 months (95%CI=40-48). The proportion of RFS survival at 24, 36, 48, and 60 months was 91.93%, 83.3%, and 67.7%, 61% respectively. Women aged 40 & below (AHR=3.32; 95%CI: 1.80-5.88), Overweight (AHR=1.95, 95%CI:1.06-3.59), surgical margin positive at diagnosis (AHR=2.1; 95%CI: 1.20-4.02), axillary node status positive (AHR=1.98; 95%CI: 1.08-3.61) and comorbidity (AHR=4.45, 95%CI: 2.39-8.30) were independent predictors for increased hazard of breast cancer recurrence.

Conclusion and Recommendation: The incidence of breast cancer recurrence is high with predictors of recurrence include comorbidity, age, overweight, positive axillary node status, lymph node involvement, and deep surgical margin contributing to higher rates. Improving awareness and patient education on prevention, screening, and treatment is crucial.

Key words: Breast, cancer, Ethiopia, Predictors, recurrence.

1. Introduction

1.1. Background

Breast cancer is a diverse illness with a range of biological characteristics, multi modal therapeutic modalities and prognoses, and uncontrollably changing the function or proliferation of the cells that make up breast tissue results to breast cancer, so these changes turn these cells cancerous and enable them to proliferate (1).

Breast cancer has surpassed lung cancer as the most frequent type of cancer, according to GLOBOCAN 2020 reports with 2.3 million new instances, or 11.7% of all cancer cases globally. And, it ranks as the fifth most common cause of cancer-related mortality worldwide, accounting for 685,000 fatalities (2). Breast cancer is now the most common type of cancer in Africa, including Ethiopia, in terms of morbidity and mortality (3).

Multiple approaches are used to treat breast cancer. The majority of women diagnosed with Stage I–III breast cancer are candidates for either a mastectomy or a combination of radiotherapy and breast-conserving surgery (4). Systemic therapy is the only treatment for breast cancer in stage IV, which is thought to be incurable unless there is a compelling need to remove the original tumor for palliative purposes(5). Adjuvant systemic therapies such as radiation, hormone therapy, and chemotherapy have been demonstrated to improve survival and reduce disease recurrence (6).

Breast cancer recurrence occurs when the disease returns following surgery (7).The annual risk of recurrence reaches its maximum in the second year after diagnosis and stays between 2% and 5% from years five to twenty (8). The molecular subtype of breast cancer determines the sites of recurrence. The most frequent locations for recurrence are the breast or chest wall for local recurrence, the bone for distant metastasis, and the lymph nodes in the region for relapse (1).

Many people believe that breast cancer is incurable because of its propensity to return. This belief is supported by the fact that, even with modern treatment and close monitoring, 5–10% of patients will have metastatic disease at diagnosis, and another 20% will experience an advanced stage of disease recurrence (9). Recurrent breast tumors are frequently characterized by a high number of aggressive cells(10).

Study conducted in Iran has revealed that the incidence rate of recurrent breast cancer was 20.2% (11). Another study conducted in Australia has shown the incidence of breast cancer recurrence within 5 years after surgery was 3.3%(6). The incidence of breast cancer recurrence was 11.7% in the Netherlands (12), and 5.9% in South Korea(13). According to the study conducted in Egypt, the cumulative incidence of breast cancer recurrence was 4.2%(10).

About 30% of all malignancies in Ethiopia are breast cancers, making it the most common disease among women and a significant public health concern. A retrospective follow-up study conducted in Black-Lion Hospital in Ethiopia has explored that the overall cumulative incidence rate of breast cancer recurrence was 18.5%(14).

1.2 Statement of problem

Breast cancer is a disease with diverse biological characteristics, multimodal therapeutic modalities, and prognoses. It results from uncontrollable changes in breast tissue cells, turning them cancerous and allowing them to proliferate (1).

Breast cancer recurrence occurs after surgery. Recurrences can often be successfully managed, but they are stressful, costly, and increase risk of mortality if not detected early(16). Studies have revealed that between 8 to 10% of women with breast cancer will have loco-regional recurrences, while 15 to 30% will have distant metastases(17).

Breast cancer is expected to kill approximately 685,000 women in 2020, accounting for one out of every six cancer deaths among women. The cumulative incidence of breast cancer recurrence within 6 years is 3.3% in Australia (18), 5.1% in South Korea(13), 4.2% in Egypt (10), and 18.5% in Ethiopia(14).

The efforts made on improvements in early diagnosis and treatment has increased breast cancer survival, and as a result, an increasing proportion of women are at risk for either a contralateral breast cancer or an ipsilateral breast tumor recurrence (14). Recurrences are linked to a poor result, including a higher chance of distant metastases and mortality from breast cancer (19).

Despite the fact that the incidence of recurrence among breast cancer is extensively recognized in the developed country, data on breast cancer recurrence is not readily available in Ethiopia. Tikur Anbessa Specialized Hospital completed a study on the incidence and predictors of recurrence among patients with breast cancer which covered a shorter duration of time(14).

This study is restricted to patients at one academic institution and only followed them for a shorter period. As a result, it was unable to determine the risk of a late recurrence of breast cancer, also not clearly identify whether early recurrence predictors or late risk factors of recurrence, and the patient sample might not be a genuine reflection of other institutions. Therefore, aim of this study was to determine time to recurrence and its predictors among women patients with breast cancer treated in selected public hospitals, Addis Ababa, Ethiopia.

1.3 Significance of the study

Recurrences are linked to a poor result, including a higher chance of distant metastases and mortality from breast cancer (16). Due to the variability and unrecognizability of time of recurrence and risk factors, patients are not screened on regular basis. The current study is important for patients, clinicians and health service planners to know the risk of recurrence after breast cancer surgery. Furthermore, early detection of tumor recurrence can result in a better prognosis.

A better assessment of the possibility of tumor recurrence will aid for the selection of therapy and to schedule follow-up care after initial treatments if the time to recurrence and predictors are identified. Besides, recognizing the time of recurrence of breast cancer can drive high-risk women to be screened, enhance adherence to screening standards, and encourage chemoprevention and other appropriate treatments to minimize the risk.

Moreover, the study will be helpful for patients in that healthcare professionals use it to determine the time and risk of recurrence of breast cancer. The efforts made on improvements in early diagnosis and treatment of breast cancer recurrence has increased breast cancer patient's survival. The findings will serve as baseline information for further large-scale studies to closely examine the predictors of breast cancer recurrence.

The finding of this study can serve as baseline data and help other investigators as references for future studies. Furthermore, the rationale of studying predictors of breast cancer recurrence will have practical value for patients, providers, researchers and policy-makers in the Ministry of Health. It will guide policymakers and government bodies in planning and providing services for preventing and treating women with breast cancer recurrence in Ethiopia.

2. Literature review

2.1 Magnitude of breast cancer recurrence

Breast cancer is the commonest type of cancer in women and the main cause of cancer death in women globally (5). Between 8 to 10% of women with breast cancer will have loco regional recurrences, while 15 to 30% will have distant metastases (12).

Study conducted in Iran has revealed that the incidence rate of recurrent breast cancer was 20.2%(19); and study conducted in Australia has shown the incidence of breast cancer recurrence within 5 year after surgery was 3.3% (17).

A 24 -year follow-up study conducted in Europe has explored that the recurrence rate of breast cancer was 10.2%, 5.3%, 8.6%, and 40.7 % with a recurrent site at local, contralateral, regional and distant site respectively (20).In addition, other studies have revealed that the incidence of breast cancer recurrence was 11.7% in Netherlands(11), and 5.9% in South Korea(21). According to the study conducted in Egypt, the cumulative incidence of breast cancer recurrence was 4.2%(10).

A retrospective follow-up study conducted in black-lion hospital in Ethiopia has explored that the overall cumulative incidence rate of breast cancer recurrence was 18.5% (13).The time of breast cancer recurrence varies and is classified as early within 5 years after initial surgery and late recurrence which occurs after 5 years (22). For the entire group, the annualized hazard of recurrence was highest during the first 5 years (10.4%), with a peak between years 1 and 2 (15.2%) (20).

On the other hands a retrospective historical cohort study conducted in Iran has revealed that the overall median recurrence free survival rate were 86% (95% CI = 81-91) and 82.5% (95% CI = 77-87), in 2.5 and 5 years respectively(19). Study conducted in Netherlands has shown that 4 year RFS was 88.4%(11). The median time of RFS is also known to be 4 years in USA(23), 45.43 in Thailand (8), 57 months in South Korea(12), and 7.2 years in France(24).

Findings from Black Lion Hospital in Ethiopia revealed that an overall median RFS time was 60.33 months (95% CI: 55.46-62.20), and the estimated recurrence free survival was found to be 98.1%, 91.5%, 82.4%, 68.8%, 50.5% and 28.5% at 12, 24, 36, 48, 60, and 72 months, respectively (13).

2.2 Predictors of breast cancer recurrence

2.2.1 *Socio-demographic factors*

Meta-analysis study conducted in China concluded that younger age was a significant predictor of loco-regional recurrence of breast cancer(25). In addition, retrospective cohort studies done in Denmark has identified that women with younger age (commonly age $\leq$ 40 years, HR = 1.47, 95% CI = 1.22 to 1.78) are at increased risk to develop breast cancer recurrence(26).

2.2.2 *Clinical And Pathological Predictors*

The randomized control trial study have shown that there is an association between obesity or increased BMI and breast cancer recurrence, and recurrence free survival rate (27).

Presence of positive axillary lymph node involvement predicts an increased risk of local and distant recurrence, which has a direct impact on mortality (10). Findings of retrospective cohort studies shows the adjusted recurrence hazard of positive lymph nodes 2 and 3 patients was 2.47 (95% Confidence Interval [CI] 1.72–3.56) and 2.42 (1.62–3.60), respectively, compared to pN1 patients ($p < 0.001$) (24)(28).

A study conducted in Australia has revealed that women with node-positive have 1.7 (95%CI=1.3-2.3) times higher risk to develop breast cancer recurrence (17). Study done in Black Lion, in Ethiopia, have also revealed that lymph node-positive patients have 2.6 times higher risk to develop breast cancer recurrence than lymph node negatives, and women who had advanced histologic grade initially were 2.8 times more likely to develop recurrence(13).

The status of oestrogen and progesterone is also a predictor of breast cancer recurrence. The prognosis and overall prognosis following metastasis are dependent on multiple factors. Among these are the estrogen/progesterone receptor and the degree of Human Epidermal Growth factor amplification, which determine the breast cancer metastatic molecular sub-type (29). Results from many research have demonstrated that individuals with oestrogen receptor-negative breast cancer are more likely to experience an early recurrence of the disease, whereas patients with oestrogen receptor-positive breast cancer may experience a delayed recurrence (8)(24).

A study conducted in France revealed that breast cancer patients having larger tumor size(>2cm) at diagnosis were experienced early recurrence, but those who had smaller tumor size experienced recurrence in later stage(24). Another follow-up study conducted in Australia has shown that breast cancer women with tumors larger than 2cm at diagnosis were more likely (HR=1.5; 95%CI=1.1-2.0) to have a recurrence within six years than those with a smaller initial tumor. In addition, clinical stage and histologic grade of the cancer at baseline majorly determines the median time to recurrence(13).

Furthermore, presence of comorbidity, advanced cancer stage and involvement of deep surgical margin were identified as predictors and possible risks for recurrence(13)(30).

2.2.3 Treatment-related factors

The majority of women diagnosed with early breast cancer are candidates for either a mastectomy or a combination of radiotherapy and breast-conserving surgery(6). Stage I breast cancer are still fairly small and either have not spread to the lymph nodes or have spread to only a tiny area in the sentinel lymph node (the first lymph node to which cancer is likely to spread). Surgery is the main treatment for stage I breast cancer(31).

Breast-conserving therapy (BCT) and mastectomy are both well-known local treatment options for invasive breast cancer. However, time from diagnosis to surgical treatment determine the time of breast recurrence. A study done at Iraq had shown that there was an association between delay of first complaint and surgery date, and the recurrence rate was higher among patients who delayed for longer time for surgery(32).

Adjuvant chemotherapy has been demonstrated in a meta-analysis to decrease death and recurrence in breast cancer, with a greater benefit in patients with hormone receptor's negative disease(33).

Endocrine therapy may be used to treat patients for five to ten years, and most likely longer and the tamoxifen for five years decreases the chance of recurrence by almost 50% in years 0–4 and by more than 30% in years 5–9. Moreover, annual breast cancer mortality decreased by 30% within the first 15 years (34). Breast cancer mortality was reduced by around 30% and recurrence by approximately 25% when tamoxifen was used for a longer period of time (35)

3. Objectives

3.1 General objective

To assess time to recurrence and predictors of breast cancer among women patients treated in public hospitals of Addis Ababa, Ethiopia, 2024.

3.2 Specific objectives

To determine time to recurrence of breast cancer among women patients treated in public hospitals of Addis Ababa, Ethiopia, 2024.

To identify the predictors of time to breast cancer recurrence among women patients treated in public hospitals of Addis Ababa, Ethiopia, 2024.

4. Methods and materials

4.1 Study area

The study was conducted at the largest tertiary care, specialized, referral, and teaching hospitals. There are 13 public hospitals in Addis Ababa; out of those four public have Oncology treatment center. Tikur Anbessa Specialized Hospital and St. Paul's Hospital Millennium Medical College had been selected by using simple random sampling.

The St. Paul's Hospital Millennium Medical College was established in Addis Ababa, the capital city of Ethiopia in 1968 by the late Emperor Haile Selassie. The college has more than 2800 clinical, academic and administrative and support staff that provide medical specialty services to patients who are referred from all over the country, teaching medicine and nursing students and doing basic and applied research. The College can accommodate more than 700 inpatient beds, but on a daily average, 1200 emergency and outpatient patients are seen. St. Pauls' Hospital Millenium Medical College oncology unit was established on August 1, 2018. It was the second hospital offering cancer treatment in the country(37).

Tikur Anbessa Specialized Hospital is the largest tertiary care, specialized, referral, and teaching hospital in the country that is owned by the government and established in 1973. TASH has 51 specialty outpatient clinics, serving 500,000 patients annually(14).

4.2 Study design and period

Institution-based retrospective cohort study was conducted at Saint Paul's Hospital Millennium Medical College (SPHMMC) and Tikur Anbessa Specialized Hospital (TASH) from April 30-May 30, 2024. The study covered a period from September 11, 2018 to September 12, 2023. The starting time of the study is a time where the breast treatment was started at Saint Paul's Hospital Millennium Medical College (SPHMMC), and the end time was decided for outcome ascertainment in succeeding period.

4.3 Population

4.3.1 Source population

All medical records of breast cancer patients‘ treated in public hospitals in Addis Ababa, from September 11st 2018 to September 12st 2023.

4.3.2 Study population

All medical records with breast cancer who had breast surgery in selected public hospital in Addis Ababa, from September 11st 2018 to September 12st 2023.

4.3.3 Study unit

All randomly selected patients’ medical records underwent breast surgery and those fulfilling the inclusion criteria.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

All medical records of breast cancer patients who had breast surgery in the SPHMMC and TASH hospitals from September 11st 2018 to September 12st 2023 are included in the study.

4.4.2 Exclusion criteria

Patients who have metastasis breast cancer (stage IV) at diagnosis.

Patient whose Medical chart was lost

Medical records with incomplete baseline variables

4.5 Sample size determination

As the study was cohort study, the sample size needed for acquiring statistically significant results was determined using two population proportion formula. Therefore, sample size was calculated by taking into account the predictors variables and using open epi version 7.2.6 statistical package(38). Among predictors variables, lymph node status is chosen as main predictor's variable of breast cancer recurrence during the 6 years of follow up since it was considered to give the optimal sample size and most significant result. In this regard, a 5% level of significance (two sided), a power of 80% and a ratio of unexposed to exposed of 1:1, estimated proportion of recurrence in Ethiopia was taken 10% for non-exposed group (negative lymph node status) and 22.4% for exposed group (positive lymph node status) (14) (Table 1). However, in practice getting 153 patients in their positive lymph node was difficult and the rest were from negative lymph node. Thus, the total sample size was 306. Finally, by adding 10% for incomplete data, the final sample size required was 337.

Table 1: sample size calculation for time to recurrence and predictors of breast cancer recurrence among patients treated in public hospital, Addis Ababa, Ethiopia 2024 by using open epi version 7.2.6 Software.

Assumptions		Major predictors variable	Sample size by Fleiss with CC Formula	Total sample size
Two-sided significance level:	0.05	Lymph node status (positive exposed; negative un exposed)	Number of exposed=153	306
Power:	80			
Ratio of sample size:	1:1			
% of Unexposed with Outcome	10		Number of unexposed=153	
% of exposed with Outcome	22.4			
Hazard ratio	2.6			
Relative risk	2.24			

4.6 Sampling technique and sampling procedure

Four oncology treatment center hospitals are found in Addis Ababa. By using simple random sampling two public hospitals were selected. From both selected hospitals all medical numbers of breast cancer patients who had breast surgery from September 11th 2018 to September 12th 2023 were collected from the Health Management Information System (HMIS) registered book. After screening the medical record for metastasis and lost charts the calculated sample size was proportionally allocated to both hospitals. Simple random sampling technique was performed by using computer based random number generation to obtain the sample from both Hospitals. Finally data was extracted from those that fulfill inclusion criteria.

4.6.1 Sampling procedure

Proportional allocation was used to select study participants from each hospital.

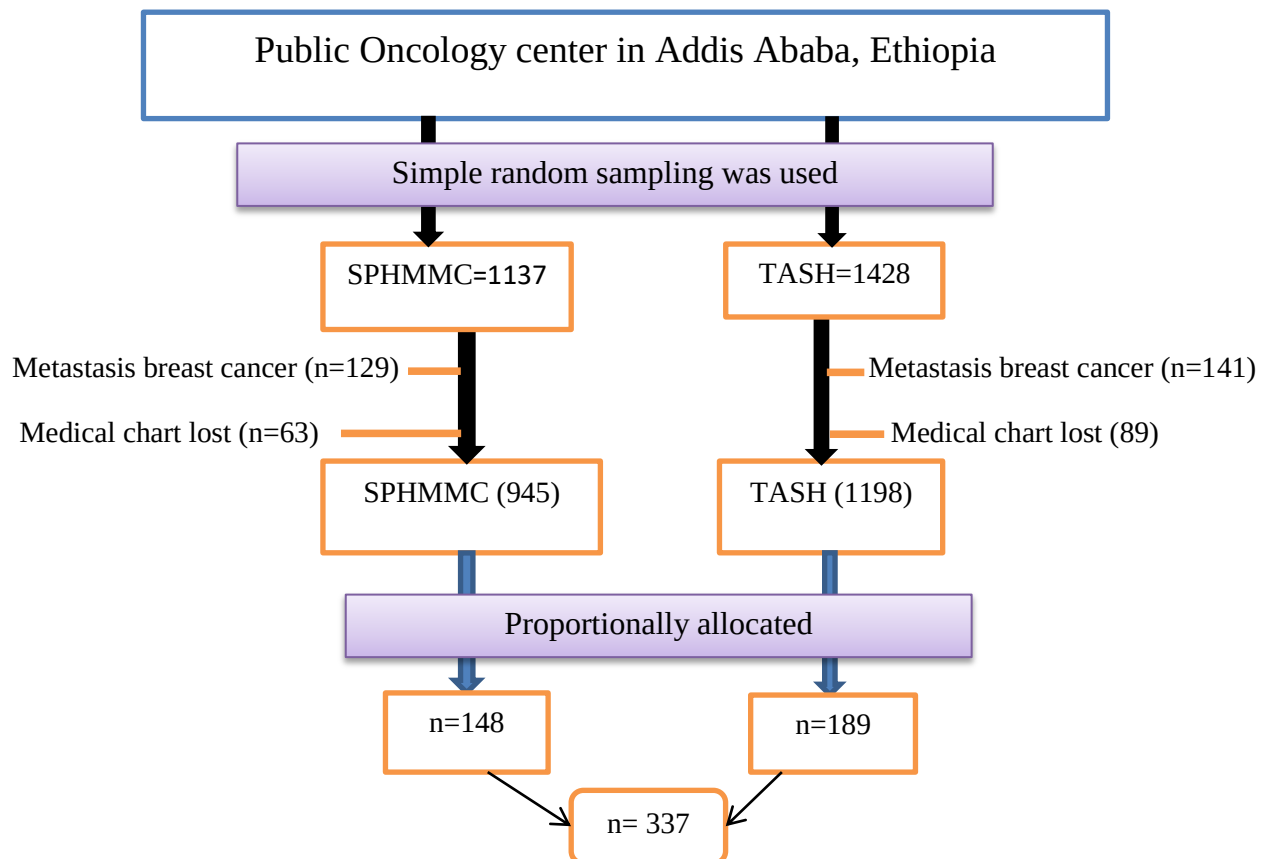


Figure 1: Schematic presentation of sampling procedure among women patients treated with breast surgery in public hospital, Addis Ababa, Ethiopia, 2024

4.7 Data collection technique

Data extraction tool was developed from related literature to collect information from patients' medical records. Socio-demographic, clinic-pathological, and treatment related factors that are supposed to be predictors for breast cancer recurrence was extracted from the patient's medical records by using the kobo toolbox. Data were collected by four BSc nurses and supervised by two MSc Oncology nurses.

4.8 Data quality control

Before the data is collected, 5% (17) of total sample size was undergone pretest at SPHMMC to ensure that the questionnaires are clear and easy to access on the chart. After pre-testing the checklist, cronbatch's Alpha was calculated by using Stata version 15 to test internal consistency (reliability) of the item and the result was 0.79. Study variables are identified based on similar studies and data extraction tool was developed in accordance with the information available in the patient's medical record at cancer treatment center. Training on how to collect data by kobo toolbox was given for data collectors and supervisors before one day to data collection. Senior experts to the area of study for content validity examined for the data extraction tool. The entire data collection process was closely supervised by the supervisors and principal investigator. Supervisors were checked the ID of the patient with the registry code whether clinically matched (at diagnosis stage I-III) or not.

4.9 Data management and analysis

Data was entered, checked and arranged in Kobo toolbox software. After Coding, editing and cleaning analysis were done in StataVers.15. To summarize the cohort's characteristics, descriptive statistics such as frequency tables, life tables, graphs, median, and Inter quartile range were used. The incidence density rate was computed over the period of the study. The survival time was estimated using the Kaplan–Meier survival curve. Log-rank test was performed for the presence of any differences in time to recurrence among different categorical variables. Those variables which the test statistics & Kaplan-Meier analysis displayed as a significant difference in RFS function among categorical variables are considered as having significant evidence of differences in time to recurrence. To identify predictor's variables, the Cox proportional hazard model was used. The Cox-proportional hazard model assumption was checked using Schoenfeld residual/global test (0.79). Overall the fitness' of proportional hazard model was assessed by using cox Snell residual graph. Multi-collinearity was checked using variance inflation factor (3.72). Variables with P-value < 0.25 in bivariate analysis were entered into the final multivariate analysis. Variable with P-value <0.05 at 95% confidence level were considered as independent predictors of recurrence.

4.10 Operational definition and definitions of terms

Time to recurrence: time from the date of breast surgery to the occurrence of event (recurrence) during the follow up period.

Survival status: the outcome of women underwent breast surgery that develop recurrence or recurrence free/survival

Recurrence (Event): a registered confirmed physician diagnosis of return or recurrence of breast cancer after surgery based on clinical, imaging and biopsy findings (14).

Recurrence Free Survival (RFS): time interval from date of surgery for breast cancer to date of LRR, distant metastasis or last date of follow-up, whichever comes first(36).

Censored: Patients whose status was unknown, patients who did not develop recurrence at the end of the follow-up period

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Loco regional Recurrence (LRR): Tumor reappearance in the opposite breast, ipsilateral chest wall, and/or regional lymph nodes (axillary, internal mammary, infraclavicular or supraclavicular lymph nodes) on the side previously affected by cancer(10).

Comorbidity: presence of one or more additional disorders (diseases) co-occurring with a primary disease or disorder.

Distant recurrence: tumor recurrence in chest wall, bone, skin, lung, or elsewhere in the body(22)

BMI: based on WHO classification normal (18.5 kg/m²-<25 kg/m²), overweight (25 kg/m²-<30 kg/m²) and obesity ($\geq$ 30 kg/m²).

Stage at diagnosis: The American Joint Committee on Cancer TNM classification scheme for staging breast cancers to be used. In this research, the coding for those diagnosed at stages I and IV remained. Stages IIA and IIB were collapsed as stage II, and stages IIIA, IIIB and IIIC were collapsed as stage III(39).

4.11 Ethical considerations

The ethical clearance was obtained from SPHMMC the institutional review board (IRB) (Ref. No;-Pm 23/1138). Then a support letter was submitted to the respective hospital authorities and permission was granted. Finally, the questionnaire was kept locked after the data entry.

4.12 Dissemination of results

After the result of the study will be submitted and presented to SPHMMC, the department of Nursing, as a requirement for partial fulfillment of master's degree in clinical oncology Nursing, the copies of study results will be given to the SPHMMC and TASH. Efforts will be made to publish in peer reviewed reputable journals. Depending on the opportunities, the finding will be presented in conferences or seminars.

5. Results

5.1 Socio-demographic characteristics of the study participants

Out of 337 study participants of this study, 322 complete record reviews were done. This makes the response rate of the study 96%. Inadequate staging of tumors at the time of diagnosis were considered as non-respondents. The median age at diagnosis was 43 years (Interquartile range: 34-51). Of the 322 study participants, 162(50.31%) were diagnosed at age 40 and above. One hundred sixty two 81.37%) were married, 195 (60.56%) were from rural areas (Table 2).

Table 2: Socio-demographic characteristics of breast cancer patients who had surgical treatment in selected public hospital, Addis Ababa, Ethiopia, 2024(n=322)

Variables	Category	Frequency, (%)	Outcome	
			Recurrence N (%)	Censored N (%)
Age at dx	=>40	190 (59.01)	31 (16.31)	159 (83.69)
	< 40	132 (40.99)	32(24.24)	100(75.76)
Marital status	Single	42 (13.04)	6(14.28)	36 (85.72)
	Married	162 (81.37)	57(35.18)	205(64.82)
	Widowed	11 (3.42)		11(100)
	Divorced	7 (2.17)		7(100)
Residence	Urban	195 (60.56)	35(17.94)	160(82.06)
	Rural	127 (39.44)	28(22.04)	99 (77.96)

5.2 Baseline clinical, pathological and treatment characteristics of the study participants

Eighty six (26.71%) women had preexisting comorbidity at the time of diagnosis, 152 (47.20%) cases were in clinical stage III cancer; and 135(41.93%) were moderately differentiated (grade II) histologic cancer cases at a time of diagnosis. Out of total 151 (46.8%) women were overweight during diagnosis. Invasive carcinoma was a commonest histologic type; accounting for 256(79.50%) of all cases. One hundred seventy one (53.11%) cases had positive lymph involvement of two or above; and 160 (39.69%) cases had tumor size of 2 to 5 cm at a time of diagnosis. Ninety eight (30.43%) cases had involved surgical margin status. About 157 (48.76 %) women had positive axillary node status. One hundred sixty one (50%), 147(45.65%) of study participants had positive estrogen and progesterone receptors respectively (Table 3).

Table 3: Clinical and pathological characteristics of breast cancer patients who had surgical treatment in selected public hospital, Addis Ababa, Ethiopia, 2024 (n=322)

Variables	Category	Frequency, (%)	Outcome status	
			Recurrence N (%)	Censored N (%)
Comorbidity	Yes	86 (26.71)	40(46.51)	46(53.49)
	No	236 (73.29)	23(9.74)	213(90.26)
BMI at diagnosis	Normal weight	171 (53.11)	16(9.35)	155(90.65)
	Overweight	151 (46.89)	47(31.12)	104(68.98)
Laterality	Left	147(45.65)	28(19.05)	119(80.95)
	Right	175(54.35)	35(20)	140(80)
Cancer stage at diagnosis	I	30 (9.32)	2(6.66)	28(93.34)
	II	140 (43.48)	14(10)	126(90)
	III	152 (47.20)	47(30.92)	105(69.08)

Histological grade	Grade I	65 (20.19)	5(7.70)	60(92.30)
	Grade II	135 (41.93)	18(13.33)	117(86.67)
	Grade III	122 (37.89)	40(37.78)	82(62.22)
Histological type	Non invasive	66 (20.50)	4(6.06)	62(93.94)
	Invasive	256 (79.50)	59(23.04)	197(86.96)
Surgical margin	Free	224 (69.57)	25(11.16)	199(88.84)
	Involved	98 (30.43)	38(38.78)	60(61.22)
Number of + lymph node involved	< 2	151 (43.89)	16(10.60)	135(89.40)
	>= 2	171 (53.11)	47(27.48)	124(72.52)
Axillary node status	Negative	165 (51.24)	17(10.30)	148(89.70)
	Positive	157 (48.76)	46(29.29)	111(70.71)
Tumor size at diagnosis	< 2 cm	36 (11.18)	3(8.33)	33(91.67)
	2-5 cm	160 (39.69)	24(15.00)	136(75.00)
	>5cm	126 (29.13)	36(28.57)	90(71.43)
Estrogen receptors	Positive	161 (50.00)	35(21.74)	126(78.26)
	Negative	129 40.06)	26(20.16)	103(79.84)
	Not determined	32 (9.94)	2(6.25)	30(93.75)
Progesterone receptor	Positive	147 (45.65)	25(17.00)	122(83.00)
	Negative	142 (44.10)	36(25.35)	106(74.65)
	Not determined	33 (10.25)	2(6.06)	31(93.94)

According to this study finding about 55.28% women surgery was done after 30 days starting from the date of diagnosis. Three hundred eight (95.56%) cases had undergone Modified Radical Mastectomy. Three hundred forty (81%) women were using adjuvant chemotherapy and out these ACT is the commonest chemotherapy used as Adjuvant regimen 173(53.7%). About Two hundred fourteen (66.46%) were using hormone therapy. Out of 214 about 148 (69.16) of women who were diagnosed with early stage of breast cancer used the Tamoxifen regimen of hormonal therapy during these follow up (Table 4).

Table 4: Treatment characteristics of breast cancer patients who had surgical treatment in selected public hospital Addis Ababa, Ethiopia, 2024 (n=322)

Variables	Category	Frequency ,%	Recurrence(63) N (%)	Censored (259) N (%)
Duration from diagnosis to surgery	< =30 days	144 (44.72)	23 (15.97)	121(84.03)
	>30 days	178 (55.28)	40 (22.47)	138(77.53)
Neo-adjuvant chemotherapy use	Yes	38(11.80)	11 (28.94)	27(71.06)
	No	284(88.20)	52 (19.79)	232(80.21)
Adjuvant chemotherapy use	Yes	288 (89.44)	57(19.79)	231(80.21)
	No	34 (10.56)	6(17.65)	28(72.35)
Chemotherapy regimen used	ACT	173 (53.7)	36(20.80)	137(79.20)
	AC	75 (23.3)	12 (16.00)	63(84.00)
	Paclitaxel	40 (12.4)	9 (22.50)	31(77.50)
Use of hormonal therapy	Yes	214 (66.46)	43(20.09)	171(79.91)
	No	108 (33.54)	20(18.51)	88 (81.49)
Regimen of hormonal therapy	Tamoxifen	148 (69.16)	27(18.24)	121 (81.76)
	Anastrozole	66 (30.84)	16(24.24)	50 (75.76)

5.3 Over all status of breast cancer patients

In this study, 322 women patients' with breast cancer who underwent surgery were followed retrospectively. The median follow up time was 33 months, with a minimum and maximum follow-up time of 5 and 60 months, respectively. The recurrence free survival status at median follow up time was 85.73% (95%CI =80.8%-89.4%). In this study 63 (19.56%) patients were develop recurrence (Figure 3).

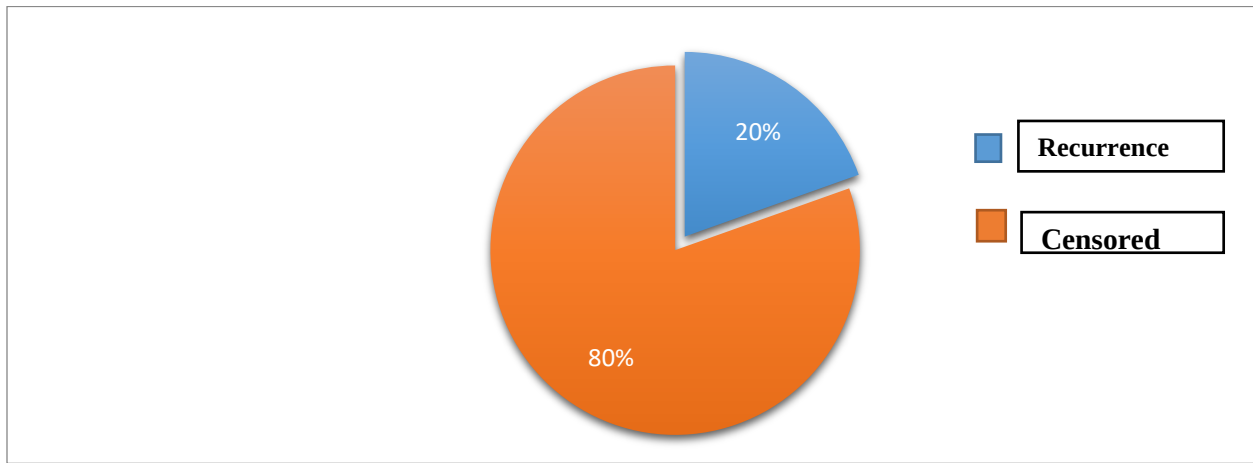


Figure 2: Survival status of breast cancer patients who underwent surgery in selected public hospitals of Addis Ababa, Ethiopia, 2024.

5.4 Incidence of breast cancer recurrence

The overall incidence rate of breast cancer recurrence in the cohort during the 919 person - years of observation was 6.8 per 100 person-years (95%CI=5.35-8.14) follow-up. In this study, the 75% Recurrence Free Survival (RFS) time was 44 months (95%CI=40- 48.00). The estimated overall RFS survival at 24, 36, 48, and 60 months was 91.93%, 83.3%, and 67.7%, 61% respectively (Figure 4). There were 32(50.79%) distant recurrences & 31 (49.21%) loco regional recurrences; and regarding the site of recurrence, axillary and opposite breast recurrence for loco regional type, and lung & chest wall for the distant recurrence were the commonest sites.

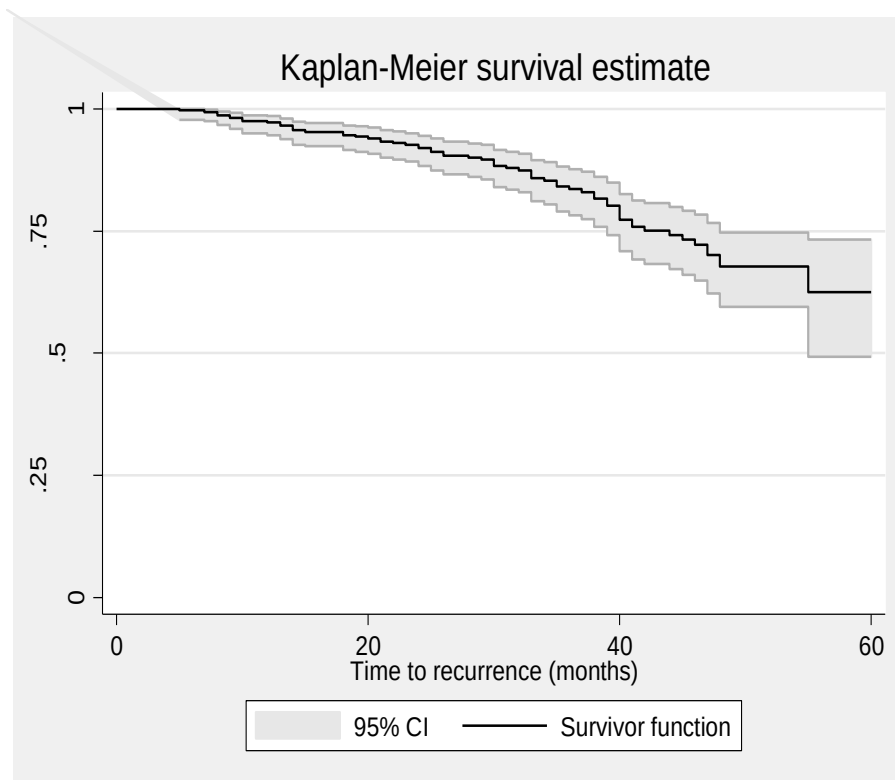


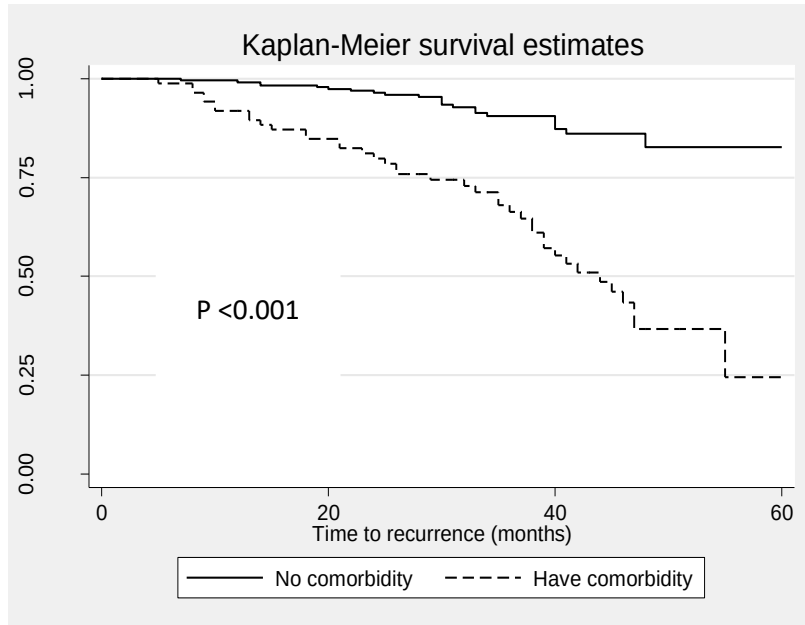
Figure 3: An overall Kaplan-Meier analysis of recurrence-free survival of breast cancer patients who had surgery at selected public hospital, Addis Ababa, Ethiopia, 2024

5.5 Comparison of time to breast cancer recurrence among categorical variables

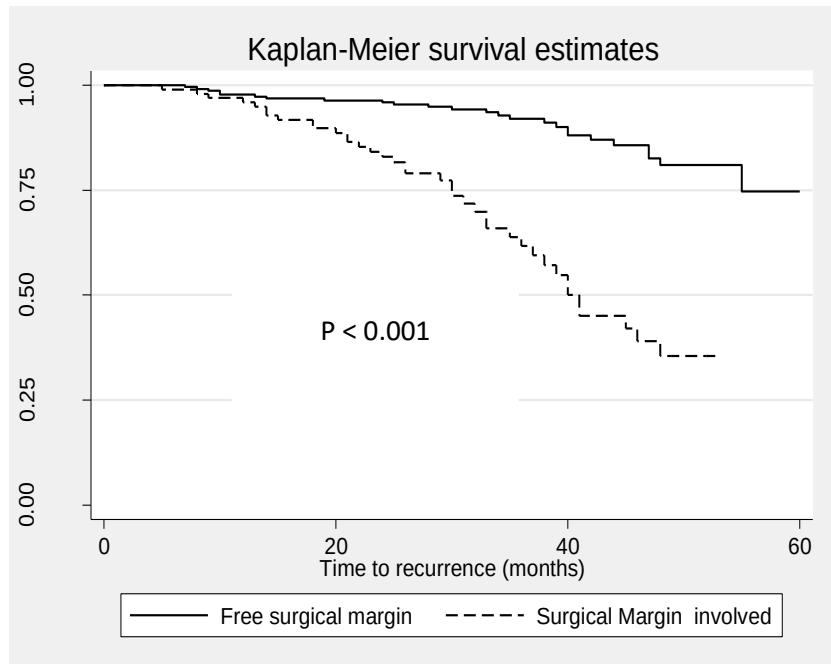
Log rank test was performed to determine for the presence of significance difference in recurrence rate among categorical variables such as;-Age of patients at diagnosis, Preexisting comorbidity status , Surgical margin status, Clinical stage of cancer and Axillary node status at 5% level of significance (Table 5).The Log rank (LR) test has shown that women who were at age 40 and below, and those above 40 years at diagnosis had difference in their time recurrence free survival time (P value for LR test= 0.041). Also, the recurrence free survival time was different among women who had preexisting comorbidity and those with no preexisting comorbidity at baseline (P value for LR test <0.001). In addition, patients who were diagnosed at clinical stage III cancer have shorter median time to recurrence compared to those who were presented with clinical stage I&II cancer (P value for LR <0.001). The graph of log-rank has displayed that there was difference in recurrence free survival time among women were presented with histologic grade I & II, and those with grade III. The median time to recurrence is longer is grade I and II than histological grade III; and this difference was significant at log rank test P value of < 0.001. Additionally, the median time to recurrence was shorter in women who had two or more lymph node involvement than those with less than two lymph node involvement (P value for LR-test=0.0012) (figure 5).

Table 5: Log rank test for categorical independent variables among breast cancer recurrence patients who had surgical treatment in Addis Ababa, Ethiopia, 2024.

Variables	Chi-square	Df	p-value
Age	4.15	1	0.0417
Stage of cancer	24.82	2	<0.001
Comorbidity	49.11	1	< 0.001
Histological grade	24.91	2	< 0.001
Body mass index	18.98	1	0.001
Surgical margin	47.38	1	< 0.001
Lymph node	10.58	1	0.0012
Tumor size	12.15	1	0.0023
Axillary node status	19.54	1	<0.001

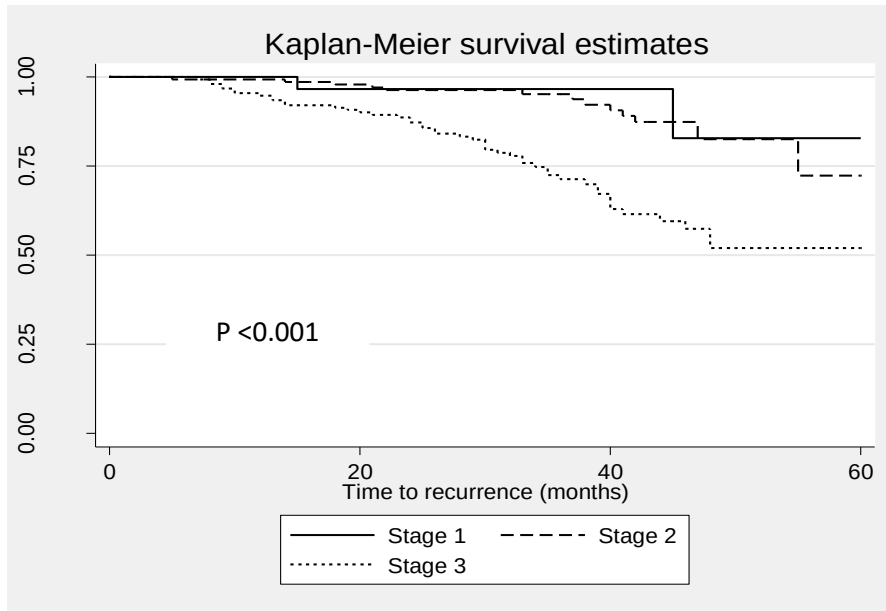


A.



B.

C.



D.

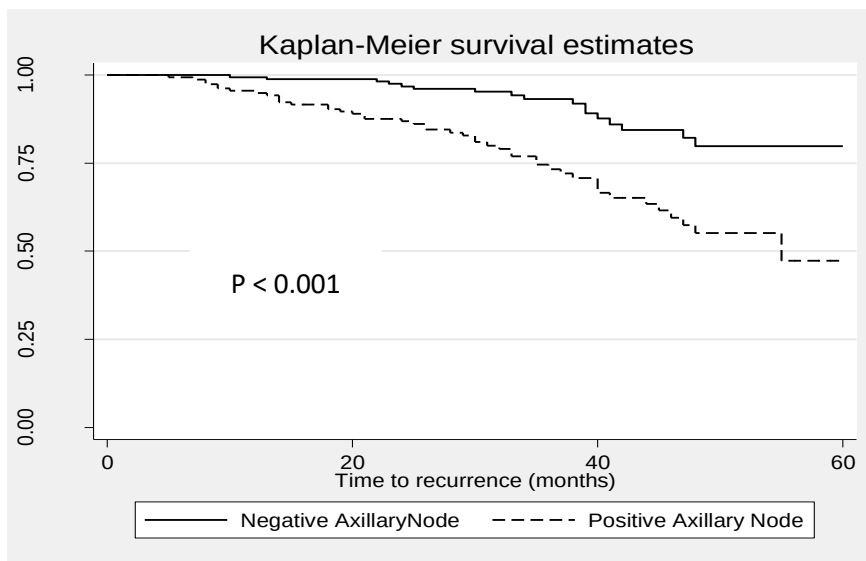


Figure 4: Kaplan-Meier recurrence free survival function among different groups of breast cancer patients with log rank test P-value by Preexisting comorbidity status ($P < 0.001$) (A), Surgical margin status ($P < 0.001$) (B), Clinical stage of cancer ($P < 0.001$) (C), and Axillary node status ($P < 0.001$) (D) at selected public hospital Addis Ababa Ethiopia , 2024.

5.6 Cox proportional hazard Assumption

The cox proportional hazard assumptions were checked statistically using a global test. All the covariates met the proportional hazard assumption, and the p value over all Schoenfeld global tests was 0.7933 (Table 6).

Table 6: Proportional Hazard assumption model of the Cox model for breast cancer patients who had surgical treatment in selected public hospitals Addis Ababa, Ethiopia, 2024

Variables	Rho	Chi-square	Df	Pro>chi2
Age	-0.05794	0.24	1	0.6262
Comorbidity	-0.06379	0.30	1	0.5861
Cancer stage	-0.12249	1.05	1	0.3066
BMI	0.06916	0.34	1	0.5587
Histological type of cancer	-0.12654	1.06	1	0.3023
Histological grade	0.16340	2.12	1	0.1453
surgical margin status	0.12185	1.20	1	0.2742
Lymph node involvement	0.00868	0.00	1	0.9474
Axillary node status	-0.17863	1.65	1	0.1993
Tumor size	-0.04265	0.13	1	0.7220
Global test		6.26	10	0.7933

Model goodness-of-fit

After fitting a multivariable Cox Proportional Hazard Model, the adequacy of the fitted model was evaluated using Cox Snell residuals. The hazard function follows the 45°-line, which approximately, indicates that the model fits the data well (Figure 6).

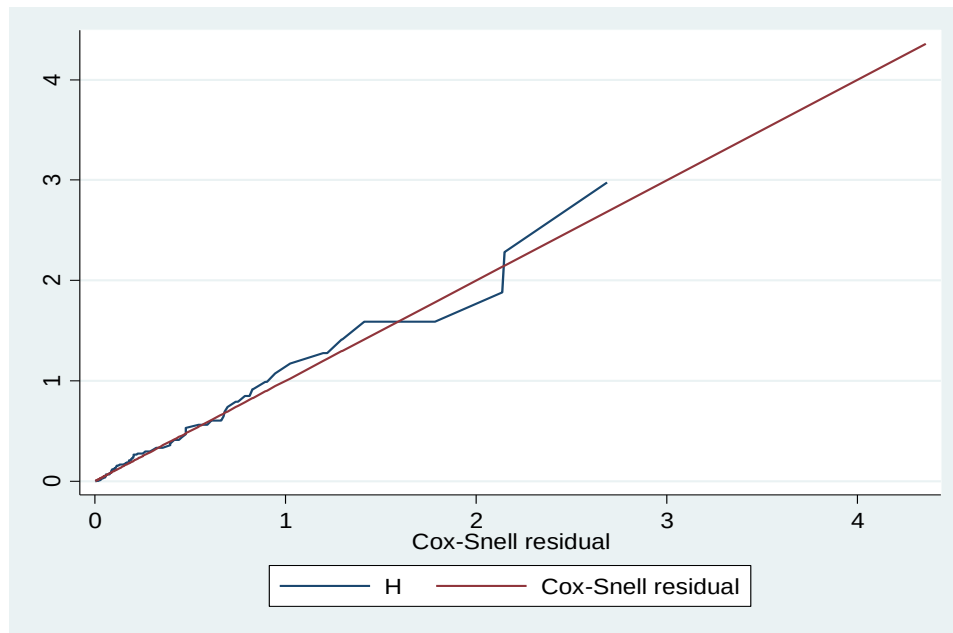


Figure 5: Cox Snell residual test for the model's overall fitness.

5.7 Predictors of breast cancer recurrence

Covariates selected for the final model were age at diagnosis, preexisting comorbidity, BMI at diagnosis, histologic grade, histological type of cancer, stage of cancer, surgical margin, axillary node status, number of positive lymph nodes involved, and histological type of cancer. According to the results of multivariate Cox proportional hazard analysis, women aged 40 & below were nearly 3 times more at risk to increase time to breast cancer recurrence than those with age above 40 years (AHR= 3.32; 95%CI: 1.8- 5.88). Similarly, women who were presented with body mass index $\geq 25 \text{ mg/m}^2$ at diagnosis had nearly 2 times higher risk to develop recurrence than those who were body mass index $< 25 \text{ mg/m}^2$ (AHR=1.95 ;95%CI: 1.06 - 3.59). On the other hand, women who were surgical margin positive at diagnosis had 2 times higher risk to develop recurrence than those who were surgical margin negative (AHR=2.1 ;95%CI: 1.20 - 4.02). In addition, women who had axillary node status positive were nearly 1.9 times at higher risk of developing recurrence than those with axillary nodes negative (AHR=1.98 ;95%CI: 1.08 -3.61). Similarly, presence of preexisting comorbidity (AHR=4.45; 95%CI: 2.39-8.30) was 4 times more at risk for recurrence than counterpart (Table 7).

Table 7: Bivariate and multivariate Proportional Cox Hazard regression analysis of predictors associated with breast cancer recurrence in patients who had surgical treatment in Addis Ababa, Ethiopia, 2024.

Variables	Category	Outcome		CHR with 95% CI	AHR with 95%CI	P-value
		Recur- rence	Cen- Sored			
Age at dx	≥ 40	31	159	1	1	
	< 40	32	100	1.66(1.01-2.72)	3.3(1.8 - 5.8)	$< 0.001^{**}$
Comorbidity	Yes	40	46	5.16(3.09-8.6)	4.45(2.39 - 8.30)	$< 0.001^{**}$
	No	23	213	1	1	
BMI at diagnosis	Normal	16	155	1	1	
	weight	47	104	3.2 (1.8-5.7)	1.95(1.06 - 3.59)	0.032*
	Overweight					
Cancer stage at	I	2	28	1	1	
	II	14	126	1.18(0.26 - 5.21)	1.16(0.24 - 5.58)	0.851

diagnosis	III	47	105	4.43 (1.07 - 18.2)	2.26(0.47- 10.75)	0.302
Histological grade	Grade I	5	62	1	1	
	Grade II	18	116	1.7(.60 - 4.6)	0.93 (0.31 -2.49)	0.859
	Grade III	40	81	5 (1.9 - 12.6)	0.96(0.31 - 2.76)	0.949
Histological type	Non invasive	4	62	1	1	
	Invasive	59	197	4.77(1.72 - 13.21)	1.8(0.58- 5.71)	0.303
Surgical margin	Free	25	199	1	1	
	Involved	38	60	5.08(3.0 - 8.5)	2.19(1.20 - 4.02)	0.011*
Number of + lymph node involved	< 2	16	135	1	1	
	>= 2	47	124	2.48(1.40 - 4.37)	1.4(.72 -2.61)	0.339
Axillary node status	Negative	17	148	1	1	
	Positive	46	111	3.26(1.86 5.69)	1.98 (1.09 - 3.60)	0.025*
Tumor size at diagnosis	< 2 cm	3	33	1	1	
	2-5 cm	24	136	1.44(.433 - 4.79)	0.5(.13- 1.83)	0.306
	>5cm	36	90	3.2(.98 - 10.12)	0.7(0.19- 2.5)	0.635

CHR=crude hazard ratio, **AHR**=adjusted hazard ratio, **BMI**=body mass index, **1**= references

6. Discussion

Breast cancer recurrence occurs when the disease returns following the breast surgery (7). The annual risk of recurrence reaches its maximum in the second year after diagnosis and stays between 2% and 5% from years five to twenty (8). The molecular sub type of breast cancer determines the sites of recurrence. The most frequent locations for recurrence are the breast or chest wall for local recurrence, the bone for distant metastasis, and the lymph nodes in the region for relapse (1).

Though breast cancer recurrences are distressing, expensive, and raise the risk of death if not identified early, they may frequently be effectively managed. Despite the fact that data on time to recurrence and predictors of recurrence among breast cancer is extensively recognized in the developed country, in Ethiopia data on breast cancer recurrence is not readily available. Therefore the point of this study was to assess time to recurrence and its predictors among women patients with breast cancer treated in selected public hospitals.

The study revealed that the incidence rate of breast cancer recurrence was 6.8(95%CI=5.35-8.14) per 100 person-years. The recurrence free survival status at median follow up time was 85.73%. In this study, the 75% Recurrence Free Survival (RFS) time was 44 months. The estimated RFS survival proportion at 24, 36, 48, and 60 months was 91.9%, 83%, 67%, and 61%, respectively. According to this study, age 40 or below, BMI, surgical margin, axillary node status positive, and presence of preexisting comorbidity were independent predictors of breast cancer recurrence. The incidence rate of the current study is consistent with that of findings reported in Addis Ababa (6.5%) (14), South Korea (5.9%) (13). In contrast, the incidence rate is higher to those reported in Australia (3.3%) (18). and Egypt (4.2%) (10), and lower to those reported in Netherlands (11.9%)(12).This difference might be due to most of patients included in our analysis were diagnosed at late stages, and presenting at late stage is highly associated with increased incidence of breast cancer recurrence(14)(40).

The findings of this study revealed that the 75% recurrence free survival time to recurrence of breast cancer was 44 months (95%CI:40-48.00), and this finding is consistent with findings presented in USA 48 months (23), in Thailand 45.43months(6) and in South Korea 47 months (13). On the other hand, the 75% recurrence free survival time to recurrence was higher than

those findings reported in France(24), and Addis Ababa(14). The differences might be due to 98% of our study participants having a modified radical mastectomy, using this type of surgery has been proven as effective in preventing the recurrence (41).

This retrospective cohort study revealed that the estimated recurrence free survival rate was 97.19, 91.7%, 83.3%, 67.07%, and 61.24%, at 1,2, 3, 4, and 5 years respectively. The finding has shown that patients have good recurrence free survival rate for the first 3 years which is consistent with findings reported in Iran (2.5 year RFS rate 86%) (11), Addis Ababa (2 year RFS rate 91.5%, & 3 year RFS rate 82.4%) (14). In contrast, the finding has shown that the RFS proportion has higher at 5 years. This rate was higher when compared with those values reported in Addis Ababa in which RFS rate was 50.5%, & 28.5% at 5&6 year respectively) (14),and the result was consistent with finding in Iran where 5 year RFS rate was 82.5% (11), and in Netherland at which the 4 year RFS rate was 88.4% (12). This might be due to most of the patients included in this study having 2 or more lymph node involvement, and the findings support that patients with increased lymph node involvement have less recurrence free survival proportion (10, 24, 28).

The analysis of this study has also identified those women who were diagnosed at age 40 years and below were 3 times in the higher risk to develop recurrence than those with age above 40 years. In addition, a 5-year RFS rate after surgery was 63% for women aged 40 or younger, and 60% for women over 40 years. There are previous studies supporting our finding that age ≤ 40 as an independent predictor of breast recurrence; and those studies had explored that women diagnosed at younger age (≤ 40) years were presented at an advanced stage and grade which can be associated with lymphovascular invasion (40,41). In our study, most women with age 40 years or below were presented at advanced stage (stage III cancer) when compared to those age above 40 years. A review by Anders et al., suggested that there is a higher percentage of Estrogen receptor/Progesterone receptors-negative tumor, Human epidermal growth factor receptor 2 (HER2)-positive tumor, and triple-negative tumor in young breast cancer patients compared to the old patients(44).

The study finding also revealed that women who had a preexisting comorbidity were 4 times at risk to develop recurrence. This finding can be supported by studies done in different areas. The

presence of comorbidities may cause metabolic impairment which may then interfere with treatment response(21 ,43). Women who were presented with overweight at diagnosis had nearly 2 times higher risk to develop recurrence than those who were normal. Overweight is recognized to be a state of chronic inflammation characterized by elevated circulating levels of pro-inflammatory mediators for breast cancer (40).

This study has also demonstrated that patients who had increased number of lymph node involvement risk to develop recurrence compared to those with <2 lymph node involvement; and the finding is consistent with those reported in other countries (10 , 24 ,28 , 46).

Our study demonstrated that surgical margin positive at diagnosis had 2 times higher risk to develop recurrence than those who were surgical margin negative. This finding is in agreement with that reported in different developing and developed countries (32 , 33 , 37). In addition, women who had axillary node status positive were nearly 1.9 times at higher risk to develop recurrence than those with axillary nodes negative. It is consistent with other finding from those studied in other countries (10), (24). This is due to someone being found to have cancer in the Lymph node is usually a bad sign that the cancer has or will soon recurred and spread to other organs.

In a recent study, patients who had poorly differentiated histologic grade (grade III) and were diagnosed at clinical stage III were also identified as a predictor for breast cancer recurrence. These findings are consistent with findings described in other studies (14 , 24). The reason behind recurrence risk in patients with increased lymph node involvement, late-stage cancer, and poorly differentiated histologic grade could be linked with delayed detection of tumors.

Limitation of the study

Due to incomplete data from the chart, some behavioral elements were not incorporated to the study. Second, the data were liable to selection bias, hence incomplete charts were excluded.

7. Conclusion

Overall the incidence rate of breast cancer recurrence was high. Comorbidity, Age less than 40 years, overweight, axillary node status positive, more number of lymph nodes involved and deep surgical margin were predictors variables with higher recurrence rates.

8. Recommendation

The ministry of health and policymakers should work on awareness by letting to know the risk factors for breast cancer recurrence and to follow up their cancer status to minimize the risk of recurrence and recognizes breast cancer as an important health problem and establishing screening test and early detection policies for most risky groups. In addition it will be important to maximize supporting the cancer diagnosing and treatment center in our country. Awareness has to be given for the society on predictors of breast cancer recurrence.

Tikur Anbessa Specialized Hospital and Saint Paul's Hospital Millennium Medical College need to improve public and professional awareness, early detection and prompt treatment using feasible, effective regimens and include detailed patient characteristics in the cancer during and after breast cancer surgery. Therefore, improvement in the awareness of breast cancer recurrence prevention, screening and treatment in collaboration with public media is critical.

Moreover the oncology unit team; improvement in patient education related to the recurrence prevention such medications and recommended lifestyle changes. If women cancer is hormone receptor-positive, hormone therapy can reduce recurrence risk and self-assessment may be important and underexplored factors in post-treatment care and early initiation of management for those early stage breast cancer women especially surgery without delaying is also crucial to prevent the recurrence.

For researcher, since educational level, parity and some of the behavioral factors (smoking status, alcoholism) were not investigated due to incomplete information from the chart. As a result it is recommended to incorporate in prospective studies.

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10. Annexes

Annexes1: Fact/Information sheet

DATE-----

At SPHMMC, I am a graduate student. I am now working for a master's degree in clinical oncology nursing by conducting research on breast cancer recurrence predictors among patients treated at selected public hospital in Addis Ababa. Enhancing patient survival and quality of life requires identifying the incidence and determinants of breast cancer recurrence. Thus, the goal of this research is to evaluate the predictors of breast cancer recurrence. As such, I am respectfully requesting your consent to use the breast cancer patient's chart as a source of data for my study. A copy of this study will be provided to your establishments and utilized to enhance patient care. The material gathered will be published in any journals or conference proceedings, and the study's findings will only be utilized in the research thesis. I would like to express my gratitude in advance for your kind assistance.

Regards, Sincerely;

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Annexes II: Data extraction tool

CODE _____		Medical Record Number (MRN) _____
1: SOCIODEMOGRAPHIC CHARACTERISTICS		
Serial Number	Variables	Answers
1001	Patient Age at diagnosis	_____ Years
1002	Marital Status	1. Single 3. Widowed 2. Married 4. Divorced
1003	Place of residence	1. Urban 2. Rural 3. Unknown
2: CLINIC-PATHOLOGICAL CHARACTERISTICS		
2001	Pre-medical comorbidity at the time of diagnosis	1. Yes 2. No 3. Unknown
2002	If there is preexisting comorbidity, specify	
2003	Body mass index at the time of first diagnosis	_____ Kg/m2
2004	Date of diagnosis	____/____/____ (DD/MM/YY)
2005	Laterality breast cancer	1. left 2. right
2005	Basis of diagnosis	1. Clinically 2. Cytology
2006	Cancer stage at diagnosis	1) I 2) II 3) III
2007	Histological grades Of neoplasm	1. Well Differentiated (Grade 1) 2. Moderately Differentiated (Grade 2) 3. Poorly Differentiated (Grade 3) 4. Undifferentiated 5. Not Determined
2008	Histology type of Cancer	I. If Noninvasive carcinoma 1. Ductal carcinoma in situ 2. Lobular carcinoma in situ 3. Medullar 4. NOS (Non otherwise specified)

		5. Other: Specify II. If Invasive carcinoma 1. Ductal 2. Lobular 3. Medullar 4. NOS (Non otherwise specified) 5. Other: Specify
2009	Surgical margin conditions	1. Free 2. Involve
2010	Number of positive lymph nodes involved	
2011	Axillary Node status	1. Negative 2. Positive 3. Missing
2012	Tumor size in	1. T1<2cm 2. T2 2-5cm 3. T3 >5cm 4. T4
2013	Estrogen receptor status	1. Negative 2. Positive 3. Not determined
2014	Progesterone receptor status	1. Negative 2. Positive 3. Not determined
3. TREATMENT-RELATED VARIABLES		
3001	Date of surgery	____/____/____(DD/MM/YY)
3002	Duration of days from diagnosis to date of surgery (in days)	
3003	Type of surgery	1. Modified radical mastectomy 2. Lumpectomy 3. Breast conservative surgery
3004	Neo-adjuvant chemotherapy	
3005	If yes to # 0022, mention the Number of cycles	
3006	Use of adjuvant chemotherapy	1. Yes 2. No
3007	If yes to #0024, mention the number of cycles	
3008	The regimen of chemotherapy used	1. AC(doxorubicin, cyclophosphamide) 2. Paclitaxel 3. AC + Paclitaxel
3009	Use of hormone	1. Yes

	Therapy?	2. No
3010	If yes to #0027, mention duration in months	
3011	If yes to #0027, the regimen of hormone therapy used	1. Tamoxifen 2. Anastrozole
3012	Date of last visit	___/___/___ (DD/MM/YY)
3013	The Status of the patient recurrence during last contact	1. Recurrence 2. Censored
3014	If recurrent, type of Recurrence	1. Loco regional recurrence 2. Distant recurrence
3015	If recurrent, Site of recurrence	
3016	If recurrent, date of recurrence	
Data extractor name: _____ Date: ____/____/____		

Annex III: Charles comorbidity index

Each condition is given a score of 1, 2, 3, or 6 according to the International Classification of Diseases code 10, which is related to breast cancer survival. A patient can be classified as having comorbidity if they had any of the preexisting conditions listed below.

Conditions	Weight
Congestive heart failure	1
Myocardial infarction	1
Peripheral vascular disease	
Cerebrovascular disease i.e. hypertension	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes without complication	1
Paraplegia or Hemiplegia	1
Diabetes with end organ damage	2
Any cancer	2
Moderate or severe liver disease	3
AIDS	6

Annexes IV

The American Joint Committee on Cancer TNM classification scheme for staging breast cancers

Tumor (T) Classification:

Tis: Non-invasive tumor (in situ)

T0: No evidence of primary tumor

T1: Invasive tumor, 2 cm or smaller

T2: Invasive tumor, between 2 and 5 cm

T3: Invasive tumor, larger than 5 cm

T4: Invasive tumor of any size, attached to, or invading, surrounding tissues, including inflammatory carcinoma

Lymph Node (N) Classification:

N0: No spread to lymph nodes detected, negative lymph nodes

N1: Spread to lymph nodes in underarm, positive lymph nodes

N2: Lymph nodes in underarm attached to each other or surrounding tissue

N3: Spread to lymph nodes beside breast bone

Metastasis (M) Classification:

M0: No spread detected

M1: Spread to lymph nodes above collarbone, or spread to other parts of the body

This information is collapsed into a few categories called summary stages. These „summary stages“ can be determined clinically or pathologically or both.

Stage 0: Tis, N0, M0

Stage I: T1, N0, M0

Stage IIA: T0, N1, M0 T1, N1, M0 T2, N0, M0 /Stage IIB: T2, N1, M0 T3, N0, M0 Stage IIIA: T0-3, N2, M0 T3, N1-2, M0 56/ Stage IIIB: T any, N3, M0 T4, N0-2, M0 Stage IIIC: T any, N3, M0

Stage IV: T any, N any, M1

11. Declaration

I declare that this Research thesis entitled " Time to recurrence and predictors of breast cancer among women treated in public hospitals, Addis Ababa, Ethiopia" is my own work that have not been addressed in the study area as far as my knowledge touched and all the sources I used has been indicated and acknowledged as complete reference.

Name of investigator	Signature	Date
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Yadessa Chala	_____	_____
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2 Name of adviser/s

1. Mr. <u>Tesfaye Techane</u>	_____	_____
2. Mr. <u>Bonsisa Bekele</u>	_____	_____

Name of invigilators

1. Mr. <u>Tesfaye Girma</u>	_____	_____
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2. Mr. <u>Fissaha Zeleke</u>	_____	_____
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